NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Alnylam

2. **Company clarification response**

3. **Consultee submissions** from:
   a. Metabolic Support UK
   b. UK Kidney Association
   c. NHS England and NHS Improvement

4. **Clinical expert submissions** from:
   a) Dr Wesley Hayes, nominated by British Association for Paediatric Nephrology, endorsed by Royal College of Paediatric and Child Health

5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews (KSR)

6. **Evidence Review Group report – factual accuracy check**

7. **Evidence Review Group addendum**

Please note that the appendices to the company's submission and company model will be available as a separate file on NICE Docs for information only.

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

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Abbreviations

Term	Definition
ADA	**Antidrug antibody**
AE	**Adverse event**
AGT	**Alanine-glyoxylate aminotransferase**
AIC	**Akaike information criterion**
ALT	**Alanine transaminase**
ASN	**American Society of Nephrology**
AST	**Aspartate transaminase**
ATMP	**Advanced therapy medicinal products**
AUC	**Area under the curve**
BIC	**Bayesian information criterion**
BSA	**Body surface area**
CaOx	**Calcium oxalate**
CASP	**Critical Appraisal Skills Programme**
CBA	**Cost-benefit analysis**
CDSR	**Cochrane Database of Systematic Reviews**
CE	**Cost effectiveness**
CEA	**Cost-effectiveness analysis**
CENTRAL	**Cochrane Central Register of Controlled Trials**
CHE	**Centre for Health Economics**
CHMP	**Committee for Medicinal Products for Human Use**
CI	**Confidence interval**
CKD	**Chronic kidney disease**
CKD-EPI	**Chronic Kidney Disease Epidemiology Collaboration**
cLKT	**Combined liver–kidney transplantation**
CMA	**Cost-minimisation analysis**
CMH	**Cochran-Mantel-Haenszel**
CPCI-S	**Conference Proceedings Citation Index-Science**
CRD	**Centre for Reviews and Dissemination**
CSR	**Clinical study report**
CT	**Computed tomography**
CTR	**Clinical Trials Register**
CUA	**Cost-utility analysis**
DALY	**Disability-adjusted life-year**
DAO	**d-amino acid oxidase**
DB	**Double-blind**
EAMS	**Early Access to Medicines Scheme**
EAS	**Efficacy analysis set**
eCRF	**Electronic case report form**
ECM	**Established clinical management**
EED	**Economic Evaluation Database**
eGFR	**Estimated glomerular filtration rate**
EH	**Enteric hyperoxaluria**
EMA	**European Medicines Agency**
ENT	**Ear, nose, and throat**

EOL	**End-of-life care**
EQ-5D-3L	**EQ-5D, Three-Level Questionnaire**
EQ-5D-5L	**EQ-5D, Five-Level Questionnaire**
EQ-5D-Y	**EQ-5D, Youth version**
ESKD	**End-stage kidney disease**
ESPN	**European Society for Paediatric Nephrology**
ESRD	**End-stage renal disease**
EU	**European Union**
EUR	**Euro**
FAS	**Full analysis set**
GalNAc	**N-acetylgalactosamine**
GBP	**British pound sterling**
GEE	**Generalised estimating equation**
GLS	**Global longitudinal strain**
GO	**Glycolate oxidase**
GP	**General practitioner**
GRHPR	**Glyoxylate and hydroxypyruvate reductase**
HAO1	**Hydroxy acid oxidase 1**
HCRU	**Healthcare resource utilisation**
HD	**Haemodialysis**
HR	**Hazard ratio**
HRG	**Healthcare Resource Group**
HRQoL	**Health-related quality of life**
HTA	**Health Technology Assessment**
HUD	**Health Utilities Database**
ICER	**Incremental cost-effectiveness ratio**
ICTRP	**International Clinical Trials Registry Platform**
ICUR	**Incremental cost-utility ratio**
INR	**International normalised ratio**
IPHR	**International Primary Hyperoxaluria Registry**
IPNA	**International Pediatric Nephrology Association**
IQR	**Interquartile range**
IQWiG	**Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen**
ISN	**International Society of Nephrology**
ISPOR	**International Society for Pharmacoeconomics and Outcomes Research**
ISR	**Injection-site reaction**
ITT	**Intent to treat**
KDIGO	**Kidney Disease: Improving Global Outcomes**
KDQOL	**Kidney Disease Quality of Life**
KHI	**Kidney Health Initiative**
KM	**Kaplan–Meier**
LDH	**Lactate dehydrogenase**
LFT	**Liver function test**
LLOQ	**Lower limit of quantitation**
LSM	**Least squares mean**
LVEF	**Left ventricular ejection fraction**

LY	**Life-years**
LYG	**Life-years gained**
M	**Missense**
M or Mo	**Month**
MAA	**Managed Access Arrangement**
MDRD	**Modification of Diet in Renal Disease**
MHRA	**Medicines and Healthcare Products Regulatory Agency**
MMRM	**Mixed model for repeated measures**
mRNA	**Messenger ribonucleic acid**
N	**Nonsense**
N or No.	**Number**
N/A	**Not available**
NA	**Not applicable**
NaCl	**Sodium chloride**
NICE	**National Institute for Health and Care Excellence**
NHS	**National Health Service**
NR	**Not reported**
OHF	**Oxalosis and Hyperoxaluria Foundation**
OLE	**Open-label extension**
OWSA	**One-way sensitivity analysis**
Ox_C	**Controlled oxalate levels**
Ox_U	**Uncontrolled oxalate levels**
PASS	**Post-Authorisation Safety Study**
PbR	**Payment by results**
PedsQL	**Pediatric Quality of Life Inventory**
PD	**Peritoneal dialysis or pharmacodynamic**
PH	**Primary hyperoxaluria**
PH1	**Primary hyperoxaluria type 1**
PICOS	**Population, Intervention, Comparison, Outcomes, and Study**
PIM	**Promising innovative medicine**
PK	**Pharmacokinetic**
POx	**Plasma oxalate**
PPP	**Purchasing power parities**
PR	**Pyridoxine responsiveness**
PRIME	**Priority Medicines**
PSA	**Probabilistic sensitivity analysis**
PSS	**Personal Social Services**
PSSRU	**Prescribed Specialised Services Research Unit**
PRISMA	**Preferred Reporting Items for Systematic Reviews and Meta-Analyses**
Q3M	**Once every 3 months**
QALY	**Quality-adjusted life-years**
QM	**Once monthly**
QM×3	**Once monthly for three consecutive months**
QoL	**Quality of life**
RaDaR	**National Registry of Rare Kidney Diseases**
RCT	**Randomised controlled trial**

RDCN	**Rare Disease Collaborative Network**
RDI	**Relative dose intensity**
RKSC	**Rare Kidney Stone Consortium**
RNAi	**Ribonucleic acid interference**
RSE	**Renal stone event**
SAE	**Serious adverse event**
SC	**Subcutaneous**
SD	**Standard deviation**
SE	**Standard error**
SEE	**Structured expert elicitation**
SEM	**Standard error of the mean**
SF-12	**12-Item Short Form Health Survey**
SF-36	**36-Item Short Form Health Survey**
siRNA	**Small interfering RNA**
SLR	**Systematic literature review**
SMQ	**Standardised MedDRA query**
SWL	**Shockwave lithotripsy**
TEAE	**Treatment-emergent adverse event**
ToT	**Time on treatment**
UK	**United Kingdom**
ULN	**Upper limit of normal**
US	**United States**
US CDC	**United States Centers for Disease Control and Prevention**
US FDA	**United States Food and Drug Administration**
USD	**Urinary stone disease**
UTRI	**Upper respiratory tract infection**
VAS	**Visual analogue scale**
VAT	**Value-added tax**
WCN	**World Congress of Nephrology**
WHO	**World Health Organization**
WTP	**Willingness-to-pay**

Executive Summary

Overview of the proposed technology

Oxlumo® (lumasiran) is a novel subcutaneously administered ribonucleic acid interference (RNAi) therapeutic approved throughout the European Union (EU) and the United States (US) for the treatment of primary hyperoxaluria type 1 (PH1). The innovation represented by lumasiran was recognised by a Priority Medicines (PRIME) designation from the European Medicines Agency (EMA) and a Breakthrough Therapy Designation from the US Food and Drug Administration (FDA).[1] Furthermore, the Medicines and Healthcare Products Regulatory Agency (MHRA) awarded lumasiran a promising innovative medicine (PIM) designation on 10 July 2020, enabling patients with PH1 to enrol for treatment with lumasiran through the Early Access to Medicines Scheme (EAMS) until marketing authorisation was obtained throughout the EU on 19 November 2020.[2,3]

Lumasiran has been developed to treat PH1, a rare genetic disorder of oxalate metabolism that leads to potentially fatal disease manifestations including recurrent kidney stones, nephrocalcinosis, progressive renal failure, and, as the disease advances, multiorgan damage from systemic oxalosis.[4] Excess oxalate is the driver of PH1 morbidity and mortality.[4-6] Lumasiran is specifically designed to durably reduce oxalate by targeting a liver-specific enzyme to prevent the formation of a key substrate needed for oxalate synthesis.[7] Reduction of hepatic oxalate production is expected to halt the course of the disease.

In phase 3 clinical trials, lumasiran demonstrated the ability to significantly reduce oxalate levels. Among patients with preserved renal function, lumasiran has demonstrated the ability to reduce oxalate to normal or near-normal levels in the majority of treated patients, regardless of age.[8-10] Among patients with advanced renal disease, lumasiran treatment leads to meaningful reductions in plasma oxalate in all patients, regardless of age and whether or not the patient is receiving dialysis.[11]

Consistent with its oxalate-lowering efficacy, lumasiran has shown evidence of downstream clinical benefits, including reduction of renal stone events and reversal of nephrocalcinosis.[8-10] With continued follow-up, it is expected that additional data will become available on the ability of lumasiran to ameliorate longer-term clinical manifestations of PH1.

Nature of the condition

Disease background

PH1 is caused by a deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), which catalyses transamination of glyoxylate to glycine.[12] This deficiency is caused by pathogenic mutations of the *AGXT* gene encoding AGT.[13] The most common mutation, p.Gly170Arg (G170R), accounts for approximately 30% of all *AGXT* mutant alleles;[14,15] it causes the AGT enzyme to be mislocalised to the mitochondria of hepatocytes, where it cannot fulfil its metabolic role.[16] In PH1, AGT deficiency leads to the accumulation of glyoxylate and subsequent overproduction of oxalate from the accumulated glyoxylate substrate.[13] The core feature of PH1 is hepatic overproduction of oxalate, which is subsequently excreted by the kidneys.[4] In passing through the kidneys, however, oxalate binds to calcium to form toxic calcium oxalate crystals, which trigger a significant inflammatory response implicated in tissue damage.[4,5,17,18]

The estimated incidence of PH1 is approximately one in 100,000 live births, and the estimated prevalence is one to three per million in North America and Europe.[14,19,20] The disease is more prevalent in populations where consanguineous marriages are common, especially in the Middle East, North Africa, and South Asia (e.g., Pakistan).[21-23] Most of the understanding of the epidemiology and natural history of PH1 derives from two large disease registries, managed by groups in Europe (OxalEurope)[24] and the US (Rare Kidney Stone Consortium [RKSC]),[25] respectively, which together comprise over 800 PH1 patients.Disease manifestations

Nephrocalcinosis (chronic deposition of calcium salts in the kidney) leads to progressive loss of renal function and may also result in acute kidney injury.[4,17] Oxalate can also cause acute kidney injury via aggregation into stones and resultant obstruction of urinary outflow.[17,18] As kidney damage from oxalate accumulates, renal clearance of oxalate is impaired and oxalate levels in plasma rise, creating a feedback loop that results in further kidney damage (due to increased oxalate exposure) and further oxalate accumulation (due to worsening kidney damage resulting in impaired ability to clear oxalate), along with systemic oxalate deposition that damages organs beyond the kidneys.[26-28] Due to this feedback loop, oxalate accumulation and renal decline are understood to accelerate as the disease progresses.[29] In the natural history of PH1, oxalate accumulation drives inevitable progression to end-stage kidney disease (ESKD) due to chronic/acute loss of renal function.[17,18,30,31]

PH1 has particularly devastating consequences for children with infantile onset of PH1 (before 1 year of age), with rapid progression to ESKD (due to early oxalate load and immature renal function) and significantly reduced survival in those with earlier clinical onset of disease relative to those with later clinical onset of disease.[20,31-37] Regardless of age of onset (infantile [≤1 year] vs. non-infantile [>1 year]), the clinical manifestations of PH1 can be especially detrimental when they arise in children.[31,37-39]

Burden of disease

The impact of PH1 on health-related quality of life (HRQoL) is influenced by the degree of PH1 disease progression.[40,41] HRQoL decreases with progressive renal impairment, and advanced renal impairment can have a profound negative effect on aspects of HRQoL such as physical functioning and physical role limitations.[42,43] This was confirmed in a clinical expert–driven health-state vignette study developed to describe the HRQoL of adults and children with PH1 and different stages of chronic kidney disease (CKD). The vignette-derived utilities highlight the considerable impact of PH1 on HRQoL, particularly once patients reach the need for dialysis.[44] Chronic loss of renal function in PH1 may be punctuated by acute clinical events, which can further impair patient well-being and hasten kidney damage.[18,30,45] For instance, symptomatic renal stones negatively impact HRQoL through symptoms including renal or ureteric colic (abdominal pain), blood in the urine, painful urination, the urge to urinate often, blockage of the urinary tract, and repeated urinary tract infections.[45,46]

Along with chronic renal impairment, systemic oxalosis causes severe complications that can lead to significant morbidity and disability (e.g., vision loss, pathologic fractures, cardiac insufficiency, skeletal pain, skin ulcers, arrhythmias, and peripheral neuropathy).[20,31,47,48] Even before the onset of such manifestations, PH1 patients are burdened with fear of progression to systemic oxalosis.[45] Systemic oxalosis may also be uniquely harmful to children by impairing growth and damaging bones and vital organs during development. Systemic deposition of oxalate may cause failure to thrive, growth retardation, and disability due to bone, joint, and eye damage in children.[31,33,36-38]

Current PH1 management approaches are also burdensome. The intensity and burden of dialysis for patients with more advanced stages of renal decline is significant and difficult to sustain, both for the patient and their caregiver(s).[45] Furthermore, children with PH1 and ESKD who are on dialysis have a three-fold increased risk of death compared to children with ESKD who are on dialysis for non-PH1 conditions.[49,50] For patients with PH1 who have progressed to late-stage kidney disease, combined liver–kidney transplantation is the only option known to resolve the underlying metabolic defect and restore renal function. However, the surgical procedure significantly impacts HRQoL through risk of complications, including mortality, that is exacerbated in patients in poor pretransplantation condition due to systemic oxalosis.[51-53]

Lawrence et al. (2020) reported the widespread negative impact of PH1 on HRQoL in patients and their caregivers.[45] Patients and their caregivers reported a general fear of what is to come, no matter what stage of disease patients are in: fear of stone events, fear of kidney failure, and fear of systemic oxalosis Additionally, the emotional stress and psychologic effects resulting from diagnosis and disease management was a common theme expressed by patients. [redacted]

[redacted].[54]

Current treatment options

There were no approved drugs for the treatment of PH1 prior to lumasiran. Established clinical management (ECM) has been focused on supportive measures, such as low-oxalate diet, increased fluid intake (hyperhydration), crystallisation inhibitor use, and pyridoxine (vitamin B6) supplementation. Hyperhydration and citrate supplementation, which are intended to prevent oxalate crystallisation in the kidneys of patients with preserved renal function, do not address the underlying defect in PH1, have limited efficacy, and are ineffective at slowing disease progression.[4,34,48,55,56] Pyridoxine is one of the few non-invasive options that has been historically available to patients with preserved renal function. There is evidence that a very small, genetically distinct subpopulation (G170R homozygotes) that accounts for approximately 5%–10% of the overall PH1 population retain some degree of AGT activity and have the potential to fully respond to pyridoxine.[19,32,57] However, treatment with pyridoxine does not necessarily lead to normalisation of oxalate levels even in this subset of patients.[19,24,32,57,58] In more advanced stages of renal decline, dialysis may be initiated to slow the build-up of systemic oxalate and/or replace lost renal function.[4,34] For patients with PH1 who have progressed to later-stage kidney disease, combined liver–kidney transplantation is the **only option** known to resolve the underlying metabolic defect and restore renal function.[4,20,51,52,59-61]

Impact of the new technology

Lumasiran represents a paradigm shift in the management of PH1 by offering a pharmacologic option with the ability to normalise or near-normalise oxalate overproduction, the central driver of morbidity in patients with PH1. Therefore, treatment with lumasiran offers the possibility to halt disease progression. Lumasiran has a mechanism of action that is distinct from all previous treatments for PH1. It is unique in its ability to reduce the level of endogenous oxalate production and address issues with current clinical practice.[7] None of the current approaches, with the exception of liver–kidney transplantation, is successful at removing the source of the pathogenic metabolite (oxalate) and preventing/correcting ESKD,[20,34,62] which is an enormous burden for patients, their families, and society.[51-53]

For patients initiating lumasiran in the earlier stages of disease, the oxalate-lowering effect of lumasiran[8,9,63] is expected to halt disease progression and prevent the onset of serious complications.[6] Patients are expected to have less renal impairment and experience fewer consequences of PH1 progression. It is currently unknown whether clinicians in real-world practice will initiate lumasiran in patients with early-stage disease without rapid signs of progression; furthermore, it is unknown how clinical practice will vary by patient characteristics (e.g., age, age at disease onset).

For patients in the later stages of disease, it is important to lower oxalate levels and achieve the best pretransplantation health state possible, to minimise morbidity and mortality risks associated with transplantation. For patients initiating lumasiran in the later stages of disease, the resulting reduction in oxalate is expected to reduce the need for dialysis, stabilise the disease, and prevent the incidence of new complications of systemic oxalosis or promote reversal of systemic oxalosis among affected individuals. These improvements are expected to enable more patients to reach transplantation and achieve better outcomes post transplantation. [redacted][64][redacted]

Due to the establishment of a Rare Disease Collaborative Network (RDCN), the majority of the most severely affected PH1 patients are currently managed by or in consultation with the leading paediatric and adult nephrology centres. Lumasiran prescribing decisions will be limited to consultants at these expert centres. Therefore, the introduction of lumasiran in the United Kingdom (UK) is not expected to require further significant changes to the way current services are organised or delivered. It is anticipated that the establishment of the RDCN will eventually lead to the formation of a Highly Specialised Service.[65]

Studies across patients with PH1 across a range of ages and levels of disease severity have shown that lumasiran is efficacious in lowering oxalate production.[8,66,67] Significant reductions in urinary oxalate (percent change: −65.4% vs. −11.8%; p<0.001) and plasma oxalate (percent change: −39.8% vs. −0.3%; absolute change: −7.5 vs. 1.3 µmol/L; p<0.001 for both comparisons) from baseline were observed in PH1 patients aged ≥6 years with relatively preserved renal function who were treated with lumasiran versus placebo in the phase 3 randomised controlled trial (RCT), ILLUMINATE-A, [redacted].[8] In the phase 3 ILLUMINATE-B trial, [redacted] treatment with lumasiran resulted in substantial reductions in urinary oxalate (−72.0%) and plasma oxalate (−31.7%) from baseline in patients aged <6 years with PH1 and relatively preserved renal function.[9] In the phase 3 ILLUMINATE-C trial investigating the use of lumasiran in PH1 patients of any age with advanced kidney disease, lumasiran led to reductions in plasma oxalate from baseline in patients not yet on dialysis (−33.3%) and in patients on dialysis (−42.4%).[11,64]

The oxalate-lowering efficacy of lumasiran has been shown to translate to clinical benefit, including reduction of renal stone events and reversal of nephrocalcinosis. Renal stone events, a key driver of morbidity in the early stages of PH1, occurred less frequently upon initiation of oxalate-lowering treatment with lumasiran.[8,9,63,64,68] Nephrocalcinosis is an indicator of kidney damage and a risk factor for ESKD. Reversal of nephrocalcinosis has been observed with lumasiran[8,9,64,68] and attributed to the oxalate-lowering efficacy of lumasiran.

Impact on the NHS—costs and health effects

Value for money

Alnylam Pharmaceuticals developed a de novo Markov model to estimate the impact of treatment with lumasiran on PH1 patients in terms of costs and effects (quality-adjusted life-years; QALYs) over a lifetime horizon. The model compared ECM without lumasiran versus ECM plus lumasiran. The PH1 cohort transitioned through nine health states defined by CKD stage, plasma oxalate level, transplant status, or death.

The model incorporated data from the pivotal RCT, ILLUMINATE-A, and the single-arm, interventional, open-label, phase 3 studies, ILLUMINATE-B and ILLUMINATE-C. Model inputs and assumptions were validated by UK PH1 clinical experts from the RDCN. The model was designed to account for potential differences in natural history input values, rates of disease progression, and clinical management between patients with infantile onset of PH1 and patients who experience clinical onset of PH1 after infancy. Lumasiran compared with ECM yields an incremental gain of [redacted] QALY and a discounted incremental cost-effectiveness ratio (ICER) of £[redacted]/QALY, which includes a proposed confidential patient access scheme discount ([redacted]). Applying a highly specialised technology QALY weighting of [redacted], which is deemed appropriate for technologies with incremental QALYs gained [redacted],[69] yields a discounted ICER of £[redacted].

Budget impact

Following the introduction of lumasiran in England, [redacted] PH1 patients (assuming a [redacted] uptake) are expected to be treated in Year 1, at a net budget impact of £[redacted]; and by Year 5, [redacted] PH1 patients (assuming a [redacted] uptake) are expected to receive lumasiran at a net budget impact of £[redacted].

Impact of the technology beyond direct health benefits

Patients will be expected to retain their independence, requiring less time and assistance from others, fewer mobility aids, and fewer modifications to their homes and vehicles. Lumasiran is anticipated to result in significant economic benefits outside the National Health Service (NHS) in terms of improved patient and caregiver productivity, mental health, and ability to participate in activities of daily living.

Conclusions

Lumasiran is a novel, subcutaneously administered RNAi therapeutic specifically designed to address the underlying cause of PH1. It has been studied across a range of ages and levels of disease severity in three phase 3 clinical trials with ongoing extension periods, a phase 1/2 trial, and an ongoing phase 2 open-label extension.[8-11,63,66] Furthermore, lumasiran has been evaluated on efficacy endpoints that are inherently biological, highly relevant to PH1, and supported by regulatory agencies[70,71] and disease experts.[27] Therefore, the two open-label phase 3 lumasiran trials are unlikely to be affected by biases that inherently influence open-label trials.

Lumasiran represents the first approved treatment for PH1 that significantly reduces oxalate levels, typically to normal or near-normal levels, in patients of any age with relatively preserved renal function.[8,10,63] Lumasiran has also demonstrated strong evidence of clinical efficacy in patients with PH1 and advanced renal decline, including renal decline that is sufficiently advanced to require dialysis.[11,64] Consistent with its oxalate-lowering efficacy, lumasiran has shown evidence of downstream clinical benefits, including reduction of renal stone events and reversal of nephrocalcinosis.[8,10,63] With continued follow-up, demonstration of amelioration of longer-term clinical manifestations of PH1 is anticipated.

Due to the establishment of the RDCN, introduction of lumasiran will not require further significant changes to the way services are organised or delivered. The QALY-weighted ICER for lumasiran is in the range of ICERs for medicines previously approved under the NICE highly specialised technology process.[72] Treatment and management will be via the expert centres within the RDCN, and the budget impact is estimated to be below £[redacted] in each of the first five years. Lumasiran represents a unique opportunity to address excess oxalate production that drives morbidity and mortality in the rare genetic disorder, PH1.[4-6]

Section A – Decision problem

1 Statement of the decision problem

Table A1 summarises the statement of the decision problem.

Table A1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with primary hyperoxaluria type 1	None	NA
Intervention	Lumasiran (OXLUMO™)	None	NA
Comparator(s)	• Established clinical management without lumasiran (including vitamin B6 and an oxalate-controlled diet) • Liver transplant with or without a combined or sequential kidney transplant • Haemodialysis • Hyperhydration	The economic model considered established clinical management without lumasiran to include: • Pyridoxine • Oxalate-controlled diet • Liver transplant with a combined or sequential kidney transplant in patients with advanced PH1 • Haemodialysis • Hyperhydration Isolated liver transplantation (i.e., liver transplant without a kidney transplant) has not been included in the economic model.	Although isolated liver transplantation is a potentially useful procedure to correct the underlying metabolic defect in patients with PH1, it cannot restore lost renal function to the patient.[34] European PH1 treatment guidelines do not recommend pre-emptive isolated liver transplantation, except in highly selected patients.[20] The procedure is not considered standard practice and may be associated with poorer outcomes than those achieved with combined/sequential liver–kidney transplantation.
Outcomes	The outcome measures to be considered include: • Oxalate levels in urine • Oxalate levels in plasma • Change in eGFR • Need for liver transplant with or without a kidney transplant • Mortality • Adverse effects of treatment • Health-related quality of life	The following measures were considered in the economic model: • Oxalate levels • Change in eGFR • Need for liver transplant with a kidney transplant • Mortality • Adverse effects of treatment • Health-related quality of life • Renal stone events • Systemic oxalosis	Excess oxalate production by the liver, regardless of how it is measured, is the driver of PH1 morbidity and mortality.[4] As described above, isolated liver transplantation is not considered standard practice. Renal stone events and systemic oxalosis impact quality of life and can be key drivers of disease progression in PH1.[17,18,30,31]
Subgroups to be considered	If the evidence allows the following subgroups will be considered: infants with rapid and progressive disease; children with a family history confirmed by cord blood testing; and children and adults presenting with kidney stones • Guidance will only be issued in accordance with the marketing authorisation	The following subgroups were considered in the economic model: • Patients of all ages with initial infantile onset of PH1 • Infants with infantile onset of PH1	PH1 has particularly devastating consequences for children with infantile onset, with rapid progression to ESKD and significant excess mortality.[20,31-37] The lumasiran treatment effect is the same across patients, but the derived

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
			benefits may be quite different for different patient types. The potential years of life gained are greater for younger patients than for adults. There is inadequate evidence to consider subgroup analysis for: • Children with a family history confirmed by cord blood testing, as cord blood testing is not a part of standard clinical practice in PH1 • Children and adults presenting with kidney stones, as eventually, all patients with PH1 are expected to develop renal stones, based on the natural history of the disease.[34]
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	None	NA
Cost to the NHS and PSS, and value for money	• Cost effectiveness using incremental cost per quality-adjusted life-year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	None	NA
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and PSS • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise	None	NA
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation	None	NA

*Infantile onset of PH1 is defined as the onset of symptoms before 1 year of age.
eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; NA=not applicable; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PH1=primary hyperoxaluria type 1; PSS=Personal Social Services

2 Description of technology under assessment

2.1 Brand name, approved name and therapeutic class

Oxlumo (lumasiran) is a ribonucleic acid interference (RNAi) therapeutic (anatomic therapeutic chemical code A16AX18[73]).

2.2 Mechanism of action of the technology

Lumasiran is an RNAi therapeutic approved for use in the European Union (EU) and United States (US).[73,74] RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals.[75] Small interfering RNA (siRNA) molecules bind to specific messenger RNA (mRNA) sequences in a way that leads to the degradation of those targeted mRNA strands, thereby inhibiting the synthesis of the corresponding protein. RNAi therapeutics use the same mechanism of action to inhibit the production of specific disease-causing proteins.[76] The discovery of RNAi was awarded the 2006 Nobel Prize in Physiology or Medicine.[77] Alnylam's drug discovery platform focusses exclusively on developing RNAi medicines to target the cause of diseases by potently silencing specific mRNAs.[78]

Primary hyperoxaluria type 1 (PH1) is a rare, chronic, autosomal recessive, genetic disorder of oxalate metabolism that is fatal in most patients if not adequately treated.[30] The core feature of PH1 is hepatic overproduction of oxalate that is subsequently excreted by the kidneys.[4] Lumasiran is a novel, subcutaneously administered RNAi therapeutic specifically designed to address the underlying cause of PH1 through durable reduction of oxalate to normal or near-normal levels in adult and paediatric patients.[8,63,66,67,73,79] Lumasiran has been designed to target the mRNA sequence of the *hydroxy acid oxidase 1* (*HAO1)* gene, which encodes the enzyme glycolate oxidase (GO).[6-8,80] To enhance its therapeutic potential, the chemically synthesised, double-stranded siRNA in lumasiran is conjugated to *N*-acetylgalactosamine (GalNAc) that is designed to be delivered specifically to hepatocytes, where GO is produced.[81,82]

Lumasiran degrades *HAO1* mRNA in the liver, thus decreasing GO production in hepatocytes. As GO is a critical enzyme in the biosynthesis of oxalate in the liver, the action of lumasiran reduces hepatic production of oxalate, the driver of PH1 morbidity and mortality. Reduction of hepatic oxalate production by lumasiran lowers plasma oxalate and urinary oxalate levels,[6,8] and is expected to halt the course of the disease.

The innovation represented by lumasiran has been recognised by both US and EU Orphan Drug Designations, a Breakthrough Therapy Designation from the US Food and Drug Administration (FDA), a Priority Medicines (PRIME) designation from the European Medicines Agency (EMA), and a promising innovative medicine (PIM) designation from the Medicines and Healthcare Products Regulatory Agency (MHRA).[1]

2.3 Dosing information

Table A2 summarises the dosing information for lumasiran.

Table A2. Dosing information of technology being evaluated

Pharmaceutical formulation	**Solution for injection[73]**
Method of administration	Subcutaneous injection[73]
Doses	Dosing is based on body weight:[73] • Patients <10 kg: 6 mg/kg once monthly for 3 months (loading dose), then 3 mg/kg once monthly (maintenance dose) • Patients 10 kg to <20 kg: 6 mg/kg once monthly for 3 months (loading dose), then 6 mg/kg every 3 months (maintenance dose) • Patients ≥20 kg: 3 mg/kg once monthly for 3 months (loading dose), then 3 mg/kg every 3 months (maintenance dose)
Dosing frequency	Refer to the weight-based dosing regimen above for dosing frequency

Average length of a course of treatment	The required volume of lumasiran based on the recommended weight-based dose is administered by subcutaneous injection by a healthcare professional, according to the dosing frequency described above.[73] Administration is assumed to take minutes It is expected that patients will be treated with lumasiran for the duration of their lives or until combined/sequential liver–kidney transplantation, subject to the clinical judgement of the treating physician
Anticipated average interval between courses of treatments	Refer to the weight-based dosing regimen above for the anticipated interval between courses of treatment
Anticipated number of repeat courses of treatments	It is expected that patients will be treated with lumasiran for the duration of their lives or until combined/sequential liver–kidney transplantation, subject to the clinical judgement of the treating physician
Dose adjustments	No dose adjustments necessary beyond the weight-based regimen described above[73]

3 Regulatory information

3.1 Marketing authorisation

A positive Committee for Medicinal Products for Human Use (CHMP) opinion was published on 15 October 2020.[83] Lumasiran received centrally authorised EU marketing authorisation on 19 November 2020,[2] which was automatically converted to a UK marketing authorisation (effective in Great Britain only). Lumasiran was issued with a UK marketing authorisation number (PLGB 50597/0005) on 1 January 2021.

3.2 Timeline of availability

It is anticipated that lumasiran will be launched in the United Kingdom (UK) shortly after National Institute for Health and Care Excellence (NICE) approval.

3.3 Regulatory approval outside the UK

Lumasiran is approved for use in the EU,[73] US,[74] Brazil,[84] and Switzerland[85].

3.4 Current use in England

Lumasiran is available to [redacted] patients who entered the Early Access to Medicines Scheme (EAMS), which was open to enrolment from the date of EAMS Scientific Opinion (10 July 2020[86]) to the date of marketing authorisation in the EU (19 November 2020[2]). Lumasiran is also available to [redacted] patients under *named patient supply* (i.e., following unsolicited requests from clinicians) who were identified after the end of the EAMS enrolment period. [redacted] further requests are pending.

4 Ongoing studies

4.1 Ongoing studies

The efficacy and safety of lumasiran are currently being evaluated in three phase 3 studies (ILLUMINATE-A, -B and -C) and in one phase 2 extension study (ALN-GO1-002).

ILLUMINATE-A (ALN-GO1-003; NCT03681184) is a phase 3 randomised, double-blind, placebo-controlled study followed by an extended dosing period, during which all patients are treated with lumasiran. This phase 3 trial evaluates the efficacy and safety of lumasiran in patients ≥6 years of age with PH1 and relatively intact renal function. Primary analysis of the 6-month double-blind period is complete.[87] The results of the ILLUMINATE-A trial were published in the *New England Journal of Medicine* on 1 April 2021.[8] Data to Month 12 in the extended dosing period were accepted for publication in *Kidney International Reports* on 3 December 2021.[10] The estimated completion date for the extended dosing period is January 2024.[87]

ILLUMINATE-B (ALN-GO1-004; NCT03905694) is an open-label phase 3 study evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients <6 years of age with PH1 and relatively intact renal function.[88] The primary analysis has been accepted for publication in *Genetics in Medicine*.[9] The estimated study completion date is August 2024.[88]

ILLUMINATE-C (ALN-GO1-005; NCT04152200) is a single-arm phase 3 study evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in patients of all ages with PH1 and advanced renal disease.[64,89] The primary analysis has been published in abstract form.[11] The estimated study completion date is July 2025.[89]

The ongoing phase 2 open-label extension (OLE) study in patients with PH1 (ALN-GO1-002; NCT03350451) is assessing continued therapy with lumasiran in patients who had initially been treated with lumasiran in a parent phase 1/2 study.[90,91] Interim data from the phase 2 OLE have been published in abstract form.[66] The estimated study completion date is June 2023.[90]

On 17 March 2020, Alnylam submitted an application to the UK MHRA for assessment for inclusion in EAMS. The MHRA provided its positive Scientific Opinion for EAMS on 10 July 2020.[86] Lumasiran was made available in the UK through EAMS until EU marketing authorisation was obtained (Section 3). Data collection was not mandated for the [redacted] UK patients who continue to access lumasiran through EAMS, and no evidence is anticipated to be released.

4.2 Additional assessment in the UK

The UK National Registry of Rare Kidney Diseases (RaDaR) registry is currently collecting data on patients with PH1.[92] A global, observational, longitudinal study with retrospective and prospective components (ALN-GO1-007, BONAPH1DE)[93] is currently underway and recruiting clinical sites. The study will characterise the long-term real-world safety and efficacy of lumasiran, including in UK patients, and will describe the natural history and progression of patients diagnosed with PH1. Study ALN-GO1-007 will not be restricted to lumasiran treatment. No data on treatments and outcomes are anticipated from RaDaR and BONAPH1DE within the next 12 months.

5 Equality

- PH1 is a rare, chronic, autosomal recessive, genetic disorder of oxalate metabolism that typically first manifests in childhood and persists into adulthood.
- PH1 has particularly devastating consequences for children with infantile onset, with rapid progression to ESKD and significantly greater mortality in those with earlier clinical onset of disease, suggesting that young children are disproportionately affected.
- PH1 disproportionately affects children from specific minority groups, including those of Middle Eastern, North African, Pakistani, and other South Asian heritage.

5.1 Equality assessment

Until now, there have been no approved treatments for PH1.[2,73,74,94] Current PH1 treatments are limited; treatment strategies, except for liver transplantation, do not address the underlying cause of disease and therefore do not measurably impact the inevitable progression to end-stage kidney disease (ESKD), as demonstrated by data from long-term and large-scale registry studies.[17,28,56] Pyridoxine treatment has generated some evidence of efficacy in a small, genetically defined subset of patients, but despite considerable discussion, the evidence base is poor.[4,16,32,95] In addition to the current lack of effective and safe treatments, PH1 is associated with an unacceptable quality of life for most patients. Advanced PH1 disease

may lead to a state of continuous pain, disability, decreasing independence, unemployment, depression, and sometimes suicide.[26]

PH1 disproportionately affects populations in which rates of consanguinity are high, and as a result, PH1 is seen with increased prevalence in Middle Eastern, North African, and South Asian (e.g., Pakistani) heritage populations.[21-23]

As a genetic condition, PH1 is present from birth, and the onset of clinical manifestations typically occurs during childhood.[30,32] Approximately 85% to 90% of individuals become symptomatic in childhood or adolescence.[30,34] PH1 has particularly devastating consequences for children with infantile onset, with rapid progression to ESKD and significantly greater mortality in those with earlier clinical onset of disease.[20,31-37] Regardless of age of onset (infantile [≤1 year] vs. non-infantile [>1 year]), the clinical manifestations of PH1 can be especially detrimental when they arise in children. Renal impairment, an inevitable consequence of PH1—even in the presence of current treatment strategies—is associated with growth impairment, skeletal deformities, cognitive impairment, reduced physical function, and cardiac abnormalities in children.[31,37-39] Systemic oxalosis may also be uniquely harmful to children by impairing growth and damaging bones and vital organs (i.e., eyes) during development.[31,37,38,48] Young people, their families, and caregivers (predominantly female[96]) are therefore disproportionately affected.

5.2 Equality of technology

Lumasiran targets a hereditary genetic disease that, in England, disproportionately affects children from specific ethnic minority groups, including those of Pakistani and other South Asian heritage. There is no single Highly Specialised Service for PH1, due to the rarity of the disease, the wide demographic distribution of patients (from neonates to adults), and the lack of approved treatments beyond supportive care with subsequent dialysis and possible transplantation. Hyperoxaluria has been designated by NHS England as a new Rare Disease Collaborative Network (RDCN), comprising expert centres at the Birmingham Women's and Children's NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Great Ormond Street Hospital, and the Royal Free London NHS Foundation Trust. The establishment of the RDCN will bring improvements in diagnosis and access to clinical trials and treatments. It is anticipated that the RDCN will eventually lead to the formation of a Highly Specialised Service.[65]

Section B – Nature of the condition

6 Disease morbidity

6.1 Disease overview

- PH1 is a rare, chronic, autosomal recessive, genetic disorder of oxalate metabolism. Disease progression is inexorable and patients with PH1 inevitably reach ESKD and die prematurely.
- Clinical manifestations of PH1 typically first appear in childhood and persist into adulthood.
- Renal pathology in PH1 has two main manifestations: chronic nephrocalcinosis due to oxalate accumulation in the kidneys leading to progressive loss of renal function; and acute, painful, and potentially debilitating oxalate renal stones. Oxalate accumulation and renal decline are believed to accelerate as the disease progresses.
- Disease progression leads to renal morbidity (declining renal function and ultimately ESKD), systemic oxalosis, and premature death. The median time to ESKD from birth is 24 years. PH1 can be fatal if not adequately treated.
- Approximately 1 in 5 (19%) of patients with infantile onset of PH1 will progress to ESKD or die by 10 years of age.

- For patients with PH1 who have progressed to late-stage kidney disease, combined/sequential liver–kidney transplant is the only option known to resolve the underlying metabolic defect and restore renal function. For patients in the later stages of disease, it is important to lower oxalate levels to achieve the best pretransplantation health state possible, to minimise morbidity and mortality risks associated with transplantation.

6.1.1 Pathophysiology

Primary hyperoxaluria (PH) is a group of rare, genetic disorders of oxalate metabolism comprising subtypes 1 (PH1), 2, and 3.[4] PH1 is the most common of all subtypes (70%–80% of PH cases) and the most severe.[4,97,98] PH1 is a serious condition that can be fatal if not adequately treated, due to its ability to cause severe damage to the kidney and subsequently in other organs.[18,30,31] Excess oxalate is the driver of PH1 morbidity and mortality.[4-6]

PH1 is caused by a deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), which catalyses transamination of glyoxylate to glycine.[12] This deficiency is caused by pathogenic mutations of the *AGXT* gene encoding AGT. In PH1, AGT deficiency leads to the accumulation of glyoxylate and subsequent overproduction of oxalate from the accumulated glyoxylate substrate (Figure B1).[13] Oxalate (IUPAC: ethanedioate) is a dianion with the formula $(C_2O_4)^{2-}$, and readily binds to metal ions, such as calcium, to form insoluble precipitates.[99,100]

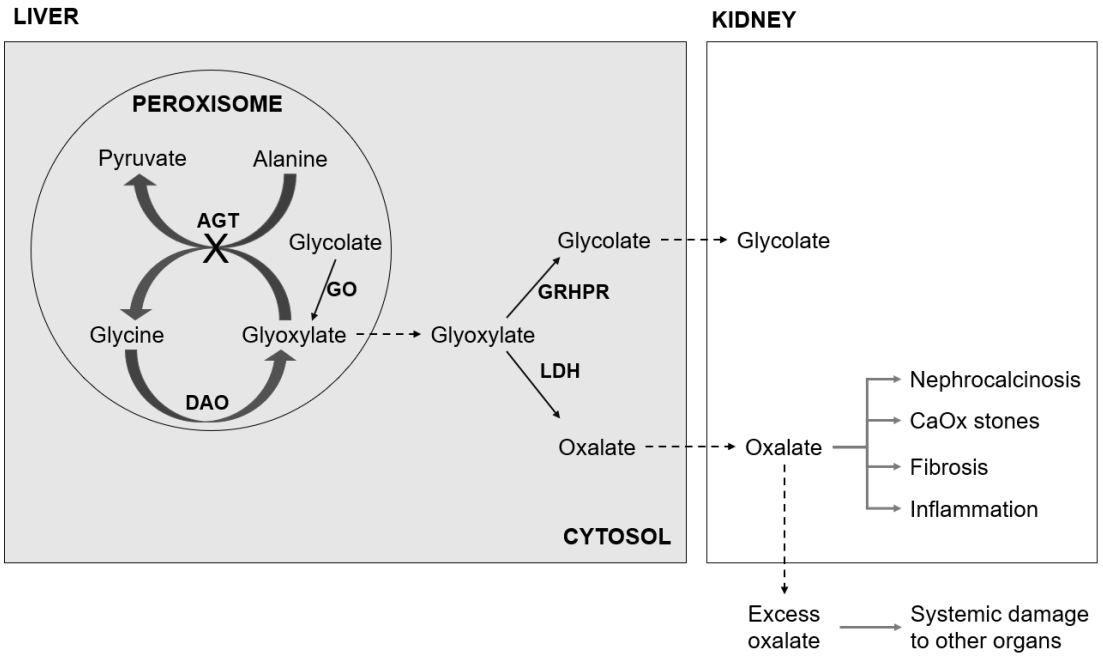

Figure B1. Metabolic pathways involved in the pathophysiology of PH1
Solid arrows: metabolic conversions; dashed arrows: membrane or other transport.
AGT=alanine-glyoxylate aminotransferase; CaOx=calcium oxalate; DAO=d-amino acid oxidase; GO=glycolate oxidase; GRHPR=glyoxylate and hydroxypyruvate reductase; LDH=lactate dehydrogenase
Source: Danpure (2006)[13]; Coe et al. (2005)[101]; Mulay et al. (2013)[5]

The core feature of PH1 is hepatic overproduction of oxalate, which is subsequently excreted by the kidneys.[4] In passing through the kidneys, however, oxalate binds to calcium to form toxic calcium oxalate crystals, which trigger a significant inflammatory response implicated in tissue damage.[4,5,17,18]

Chronic deposition of calcium salts in the kidney, known as nephrocalcinosis, leads to progressive loss of renal function and may also result in acute kidney injury.[4,17] Oxalate can also cause acute kidney injury via aggregation into stones and resultant obstruction of urinary outflow.[17,18] As kidney damage from oxalate accumulates, renal clearance of oxalate is impaired and oxalate levels in plasma rise, creating a feedback loop that results in further kidney damage (due to increased oxalate exposure) and further oxalate

accumulation (due to worsening kidney damage) along with systemic oxalate deposition that damages organs beyond the kidneys.[26-28] Due to this feedback loop, oxalate accumulation and renal decline are believed to accelerate as the disease progresses, such that a patient's rate of renal decline is nonlinear.[29] In the natural history of PH1, oxalate accumulation drives inevitable progression to ESKD due to chronic/acute loss of renal function.[17,18,30,31]

Over 190 mutations of the *AGXT* gene (encoding the AGT enzyme) have been identified in PH1 so far.[102] In PH1, oxalate overproduction is caused by reduced conversion of glyoxylate to glycine due to loss of peroxisomal AGT enzyme activity, which leads to shunting of the AGT substrate glyoxylate into the cytosol, where it is converted into oxalate (Figure B1). The most common mutation, p.Gly170Arg (G170R), accounts for approximately 30% of all *AGXT* mutant alleles[14,15] and causes the AGT enzyme to be mislocalised to the mitochondria of hepatocytes, where it cannot fulfil its metabolic role.[16] There is evidence that a very small, genetically distinct subpopulation (G170R homozygotes) that accounts for approximately 5%–10% of the overall PH1 population retain some degree of AGT activity and have the potential to fully respond to pyridoxine, which may serve as a cofactor involved in AGT localisation.[19,32,57]

6.1.2 Clinical features

As a genetic condition, PH1 is present from birth, and the clinical manifestations typically first arise in childhood and persist into adulthood.[30,32] The disease course of PH1 may vary from patient to patient, even within a family, and disease progression can be rapid and unpredictable.[30,48,103]

Excess oxalate produced by the liver causes chronic, progressive kidney damage that can be accompanied by sudden, acute declines in renal function, ultimately leading to ESKD.[18,30,45] Furthermore, loss of renal function in PH1 puts patients at risk for severe and debilitating systemic complications that can lead to significant morbidity, including vision loss, pathologic bone fractures, and cardiac failure (Figure B2).[20,31,47,48]

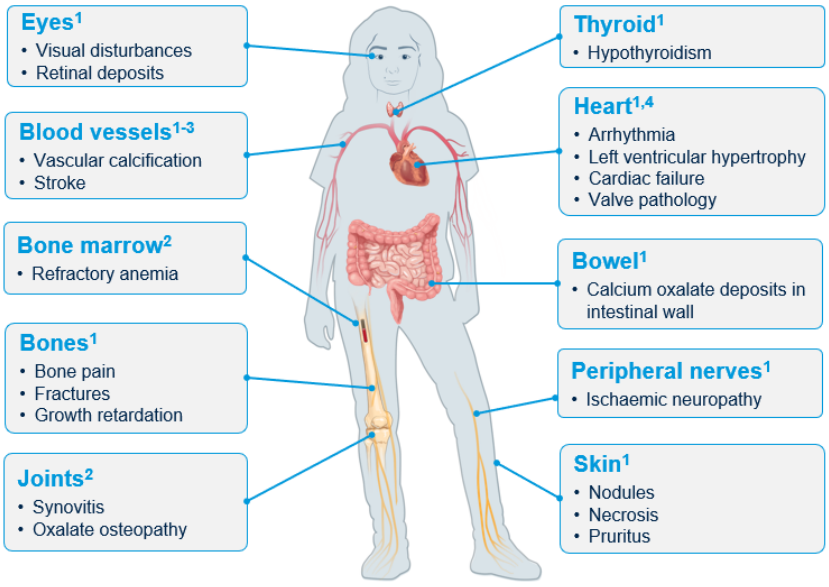

Figure B2. Common signs and symptoms of systemic oxalosis
Source: 1. Cochat et al. (2012)[20]; 2. Bhasin et al. (2015)[31]; 3. Ben-Shalom et al. (2015)[48]; 4. Mookadam et al. (2010)[47]

Renal manifestations

The hallmark renal morbidity observed in PH1 has both chronic and acute components. Nephrocalcinosis, the chronic accumulation of oxalate in the kidneys, leads to progressive loss of renal function.[4,17] Painful and potentially debilitating oxalate renal stones are also observed in PH1 and may cause acute loss of renal function due to obstruction of urinary outflow.[18] The occurrence of chronic and/or acute renal decline in PH1 inevitably leads to ESKD.[30] Consistent with the causative role of oxalate, nephrocalcinosis, urinary oxalate

excretion, and plasma oxalate levels are all significantly associated with risk of progression to ESKD in patients with PH1.[17,28,56,104]

PH1 has particularly devastating consequences for patients with infantile onset of PH1, with rapid progression to ESKD (due to early oxalate load and immature renal function) and significantly reduced survival in those with earlier clinical onset of disease relative to those with later clinical onset of disease.[20,31-37] Patients with infantile clinical onset of PH1 have a statistically significant 6.0-fold increase in hazard of progression to ESKD versus patients with later clinical onset of PH1.[32] Approximately 1 in 5 (19%) of patients with infantile onset of PH1 will progress to ESKD or die by 10 years of age.[32] In addition, regardless of age of onset (infantile vs. non-infantile), the clinical manifestations of PH1 can be especially detrimental when they arise in children. Renal impairment is associated with growth impairment, skeletal deformities, cognitive impairment, reduced physical function, and cardiac abnormalities in children.[31,37-39] Paediatric patients with chronic kidney disease (CKD) are also at risk for disorders of mineral and bone metabolism, anaemia, and abnormalities of the developing heart.[37-39]

In the natural history of PH1, oxalate accumulation drives inevitable progression to ESKD due to chronic/acute loss of renal function.[17,18,30,31] The Harambat et al. (2010)[32] study reported that the median time to ESKD from birth was 24 years (95% confidence interval [CI], 20–32 years). The International Primary Hyperoxaluria Registry has reported a median age of 33 years at progression to kidney failure.[105,106] The OxalEurope registry has reported cumulative ESKD-free survival rates according to genotyping. Cumulative survival free from ESKD at age 50 years was 20% in patients with heterozygous G170R genotype and 7% in patients with no G170R alleles.[32]

Systemic oxalosis manifestations

As oxalate-mediated renal impairment progresses and the kidneys can no longer clear the body's daily oxalate load, oxalate levels in the body rise and toxic oxalate crystals may be deposited systemically.[30,31] Such crystals may deposit in a range of tissues, including bone, heart, skin, joints, and eyes, with debilitating consequences (Figure B2).[20,31,47,48,107] Systemic oxalosis causes severe complications that can lead to significant morbidity and disability (e.g., vision loss, pathologic fractures, cardiac insufficiency, skeletal pain, skin ulcers, arrhythmias, and peripheral neuropathy).[20,31,47,48]

Systemic oxalosis may also be uniquely harmful to children by impairing growth and damaging bones and vital organs during development. Systemic deposition of oxalate may cause failure to thrive, growth retardation, and disability due to bone, joint, and eye damage in children.[31,33,36-38]

Bone and bone marrow

In PH1 patients, progression to systemic oxalosis can result in deposition of calcium oxalate crystals in the bone.[108] Oxalosis can impact bone metabolism, leading to accelerated bone maturation in young patients, reduced total volumetric bone mineral density, and altered bone microarchitecture.[109] Skeletal manifestations can vary. Less specific radiological signs, such as renal osteodystrophy, are reported in early disease. Advanced PH1 is often characterised by radiological signs rarely seen in the absence of oxalosis, and patients may experience bone pain and pathological fractures.[110] In children with PH1, bone disease is the first manifestation of systemic oxalosis and can rapidly progress to pathological fractures in long bones (Figure B3).[111]

Involvement of bone in PH1 may also lead to haematologic complications. Diffuse replacement of bone marrow parenchyma by calcium oxalate crystals can cause cytopenias, leukoerythroblastic reactions, and refractory anaemia.[112,113]

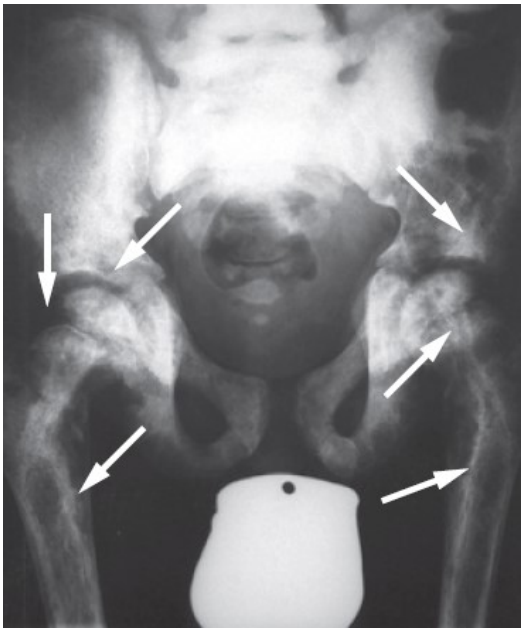

Figure B3. Osteolytic lesions in a 7-year-old boy with ESKD
Arrows indicate osteolytic lesions. The patient was on chronic haemodialysis six times a week.
ESKD=end-stage kidney disease
Source: Hoppe (2012)[62]

Cardiac and vascular complications

Cardiac findings in PH correlate with declining renal function. Commonly found cardiac abnormalities include increased left ventricular mass index, left atrium enlargement, pulmonary hypertension, and diastolic dysfunction. Valve pathology may also occur. Oxalosis involving the myocardium or the cardiac conduction system can lead to heart failure and fatal arrhythmias.[20,47]

Calcium oxalate crystals can also be deposited in the walls of blood vessels in the skin, retina, heart, liver, and neural tissues. Resulting vascular complications depend on which blood vessels in the body have been impacted by calcium oxalate crystal deposits,[114,115] and can include vascular calcification and stroke.[20,31,48]

Skin

Vascular oxalate deposition can also result in cutaneous manifestations, such as painful skin nodules, skin necrosis, gangrene, calciphylaxis-like skin lesions, and pruritus (Figure B4).[20]

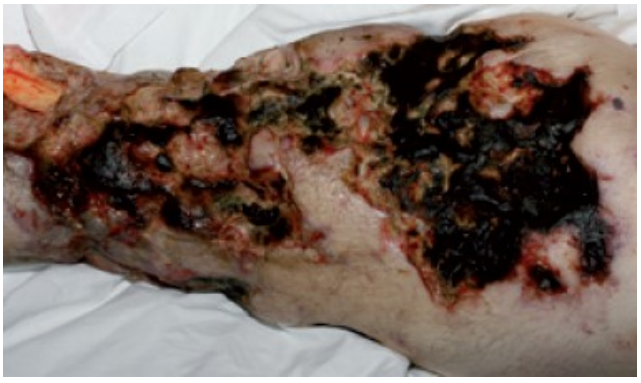

Figure B4. Calcification of the skin in a 33-year-old patient with systemic oxalosis
Source: Hoppe (2012)[62]

Joints

Systemic oxalosis can lead to synovitis and oxalate osteopathy.[31] Calcium oxalate crystals may accumulate in the bones, tendons, cartilage, and synovial tissue causing oxalate arthritis, which is often difficult to distinguish from other causes of crystalline arthritis. Oxalate arthritis is generally symmetric and polyarticular,

and may be either acute or chronic.[114] Frequently involved joints include the knuckles of the hand, knees, elbows and ankles.[116]

Eyes

Severe ocular alterations including macular crystals, hyperpigmentation, subretinal fibrosis, and chronic retinal oedema can occur in patients with PH1, with the potential to result in significantly reduced visual acuity. Ocular complications are more common in patients with infantile onset of PH1.[117] Oxalate deposition in the retinal pigment epithelium can be irreversible, and more severe retinopathy has been observed in PH1 patients with early onset of ESKD.[118]

Nervous system

PH1 patients may also present with nerve pain and neuronal damage (ischaemic neuropathy) due to demyelination and axonal degeneration caused by the deposition of oxalate crystals in neuronal tissues.[20,119] [20,119]

6.1.3 Diagnosis

The main challenge in diagnosing PH1 is its association with a low index of suspicion, which is due to the rarity of PH1 and its non-specific symptoms (e.g., renal stones, renal impairment).[120] Given its rarity, PH1 can remain undiagnosed for several years after the onset of symptoms. Evaluation in accordance with published algorithms can facilitate earlier diagnosis.[20,121] Diagnosis of PH1 depends on diverse diagnostic tools including biochemical urine analysis and genetic studies.[120]

Presentation with symptoms such as nephrocalcinosis, recurrent renal stones in adults, and any renal stones in children may trigger metabolic evaluation of urine (e.g., 24-h urine test). Test results that show excess oxalate excretion can indicate hyperoxaluria (Table B1). Subsequent genetic testing can confirm whether the hyperoxaluria is associated with an underlying genetic defect (i.e., PH) and determine which gene is involved (i.e., *AGXT* if PH1).[4]

Table B1. Age-related reference ranges of metabolites in PH patients

Urinary excretion	Reference range
24-h specimen	
Oxalate, all ages[62]	<0.5 mmol (<45 mg)/1.73 m^2
Glycolate, all ages[62]	<0.5 mmol (<45 mg)/1.73 m^2
Random (spot) specimen	
Oxalate:creatinine[122]	
<6 months	0.07–0.22 mmol/mmol (56–175 µg/mg)
6 months to 1 year	0.06–0.17 mmol/mmol (48–139 µg/mg)
1 to 2 years	0.05–0.13 mmol/mmol (40–103 µg/mg)
2 to 3 years	0.04–0.10 mmol/mmol (32–80 µg/mg)
3 to 5 years	0.03–0.08 mmol/mmol (24–64 µg/mg)
5 to 7 years	0.03–0.07 mmol/mmol (24–56 µg/mg)
>7 years	0.02–0.06 mmol/mmol (16–48 µg/mg)
Glycolate:creatinine[4,123]Glycolate:creatinine[4,123]	
<1 year	0.0079–0.070 mmol/mmol (5.4–47.0 µg/mg)
1 to <5 years	0.0057–0.091 mmol/mmol (4.0–61.4 µg/mg)
5 to 12 years	0.0057–0.046 mmol/mmol (4.0–31 µg/mg)
>12 years	0.0040–0.041 mmol/mmol (2.7–27.0 µg/mg)

Values are laboratory and method dependent.
Source: Barratt et al. (1999)[123]; Cochat and Rumsby (2013)[4]; Hoppe (2012)[62]; Matos et al. (1999)[122]

A proportion of patients with PH1 are diagnosed not on the basis of clinical and biochemical manifestations (as described above) but rather based on familial screening, which focuses on siblings of already diagnosed patients. Based on consultation with PH1 experts in the UK, prenatal screening is not routinely performed.

An analysis of the OxalEurope cohort by Mandrile et al. (2014)[24] found that most patients diagnosed via familial genetic screening had, in retrospect, presented with unrecognised PH1-related symptoms prior to diagnosis. On the other hand, 4% of all patients were truly presymptomatic at the time of diagnosis. In addition, at any time before or after diagnosis, patients with PH1 may be clinically silent. Data from the OxalEurope register show that PH1 is not diagnosed until after the occurrence of ESKD in 43% of patients with PH1; rates of ESKD at diagnosis are 29% for patients diagnosed in childhood and 70% for patients diagnosed in adulthood. Despite the potential absence of signs and clinical symptoms, the pathophysiology of PH1 is such that the disease process is chronically active, even if detectable signs and symptoms are absent. Likewise, it is recognised that PH1-related nephrocalcinosis can progress and cause kidney damage subclinically over extended time intervals.[24]

6.1.4 Specific patient needs addressed

Until now, there have been no approved treatments for PH1.[2,73,74,94] Historically available PH1 treatments do not address the underlying cause of disease, are only effective in a small, genetically defined subset of patients, and/or carry serious safety risks (see Section 8.2.1).[4,16,32,95] Lumasiran, the first approved treatment for PH1, is a novel siRNA therapeutic that has been shown to significantly reduce oxalate levels, typically to normal or near-normal levels, in patients across all ages with relatively preserved renal function. The oxalate-lowering efficacy of lumasiran has been shown to translate to clinical benefit, including reduction of renal stone events and reversal of nephrocalcinosis (see Section 9.6 for more detail). Lumasiran treatment also leads to substantial reductions in oxalate in patients with PH1 and advanced renal disease. Lumasiran has a favourable safety profile and has been well characterised in both placebo-controlled and open-label interventional phase 3 studies (see Section 9.7 for detail).[8,11,63,66,68]

6.2 Epidemiology

It is estimated that the incidence of PH1 is approximately one in 100,000 live births, and the prevalence is one to three per million in North America and Europe.[14,19,20] The disease is more prevalent in areas where consanguineous marriages are common, especially in the Middle East, North Africa, and South Asia (e.g., Pakistan).[21-23]

Most of the understanding of the epidemiology and natural history of PH1 derives from two large disease registries, managed by groups in Europe (OxalEurope)[24] and the US (Rare Kidney Stone Consortium [RKSC]),[25] respectively, which together comprise over 800 PH1 patients. Data from the two registries together confirm that PH1 is the most severe and common disease (80%) amongst the various types of primary hyperoxaluria.[62]

In the UK, it is estimated there are [redacted] people with PH1, based on RaDaR estimates of the overall hyperoxaluria population (~N=120)[92] and the [redacted] diagnosis rate published by Milliner et al. (2020)[27] and Lieske (2005).[105] Expert clinician input supports an assumption that [redacted] of these patients have not already received a liver transplant or combined liver–kidney transplant. Considering that lumasiran would only be used in patients who have not already undergone these transplantation procedures, an estimated [redacted] prevalent patients with PH1 would currently be eligible for lumasiran treatment. In addition to these prevalent patients, according to expert opinion it is assumed that there will be approximately [redacted] new (i.e., incident) patients with PH1 eligible for lumasiran each year, based on the 1/100,000 incidence estimate reported by Harambat et al. (2010)[32] and the number of live births in England and Wales.[124] Of [redacted] eligible patients, [redacted] would be considered in urgent need of treatment.

6.3 Life expectancy

Mortality in PH1 is generally associated with ESKD, dialysis, transplantation, or systemic oxalosis–related complications.[125,126] Children with ESKD due to other conditions had a 5-year survival rate after renal replacement therapy of 92%, compared with 76% for PH patients. Altogether, this translates into a three-fold increased risk of death for PH patients on dialysis compared to those on dialysis due to other conditions.[49,50]

There are no published data on the average life expectancy of PH1 patients in the UK. Overall survival of PH1 patients depends on the time of clinical disease onset (e.g., infancy vs. adolescence or adulthood) and time to ESKD (i.e., renal survival).[24] The OxalEurope registry has reported cumulative patient survival rates of 95%, 93%, 85%, and 74% at ages 5, 10, 30, and 50 years, respectively, in a cohort of 526 PH1 patients. Among those who died during registry follow-up, 25% were younger than 2.5 years old, and the median age at death was 15.5 years.[24,32] Harambat et al. (2010)[32] has published cumulative overall patient survival in a cohort of 155 PH1 patients, as shown in Figure B5. Cumulative patient survival rates were similar to the OxalEurope registry findings described above.[24,32] In Harambat et al. (2010), 20 out of the 155 PH1 patients died at median age of 19.9 years.[32]

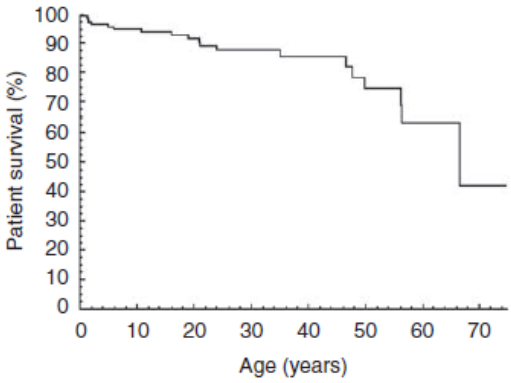

Figure B5. Cumulative patient survival in a cohort of 155 PH1 patients
Source: Harambat et al. (2010)[32]

7 Impact of the disease on quality of life

- PH1 affects patients' psychological well-being, with fear of disease progression impairing patients' and caregivers' quality of life.
- Chronic loss of renal function in PH1 may be punctuated by acute clinical events, which can impair patient well-being and further hasten kidney damage.
- Advanced renal impairment can have a profound negative effect on health-related quality of life (HRQoL), such as physical functioning and physical role limitations. Dialysis to reduce oxalate load in patients with advanced disease is also a major treatment burden for patients and their families.
- Systemic oxalosis significantly impacts HRQoL through diverse and sometimes severe, debilitating, and life-threatening systemic manifestations. Systemic oxalosis may be additionally harmful to children by impairing growth and damaging bones and vital organs during development.
- Symptomatic renal stones negatively impact HRQoL, which is further negatively impacted by urologic interventions and procedures aimed at managing renal stones.
- In addition to the effects already described, PH1 in infancy severely impedes HRQoL through failure to thrive and early onset ESKD. Significant excess mortality in PH1 patients with earlier clinical onset of disease places undue psychological stress on families.
- Transplantation significantly impacts HRQoL through risk of complications, including mortality, due to the surgical procedure. The clinical status of a patient with PH1 immediately prior to transplantation has a significant impact on their post-transplantation survival. Five-year survival following transplantation is 45% in patients with poor clinical status and 100% in patients with good clinical status prior to transplantation.
- Living with PH1 presents many challenges to patients, caregivers, and their families, adding substantial strain to the family due to the intensity of the required medical care and associated financial hardship.

7.1 Impact on quality of life

The impact of PH1 on HRQoL is influenced by the degree of PH1 disease progression, which can vary significantly between patients.[40,41]

7.1.1 Burden of renal impairment

As PH1 advances, HRQoL decreases with progressive renal impairment, and advanced renal impairment can have a profound negative effect on aspects of HRQoL such as physical functioning and physical role limitations.[42,43] Chronic loss of renal function may be punctuated by acute clinical events, which can further impair patient well-being and hasten kidney damage.[18,30,45]

The intensity and burden of dialysis for patients with more advanced stages of renal decline is significant and difficult to sustain, both for the patient and their caregiver(s).[45] It may involve daily travel to hospital for long dialysis sessions, sometimes followed by nocturnal dialysis sessions at home.[45,96] However, because conventional dialysis (three sessions per week[127]) is not effective for lowering oxalate levels in PH1, patients with systemic oxalosis on established clinical management (ECM) require up to six haemodialysis sessions per week, and even this intensive schedule is inadequate to consistently lower oxalate.[4,20,26,31,34,48,128]

7.1.2 Burden of high oxalate levels

Systemic oxalosis (a consequence of advanced renal impairment in PH1) significantly impacts HRQoL through diverse and sometimes severe, debilitating, and life-threatening systemic manifestations.[4] Even before the onset of such manifestations, PH1 patients are burdened with fear of progression to systemic oxalosis with associated anaemia, bone fractures, heart failure, joint damage, neuropathy, skin ulceration, severe weakness, and vision impairment.[45]

PH1 patients are at increased risk of developing painful and potentially debilitating renal stones, which may cause acute loss of renal function due to obstruction of urinary outflow.[18] Eventually, all patients with PH1 are expected to develop renal stones, based on the natural history of the disease.[34] Renal stones negatively impact HRQoL through symptoms including renal or ureteric colic (abdominal pain), blood in the urine, painful urination, the urge to urinate often, blockage of the urinary tract, and repeated urinary tract infections.[46] HRQoL for PH1 patients is further negatively impacted by associated urologic interventions and procedures aimed at managing renal stones.[45]

7.1.3 Added burden in childhood

Hyperhydration is particularly burdensome in childhood. Infants and younger children who are unable to comply may require a nasogastric or percutaneous endoscopic gastrostomy tube passed into the stomach through the abdominal wall, to provide a means of delivering continuous hyperhydration.[20]

PH1 has especially high disease burden among patients with infantile onset disease; patients affected during infancy experience severe impairments in HRQoL through failure to thrive, early onset ESKD, and systemic oxalosis as described in Section 6.1.2.[4,32,129]

7.1.4 Burden to families and caregivers

Living with PH1 presents many challenges to caregivers and families of patients with PH1. Although disease progression and severity are variable, caring for a child or an adult with PH can add substantial strain to the family due to intense medical requirements and associated financial hardship.[45]

The impact on caregivers, especially of young children, of continuously maintaining hyperhydration regimens over many years can be considerable.[20,45] Factors such as treatment-related interruptions to school, work and family life, financial strain due to missed work, anxiety associated with potential kidney failure, and the need for frequent dialysis have a significant negative impact on the quality of life of PH1 caregivers and families.[45] In addition, the requirement for almost daily travel to long dialysis sessions following the onset of advanced disease can become all-consuming.[45] The possibility that a child with PH1 will progress to ESKD or die by their second decade of life[32] must also significantly impact the quality of life of caregivers and families.

Patient- and caregiver-reported impact of PH1 on quality of life

Lawrence et al. (2020) reported the widespread negative impact of PH on quality of life in patients and carers as assessed via a patient and caregiver survey. Most respondents to this survey were patients with PH1 or caregivers of patients with PH1.[45] Patients and their caregivers reported a general fear of what is to come, no matter what stage of disease patients are in: fear of stone events (53% of patients; 36% of caregivers), fear of kidney failure (65% of patients; 24% of caregivers), and fear of systemic oxalosis (65% of patients; 20% of caregivers). Additionally, the emotional stress and psychologic effects resulting from diagnosis and disease management was a common theme expressed by patients and caregivers, as reported in their own voices in Table B2.[45] The burden on caregivers is greater for those caring for children with abnormal kidney function (i.e., predialysis and pretransplantation), compared with those caring for children with normal kidney function, according to an observational study on the health status of caregivers caring for children with PH1 aged 6–17 years.[54]

Table B2. Sample quotations about the impact of PH on patients' and caregivers' quality of life

Symptom/Intervention	Impact
Preservation of renal function	*"It is a daily challenge to make sure our son is drinking constantly throughout the day. He visits the school nurse every day who gives him one of his four daily doses of medication through his (gastrostomy) mickey button. As a 12-year-old, he misses sleepovers, sleep away camp, and overnight school trips."*
Renal stones	*"My son has had multiple surgical procedures beginning at 6 months old. These procedures were very traumatic both physically and emotionally."* *"Kidney stones, procedures and hospitalisations interrupt school, work and require parents to miss work, creating financial burden on the family."*
Kidney failure/dialysis	*"I've often thought back about what we did for the first 2 years of her life. Daily dialysis... sometimes up to 15 hours a day almost seems unthinkable!"* *"Our schedule began every morning at 3:30 AM when I would awaken to prepare the daily medicines for our son. We would leave town at 5 AM to start our commute, have a 4-hour session on the machine and get home by 2 PM. I would put him to bed at 8 PM and begin sterilising everything to start four 1-hour 'dwells' of peritoneal dialysis once he was asleep. I would turn on his feeding pump and finally climb into bed next to him around midnight for 3 hours of sleep."*
Systemic oxalosis	*"My brother experienced such intense nerve pain that he was unable to wear gloves during the winter. I ordered special gloves made of light but warm material for him. Unfortunately, he died before they were delivered."* *"When I first heard the crack, I was just convinced (or in denial) that anything serious had happened. Who breaks their leg playing ring around the rosie?"*
Psychological burden	*"Because (our son's) care was so intense, our other two children had to move in with my parents."* *"As a child, I viewed myself as a fragile bomb that could blow up at any time. With that type of mentality, it is difficult to dream about the future and be excited for what is to come."* *"I feel like we are declining in health before trials can begin."*
Desire for better treatments	"*We would be willing to take more risks for better quality of life, given the likelihood of kidney failure resulting from this disease. We would like to see advances in therapies for patients across the disease spectrum. We need better medications which would reduce oxalate levels and methods to preserve current kidney function."*

PH=primary hyperoxaluria
Source: Lawrence and Wattenberg (2020)[45]

7.2 Impact of the technology

There is an urgent need for a pharmacologic option to effectively suppress oxalate overproduction, the central driver of morbidity, in patients with PH1,[4] regardless of age or disease stage. Lumasiran is the first approved treatment for PH1 that has been shown to significantly reduce oxalate levels. Among patients with preserved renal function, lumasiran has demonstrated the ability to reduce oxalate to normal or near-normal levels in the majority of treated patients, regardless of age.[8-10,63,66,73,74] Lumasiran treatment also leads to meaningful reductions in oxalate in patients with PH1 and advanced renal disease, regardless of age and whether or not the patient is receiving dialysis.[11,64] Based on the known pathophysiological effects of elevated oxalate, natural history data on the association of urinary and plasma oxalate with ESKD risk, and demonstration of stabilised renal function in patients undergoing pre-emptive liver transplantation to normalise oxalate in PH1, the oxalate-lowering effects of lumasiran are fully expected to translate to real-world clinical benefit.[8-10,17,28,56,104,130,131] The introduction of lumasiran in the UK is expected to reduce the burden of PH1 on patients, caregivers, and society.

7.2.1 Impact of reduced endogenous oxalate production on disease

Natural history data support hepatic oxalate production as the primary driver and predictor of renal function decline in PH1.[4] Urinary and plasma oxalate are the best markers of hepatic oxalate production.[4,27,132]

Normalisation/near-normalisation of oxalate levels is the treatment goal as this reflects correction of the excess oxalate production that drives morbidity and mortality in PH1. However, since the risk of disease complications increases continuously as oxalate levels rise, any sustained lowering of hepatic oxalate production will be beneficial to PH1 patients.[56]

Oxalate

The primary endpoint analysis in the ILLUMINATE-A trial found that treatment with lumasiran resulted in a statistically significant percent reduction in urinary oxalate excretion (as measured by body surface area [BSA]-corrected 24-h urinary oxalate) from baseline to Month 6, compared to placebo (average of Months 3–6; least squares mean [LSM] difference: –53.5; p<0.001; LSM percent change from baseline of −65.4% for lumasiran and −11.8% for placebo). Subgroup analyses showed a consistent treatment effect of lumasiran on urinary oxalate excretion across all subgroups, including those defined by baseline urinary oxalate level, concomitant pyridoxine use, and renal function. A secondary endpoint analysis demonstrated a clinically meaningful and statistically significant absolute reduction in 24-h urinary oxalate with lumasiran compared with placebo from baseline to Month 6 (average of Months 3–6; LSM difference: −0.98 mmol/24 h/1.73 m^2; p<0.001; LSM absolute change from baseline of −1.24 and −0.27 mmol/24 h/1.73 m^2 in the lumasiran and placebo groups, respectively). In a secondary endpoint analysis at Month 6, 84% of patients treated with lumasiran had at least near-normal urinary oxalate levels (≤1.5 × upper limit of normal [ULN]) versus 0% of those receiving placebo (p<0.001), and 52% had normal urinary oxalate levels (≤ ULN) versus 0% of those receiving placebo (p=0.001).[8]

In ILLUMINATE-A, treatment with lumasiran resulted in a statistically significant percent reduction from baseline to Month 6 in plasma oxalate compared to placebo (average of Months 3–6; LSM difference: −39.5%; p<0.001; LSM percent change from baseline of −39.8% for lumasiran and −0.3% for placebo). Significant reductions in absolute plasma oxalate were also observed in the lumasiran group compared to placebo (average of Months 3–6; LSM difference: −8.7 µmol/L; p<0.001; LSM absolute change from baseline of −7.5 µmol/L for lumasiran and 1.3 µmol/L for placebo).[8]

Patients initially randomised to lumasiran in ILLUMINATE-A and who remained on lumasiran during the extended dosing period had a sustained reduction in 24-h urinary oxalate (corrected for BSA) that continued to be observed through Month 12. The mean reduction from baseline in this lumasiran/lumasiran group was 64.1% at Month 12[10] (vs. 65.4% observed to Month 6 in the primary analysis[8]). Patients initially randomised to placebo and who crossed over to lumasiran (i.e., placebo/lumasiran group) demonstrated a similar time course and magnitude of 24-h urinary oxalate reduction following 6 months of lumasiran treatment; the mean reduction in urinary oxalate from the first dose of lumasiran to Month 6 of lumasiran treatment was 57.3% ($p=1.7\times10^{-14}$).[10,63]

The primary endpoint analysis in the ILLUMINATE-B trial found that treatment with lumasiran resulted in a 72.0% reduction in urinary oxalate excretion as measured by spot urinary oxalate:creatinine ratio from baseline to Month 6 (average change of Months 3–6). The LSM (95% CI) percent change was −72.0% (−77.5%, −66.4%).[9]

Analyses of secondary endpoints revealed that the absolute reduction in oxalate:creatinine ratio from baseline to Month 6 (average of Months 3–6) with lumasiran was sustained, with an LSM (95% CI) absolute change of −0.49 (−0.52, −0.46) mmol/mmol on this measure. Treatment with lumasiran in ILLUMINATE-B led to a reduction in plasma oxalate from baseline to Month 6. The LSM (95% CI) percent change in plasma oxalate from baseline to Month 6 (average of Months 3–6) was −31.7% (−39.5%, −23.9%), while the absolute change was −5.2 (−6.2, −4.2) µmol/L. By Month 6, 6% and 50% of patients had achieved normalisation and near-normalisation of spot urinary oxalate excretion, respectively.[9]

Analysis of the primary endpoint in the ILLUMINATE-C study demonstrated that treatment with lumasiran resulted in a reduction of 33.3% in plasma oxalate from baseline to Month 6 for patients not yet on dialysis and a reduction of 42.4% in predialysis plasma oxalate from baseline to Month 6 for patients on dialysis.

At last reported follow-up, median duration of study drug exposure was 8.77 months (range, 5.6 to 13.9 months) in the overall ILLUMINATE-C study population.[19,133]

In the phase 2 OLE associated with the phase 1/2 study of lumasiran, continued dosing for a median of 15 months (range, 11 to 22 months) maintained reduction of urinary oxalate to normal or near-normal levels in 94% of patients treated with lumasiran.[66]

Renal stone events

The oxalate-lowering efficacy of lumasiran has been shown to translate to clinical benefit, including reduction of renal stone events, a key driver of morbidity in the early stages of PH1. Renal stone events occurred less frequently upon initiation of oxalate-lowering treatment with lumasiran.[8,10] The calculated incidence of renal stone events among patients in ILLUMINATE-A randomised to lumasiran decreased from a patient-reported rate of 3.19 per person-year over the 12 months prior to consent to an observed rate of 1.09 per person-year for the 6-month double-blind period, and to an observed rate of 0.85 per person-year for the first 6 months of the ensuing extension study. Renal stone event rates remained stable over the first 6 months of ILLUMINATE-A (prior to the extended dosing period) among patients randomised to placebo and then decreased in the placebo/lumasiran crossover group after 6 months of treatment with lumasiran,[8,10] which further supports the effect of lumasiran on lowering the incidence of renal stone events. In ILLUMINATE-B, renal stone event rates were relatively low (0.24 events per person-year) at baseline and remained unchanged during the 6-month primary analysis period.[9]

Nephrocalcinosis

The oxalate-lowering efficacy of lumasiran has been shown to translate to clinical benefit as evidenced by changes in nephrocalcinosis, an indicator of kidney damage and a risk factor for ESKD. Reversal of nephrocalcinosis was observed with lumasiran; this reversal is attributed to the oxalate-lowering efficacy of lumasiran,[8-10] as spontaneous improvements in nephrocalcinosis over short intervals are not expected in patients with PH1.[8,10] After 6 months of placebo treatment in ILLUMINATE-A, 0% of patients improved, 85% remained stable, and 8% worsened relative to baseline nephrocalcinosis grade (note that ultrasound images in the remaining proportion of patients were not adequate to grade nephrocalcinosis). After 6 months of lumasiran treatment in patients initially randomised to lumasiran, 13% of patients improved, 83% remained stable, and 0% worsened relative to baseline (data were unavailable in 4%). Continued treatment with lumasiran through 12 months resulted in an increase in the proportion of patients experiencing improvement, as nephrocalcinosis grade improved in 46% of patients, remained stable in 17%, and worsened in 13% relative to baseline (data were unavailable in 25%).[10]

Among the 18 patients included in the ILLUMINATE-B study, 14 had nephrocalcinosis at baseline; after 6 months of lumasiran treatment, no patient worsened, 10 remained stable, and 8 showed improvement in nephrocalcinosis, including 3 with improvement of nephrocalcinosis in both kidneys.[9,67]

7.2.2 Impact on patients, caregivers, and society

Lumasiran is an siRNA therapeutic with the ability to substantially lower endogenous oxalate levels to normal or near-normal in PH1 patients across all ages with preserved renal function. This indicates that patients with PH1 who are treated with lumasiran do not produce excess oxalate that drives disease morbidity and mortality. This represents a paradigm shift in the treatment of PH1, and is expected to bring about a life-changing impact for PH1 patients and their families and caregivers.

Patients initiating lumasiran in earlier stages of PH1

For patients initiating lumasiran in the earlier stages of disease, the oxalate-lowering effect of lumasiran[8-10] is expected to halt disease progression and prevent the onset of serious complications. Patients are expected to have less renal impairment and experience fewer consequences of PH1 progression. In essence, these patients are expected to lead relatively normal lives and not require dialysis or transplantation, in line with what was historically seen in PH1 patients who had the metabolic defect surgically corrected (i.e., isolated

liver transplantation, which is no longer recommended except in highly selected cases)[20] prior to the onset of advanced kidney damage.[130,131,134] Furthermore, pharmacologic prevention or reversal of kidney damage will free up dialysis capacity.

Patients initiating lumasiran in later stages of PH1

For patients in the later stages of disease, it is important to lower oxalate levels and achieve the best pretransplantation health state possible, to minimise morbidity and mortality risks associated with transplantation. For patients initiating lumasiran in the later stages of disease (i.e., in the presence of renal dysfunction/ESKD), the resulting reduction in oxalate is expected to reduce the need for dialysis, stabilise the disease, and prevent the incidence of new complications of systemic oxalosis or promote reversal of systemic oxalosis among affected individuals. These improvements are expected to enable more patients to reach transplantation and achieve better outcomes post transplantation. Effective oxalate-lowering treatment with lumasiran is a critical pretransplantation step, irrespective of organ availability, to position patients for better outcomes, fewer complications, and longer survival post transplantation once suitable donor organs are available. The [redacted][64] [redacted].

These anticipated effects of lumasiran treatment on post-transplant outcomes are based on the comprehensive analysis by Jamieson et al. (2005) of liver–kidney transplants for PH1 patients enrolled in a large European registry.[135] The clinical status of a patient with PH1 immediately prior to transplantation has a significant impact on their post-transplantation survival as illustrated by Jamieson et al. Patients with poor clinical status and advanced systemic oxalosis had a median survival of just 2 years and only a 45% probability of survival 5 years following transplantation. In contrast, patients with a fair clinical status had a 6-year median survival and 73% probability of survival 5 years following transplantation, while PH1 patients with good clinical status prior to transplantation (e.g., in whom dialysis resulted in the most effective removal of oxalate) had a 100% probability of survival 5 years following transplantation. These findings suggest that patients with higher oxalate levels have worse outcomes and patients with lower oxalate levels have better outcomes following transplantation. Moreover, the survival data reported by Jamieson et al. suggest that potential loss of life associated with high pretransplantation plasma oxalate is substantial, considering that patients in the analysis population had undergone transplantation for PH1 at a mean age of 16 years.

Crucially, a patient's clinical status prior to transplantation, and by extension their oxalate levels, determines their eligibility for transplantation.[136] Plasma oxalate is a key determinant of systemic oxalosis complications, since development of systemic oxalosis relates to whether plasma oxalate is above or below the saturation threshold.[34,137] Marangella et al. (1993)[138] found that calcium oxalate saturation was associated with plasma oxalate levels between 44 and 46 μmol/L, irrespective of a patient's kidney function or underlying disease. Based on these findings, the authors emphasised plasma oxalate of 50 μmol/L as a critical threshold to define the risk of systemic oxalosis and determine potential candidates for transplantation. This threshold has been used as a treatment target by Illies et al. (2006)[128] in their study on intensified dialysis in children with PH1 and more recently by Sas et al. (2021)[133] in their natural history study of patients with PH1 on long-term dialysis. Although a lower saturation threshold of 30 μmol/L in patients with PH1 has been suggested by Hoppe et al. (1999)[139] and Ogawa et al. (2006),[140] few studies in patients requiring dialysis for renal disease, even in the absence of PH1 (i.e., in the absence of elevated hepatic oxalate production), have been successful at achieving predialysis plasma oxalate levels below this threshold.[141,142] Most studies involving dialysis in non-PH1 patients with renal diseases were able to achieve predialysis plasma oxalate levels in the range of 35 to 55 μmol/L.[140,143-148] These findings, together with the finding from Illies et al. (2006)[128] that despite optimised dialysis regimens, plasma oxalate could not be lowered below the saturation threshold of 50 μmol/L in five of six PH1 patients, suggest that a plasma oxalate threshold closer to 50 μmol/L is a realistic target for patients with PH1.

In view of these considerations, lumasiran, with its ability to lower oxalate levels (Section 7.2.1),[8,63,66-68,79] is expected to stabilise a patient's condition, improve their pretransplantation clinical status and, thus, their suitability for transplantation.

8 Extent and nature of current treatment options

- Until now, there have been no approved pharmacologic treatments to effectively suppress oxalate overproduction, the central driver of morbidity, in patients with PH1.
- Established clinical management (i.e., oxalate-controlled diet, hyperhydration, citrate supplementation, pyridoxine) is ineffective at slowing disease progression, does not address the underlying metabolic defect in PH1, and in the case of pyridoxine is only potentially effective in a very small, genetically distinct subpopulation with functional AGT enzyme.
- Lumasiran is an siRNA therapeutic that significantly reduces endogenous oxalate levels, the underlying cause of PH1 manifestations, typically to normal or near-normal levels in PH1 patients across all ages with preserved renal function. Lumasiran treatment also leads to meaningful reductions in plasma oxalate in patients of any age with PH1 and advanced renal disease, including patients on dialysis.
- For patients initiating lumasiran in the earlier stages of disease, the reduction in oxalate is expected to halt disease progression, prevent the onset of serious complications, and preserve renal function. By correcting the key driver of disease progression, lumasiran presents an opportunity for patients to live normal lives and avoid the subsequent consequences of disease progression (i.e., renal impairment, systemic oxalosis, kidney failure).
- For patients initiating lumasiran in the later stages of disease, it is expected to stabilise the disease, potentially prevent the incidence of new complications of systemic oxalosis or promote reversal of systemic oxalosis among affected individuals, reduce dialysis frequency and/or intensity, and enable more patients to reach transplantation and achieve better outcomes post transplantation.
- Lumasiran prescribing decisions and treatment initiation will be limited to consultants at four highly specialist treatment centres, with ongoing monitoring and administration performed locally or regionally.

8.1 Guidelines for PH1

NICE, NHS England, and other national UK guidance documents on the management of PH1 were lacking at the time of this submission. European PH1 treatment guidelines have been published on behalf of the European Hyperoxaluria Consortium (Cochat et al. 2012)[20] and by Hoppe et al. (2012).[62] These guidelines highlight the early initiation of conservative treatment, and that combined/sequential liver–kidney transplantation offers the best outcomes achieved to date in patients with PH1 and CKD stage 4 or ESKD. However, existing treatment guidelines were developed before the advent of disease-modifying pharmacologic treatment with lumasiran, and its related clinical trials, and are therefore outdated.

8.2 Current clinical pathway of care

Until now, there have been no approved treatments for PH1.[2,73,74,94] Existing treatment guidelines, developed before the advent of lumasiran, emphasise the importance of treatment of manifestations, prevention of primary manifestations, surveillance, and avoidance of exacerbating agents.[20,34,62] However, guidelines are anticipated to evolve considerably in the coming years with the introduction of new disease-modifying treatment options.

8.2.1 Prevention and treatment of PH1 manifestations with established clinical management

PH1 disease manifestations are due to hepatic oxalate overproduction, leading to the deposition of insoluble calcium oxalate crystals in kidneys and other organs. Current treatments are used to target one or more

manifestations of PH1: reduce calcium oxalate supersaturation in the urine or plasma to minimise oxalate crystallisation; treat calcium oxalate renal stones; promote catalytic activity of the mislocalised AGT enzyme; remove oxalate from plasma via dialysis; normalise hepatic oxalate production; and/or restore lost renal function via organ transplantation. Each category of treatment options is limited in some way. None of these approaches, with the exception of liver–kidney transplantation, is successful at removing the source of the pathogenic metabolite (oxalate) and preventing/correcting ESKD,[20,34,62] which is an enormous burden for patients, their families, and society.[51-53]

Supportive care measurements and pyridoxine

An oxalate-controlled diet, hyperhydration, and citrate supplementation are supportive care measures intended to prevent oxalate crystallisation in the kidneys of patients with preserved renal function. However, the evidence available suggests these measures have limited efficacy and are ineffective at slowing disease progression, since none of these approaches address the underlying defect in PH1.[4,32,34,48,56]

Pyridoxine, another established clinical management (ECM) option for some PH1 patients with preserved renal function, has the potential to normalise oxalate levels only in a very small, genetically distinct subpopulation (G170R homozygotes) that accounts for ~5% to 10% of the overall PH1 population.[19,32,57] The evidence base for pyridoxine is poor, despite there being considerable discussion on this intervention in the literature.[4,16,32,95]

Pyridoxine is a cofactor of AGT, and experiments in cell lines have demonstrated that pyridoxine promotes net expression, catalytic activity, and peroxisomal import of the AGT enzyme with the homozygous G170R genotype.[48,149] In a prospective trial, 50% of 12 PH1 patients receiving pyridoxine experienced a pyridoxine response, defined as at least a 30% reduction in urinary oxalate from baseline to Week 24. None of the patients, including the G170R homozygotes, experienced complete normalisation of oxalate levels. Only 38% (3 of 8) outside of the G170R homozygote subgroup achieved a pyridoxine response of at least a 30% reduction in urinary oxalate from baseline.[95]

Dialysis

In more advanced stages of renal decline, dialysis may be initiated to slow the build-up of systemic oxalate. It may also provide some of the key function normally carried out by the kidney in patients with ESKD.[20,150,151] However, the rate of oxalate production in PH1 patients greatly surpasses the ability to remove it since oxalate is sequestered in organs and re-enters the plasma following dialysis. Since conventional dialysis is typically insufficient for lowering oxalate levels in PH1, patients with PH1 require more frequent haemodialysis and peritoneal dialysis sessions (six to seven times per week, as contrasted with three-times-a-week conventional dialysis schedules), and even this intensive schedule is inadequate to consistently lower oxalate.[4,20,26,31,34,48,127,128]

Transplantation

In the absence of effective treatment, excessive production of endogenous oxalate will continue for as long as the native liver is present in PH1 patients. For patients with PH1 who have progressed to later-stage kidney disease, European PH1 clinical guidelines recommend combined/sequential liver–kidney transplant to resolve the underlying metabolic defect and restore renal function.[20] A dual transplant is required because transplantation of each organ serves different therapeutic goals. Transplantation of the liver resolves the endogenous overproduction of oxalate in the liver, which is the central driver of the pathology. Transplantation of the kidney is required to restore the renal function previously lost to oxalate nephropathy and thus eliminate the need for continued dialysis.[4,20] However, this intervention is associated with morbidity and mortality.[50-53,59-61] As described in Section 7.2.2, a key consideration for optimising post-transplant outcomes is the patient's clinical status prior to transplantation, which is driven by their oxalate levels. Historically, dialysis has been most often used to lower oxalate levels in preparation for combined/sequential liver–kidney transplantation, but as noted above is generally inadequate to consistently lower oxalate.

There is no literature beyond individual case reports and case series reporting isolated liver transplantation (i.e., liver transplant without a kidney transplant) as part of ECM for PH1 or regarding appropriate circumstances for use of this approach. Although isolated liver transplantation is a potentially useful procedure that can correct the underlying metabolic defect, it cannot restore lost renal function to the patient and therefore is generally considered to be a standard option for patients in later stages of renal impairment due to PH1.[34]

Other surgical procedures

Aside from the chronic, progressive manifestations of PH1, renal stones may occur frequently throughout the course of PH1,[34] with painful and potentially debilitating effects, and may require surgical remediation or other medical interventions. Shockwave lithotripsy (SWL) is a viable first option but has a low success rate, and subsequent endoscopic surgery is often needed. Calcium oxalate stones are among the hardest renal stones and thus more resistant to SWL.[152] Lithotripsy in PH1 also carries the risk that shock waves are inadvertently applied to nephrocalcinosis deposits instead of renal stones, which may alter renal tissue.[153] In cases where surgery is required, ureteroscopy is an effective method of stone removal with lower complication rates. Ureteroscopic procedures may be supplanting SWL as first-line therapy at many centres, and percutaneous nephrolithotomy should be considered as first-line therapy for larger, bulky stone burdens (>15 mm).[34]

8.2.2 Surveillance

Regular assessment of oxalate levels and serum creatinine (as an indicator of renal function) is recommended as part of monitoring for patients with PH1.[20] Renal ultrasound examination or other kidney imaging, urinalysis, and periodic fundoscopic eye examinations are also recommended to track deposition of oxalate and other manifestations of PH1 disease progression. In patients with severe kidney damage, several additional tests are recommended to ascertain systemic disease manifestations: regular x-ray examination of the long bones, electrocardiogram for detection of conduction abnormalities, echocardiogram for detection of oxalate cardiomyopathy, haemoglobin levels, thyroid function testing, and frequent clinical evaluation for additional complications of systemic oxalosis.[20,34,62]

8.2.3 Avoidance of exacerbating agents

Dehydration can lead to irreversible kidney failure and should be strictly avoided. Intake of vitamin C exceeding the recommended daily allowance, loop diuretics, high doses of nonsteroidal anti-inflammatory medications, or other medications that can compromise renal function should also be avoided. PH1 patients should also avoid consumption of large quantities of foods and beverages with high oxalate content (e.g., beetroot, chocolate, rhubarb, spinach, starfruit, tea).[20,34,62,154]

8.2.4 Evaluation of relatives at risk

Early diagnosis of at-risk relatives enables early institution of treatment and preventive measures.[34] Based on consultation with PH1 experts in the UK, prenatal screening is not routinely performed except in families with a child who has been diagnosed with PH1 (Section 6.1.3).

8.2.5 Issues with current clinical practice

As described in Section 8.2.1, ECM measures (i.e., oxalate-controlled diet, hyperhydration, citrate supplementation, and pyridoxine) used in patients with PH1 with preserved renal function do not address the underlying cause of disease, have not shown evidence of the ability to halt disease progression, and/or have limited efficacy in a narrow subpopulation (pyridoxine).[4,32,34,48,56] For patients in more advanced stages of renal decline, even intensive haemodialysis and peritoneal dialysis schedules are inadequate to consistently lower oxalate.[4,20,26,31,34,48,127,128] Combined/sequential liver–kidney transplantation is the only treatment strategy available to resolve the underlying metabolic defect and restore lost renal function among patients with advanced renal disease, although the procedure is associated with morbidity and mortality.[20,50-53,59-61] A key consideration for optimising post-transplant outcomes is the patient's clinical status prior to transplantation, which is driven by their oxalate levels (Section 7.2.2).

Lumasiran is an siRNA therapeutic that treats the underlying cause of PH1 manifestations by substantially reducing endogenous oxalate levels, typically to normal or near-normal levels in PH1 patients across all ages with relatively preserved renal function.[8-10,66] Lumasiran treatment also leads to meaningful reductions in oxalate in patients with PH1 and advanced renal disease, regardless of age and whether or not the patient is receiving dialysis.[11,64] The oxalate-lowering potential of lumasiran in patients with early- and late-stage PH1 has been described in detail in Sections 7.2.1 and 7.2.2.

Prior to lumasiran, there was no treatment option to stop PH1 progression in patients with early-stage disease, irrespective of *AGXT* variant status. For patients with PH1 who progress to advanced stages of renal disease, optimised dialysis regimens alone are unlikely to lower plasma oxalate below the critical threshold of 50 µmol/L that defines the risk of systemic oxalosis[138] and has been used as a treatment target in PH1[128,133] (Section 7.2.2). Therefore, patients with PH1 and advanced renal disease require effective medical treatment to bridge them to transplantation. Effective oxalate-lowering treatment is necessary to help keep patients in a suitable condition to remain clinically eligible for transplantation while they wait for organs to become available. It is also a critical pretransplantation step, irrespective of organ availability, to position patients for better outcomes, fewer complications, and longer survival post transplantation once suitable donor organs are available.

8.3 Proposed pathway of care

Due to the establishment of the RDCN, the majority of the most severely affected PH1 patients are currently managed by or in consultation with the leading paediatric and adult nephrology centres. Lumasiran prescribing decisions will be limited to consultants at the four expert centres within the RDCN, namely the Birmingham Women's and Children's NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Great Ormond Street Hospital, and the Royal Free London NHS Foundation Trust. Administration of at least the first four injections will be performed onsite at one of these four centres. Ongoing monitoring and administration will be performed locally or regionally. Homecare may be appropriate; however, with the infrequent dosing schedule and periodic monitoring required, homecare is not a necessity. As described in Section 5.2, it is anticipated that the establishment of the RDCN will eventually lead to the formation of a Highly Specialised Service for PH1.[65]

8.4 Innovation of the technology

Based on ground-breaking RNAi technology, lumasiran is distinct from all previous treatments for PH1, and is unique in its ability to reduce the level of endogenous oxalate production and address issues with current clinical practice (described in Section 8.2.1 and Section 8.2.5), irrespective of the underlying mutation leading to loss of normal AGT enzyme activity.[7]

In July 2020, the MHRA awarded lumasiran a PIM designation. According to the terms of the programme, the PIM designation is only granted to medicinal products treating life-threatening or seriously debilitating conditions with a high unmet medical need, those offering a major advantage over current treatment options, and where the benefits outweigh potential adverse events (AEs).[3] Thus, lumasiran has been recognised by the UK regulatory authority to be innovative in its potential to address the high unmet medical need for patients with PH1.

Lumasiran, the first approved treatment for PH1, significantly reduces oxalate levels, typically to normal or near-normal levels, in patients of any age with relatively preserved renal function. Consistent with its oxalate-lowering efficacy, lumasiran has shown evidence of downstream clinical benefits, including reduction of renal stone events and reversal of nephrocalcinosis.[8-10,67] With continued follow-up, demonstration of amelioration of longer-term clinical manifestations of PH1 is anticipated.

Lumasiran treatment also leads to meaningful reductions in plasma oxalate in patients of any age with PH1 and advanced renal disease, including patients on dialysis.[11,64]

Until now, there have been no approved treatments for PH1.[2,73,74,94] Patients with PH1 in the UK were condemned to a bleak prognosis given that most patients progressed inexorably towards ESKD and systemic oxalosis unless transplantation could be performed in a timely manner.[20,62] Lumasiran represents a paradigm shift in the management of PH1 by offering a pharmacologic option that can normalise or near-normalise oxalate overproduction, the central driver of morbidity in patients with PH1. Lumasiran presents an opportunity for patients to live normal lives. For patients initiating treatment in earlier stages of disease, lumasiran is expected to halt and thus avoid the subsequent consequences of disease progression (i.e., renal impairment, systemic oxalosis, kidney failure). For patients initiating treatment in later stages of disease, lumasiran is expected to reduce the need for dialysis, stabilise the disease, prevent the incidence of new systemic oxalosis manifestations or promote reversal of systemic oxalosis among affected individuals, enable more patients to reach transplantation, increase eligibility for transplantation, and achieve better outcomes post transplantation.

The potential for lumasiran to significantly and substantially improve patient outcomes is supported by findings described in Section C – Impact of the new technology. Based on the ILLUMINATE clinical trial programme, lumasiran is the only treatment that has demonstrated efficacy in treating PH1 in patients of all ages and all levels of renal impairment. Lumasiran is used in addition to ECM, which may include hyperhydration, crystallisation inhibitors, and pyridoxine.

8.5 Changes to current services

Due to the establishment of the RDCN, the introduction of lumasiran treatment will not require further significant changes to the way services are organised or delivered. A description of the clinical pathway model by which patients will receive lumasiran is provided in Section 8.3.

8.6 Additional administration requirements

No additional administration requirements are needed.

8.7 Additional facilities, technologies or infrastructure

No additional facilities, technology, or infrastructure are required.

8.8 Tests, investigations, interventions, facilities or technologies no longer needed

Although normalisation or near-normalisation of oxalate levels is the treatment goal, any sustained lowering of hepatic oxalate production will be beneficial to PH1 patients.[155] Lumasiran treatment, if started early in the disease course, is anticipated to preserve renal function, prevent the onset of serious complications (i.e., renal stone events, nephrocalcinosis, systemic oxalosis, and ESKD), and reduce the need for transplantation. For patients starting lumasiran treatment in the later stages of the disease, the reduction in oxalate is expected to reduce the need for dialysis, stabilise the disease, prevent the incidence of new complications of systemic oxalosis or promote reversal of systemic oxalosis among affected individuals, enable more patients to reach transplantation, and improve post-transplantation outcomes.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

- Studies across a range of ages and levels of disease severity have shown that lumasiran is efficacious in lowering oxalate production.
- In ILLUMINATE-A, treatment with lumasiran resulted in a statistically significant percent reduction in 24-h urinary oxalate (corrected for BSA) from baseline to Month 6 versus placebo (average of Months 3–6; LSM difference: −53.5%; $p=1.685\times10^{-14}$; LSM percent change of −65.4% for lumasiran and −11.8% for placebo [primary endpoint]).
- In ILLUMINATE-B, treatment with lumasiran resulted in a reduction in urinary oxalate excretion, as measured by spot urinary oxalate:creatinine ratio, from baseline to Month 6 (average change of Months 3–6: LSM [95% CI] percent change of −72.0% [−77.5%, −66.4%]) (primary endpoint).
- In ILLUMINATE-C, treatment with lumasiran resulted in a reduction of 33.3% in plasma oxalate from baseline to Month 6 for patients not yet on dialysis and a significant reduction of 42.4% in predialysis plasma oxalate from baseline to Month 6 for patients on dialysis.
- All sensitivity analyses and subgroup analyses in the respective studies demonstrated that the oxalate-lowering efficacy of lumasiran is robust with respect to patient characteristics and statistical analysis methods.
- Reduction of renal stone event incidence and clinically meaningful improvements in nephrocalcinosis were evident following lumasiran treatment, based on exploratory data.
- Lumasiran was shown to have a favourable safety profile in the three phase 3 ILLUMINATE trials, which has been confirmed with long-term data from the phase 2 OLE.
- The ILLUMINATE trial results are relevant to the UK patient population: almost half the study populations are from Europe and the Middle East [redacted] and, by permitting patients to continue their background treatment (including pyridoxine), the study populations reflect well the reality of patients with PH1 in the UK.

9.1 Identification of studies

9.1.1 Published studies

A comprehensive systematic literature review (SLR) was conducted to identify clinical efficacy and safety data for lumasiran (ALN-GO1) and established clinical management (hydration, vitamin B6 [pyridoxine], calcium oxalate crystallisation inhibitors [citrate, pyrophosphate, magnesium], haemodialysis, and combined/sequential liver–kidney transplantation or isolated kidney/liver transplant), and to identify any relevant cost, healthcare resource use, or utilities data in PH1. The SLR was conducted in accordance with the requirements of NICE[156] and the Centre for Reviews and Dissemination (CRD)[157] guidance. The detailed search strategy used is listed in Appendix 1.

9.1.2 Unpublished studies

A grey literature search was conducted, which included searches of ClinicalTrials.gov and the EU Clinical Trials Register (CTR), as well as select regulatory and health technology assessment (HTA) websites—NICE, the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), the US FDA, and the EMA.

Conference abstracts from proceedings indexed in Embase or Conference Proceedings Citation Index-Science (CPCI-S) were identified in the database search. To supplement this search, handsearching of conference abstracts from the past 4 years (2018–2021) from the following proceedings was conducted:[157]

- American Society of Nephrology (ASN) Annual Meeting
- European Society for Paediatric Nephrology (ESPN) Annual Meeting
- International Society of Nephrology (ISN) World Congress of Nephrology (WCN)
- International Pediatric Nephrology Association (IPNA) Congress
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Presentations Database

A manual search of reference lists of systematic reviews was undertaken, to identify any relevant primary publications.

9.2 Study selection

9.2.1 Published studies

The SLR selection criteria for published studies are summarised in Table C1.

Table C1. Selection criteria used for published studies

Inclusion criteria	
Population	Adult and paediatric patients (any age) with PH1
Interventions	Clinical studies: • Lumasiran (ALN-GO1) • ECM (hyperhydration, vitamin B6 [pyridoxine], CaOx crystallisation inhibitors [citrate, pyrophosphate, magnesium], haemodialysis, and combined/sequential liver–kidney transplantation or isolated kidney/liver transplantation)* Economic studies: • Studies reporting HCRU and costs in patients with PH1 regardless of intervention • HCRU and cost data on the use of kidney stone management procedures, including shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy/ nephrolithotripsy, and open surgery • Cost-effectiveness data (e.g., ICERs, QALYs) specific to the clinical interventions noted above HRQoL studies: • Studies reporting any outcome of interest in PH1
Outcomes	**Effectiveness and safety** All effectiveness and efficacy outcomes, including: • Change in 24-h urinary oxalate excretion (percent and absolute) • Change in 24-h urinary oxalate:creatinine ratio • Change in eGFR • Percentage of patients with 24-h urinary oxalate level ≤1.5×ULN • Percentage of patients with 24-h urinary oxalate level ≤ULN • Percentage of time that 24-h urinary oxalate is ≤1.5×ULN • Percentage of time that spot urinary oxalate:creatinine ratio is ≤1.5×ULN • Change in plasma oxalate (percent and absolute) • Change in predialysis plasma oxalate (percent) • Change in plasma oxalate AUC between dialysis sessions (percent) • Change in nephrocalcinosis • Change in frequency of dialysis • Change in mode of dialysis • Change in frequency of renal stone events • Change in measures of systemic oxalosis • Time to death/graft failure, whichever occurs first • Percentage of patients with graft failure, re-transplant, or need for maintenance dialysis following graft failure

Inclusion criteria	
	• 6-month and/or 1-year acute graft rejection • Incidence of graft rejection • Reduced graft function over time (eGFR<60 mL/min/1.73 m^2) • Primary graft non-function AEs, including: • Incidence of any AE and proportion of patients experiencing any AEs • Incidence of SAEs and proportion of patients experiencing SAEs • Incidence of TEAEs and proportion of patients experiencing TEAEs • Proportion of patients discontinuing due to AEs **Cost effectiveness** ICERs, including: • Costs per QALY, LYG, and DALY HCRU and costs, including: • Resource use and monitoring frequency • Direct costs (related to drugs/treatments, AEs, and health states) • Direct medical and pharmacy healthcare costs • Indirect costs for patient and caregiver (i.e., annual loss of income [employment rate], presenteeism/absenteeism, withdrawal from labour force, and work productivity) **HRQoL** Utility values, including: • Directly elicited values (time trade-off or standard gamble), generic preference-based utilities (e.g., EQ-5D), and non–preference-based utilities (e.g., SF-36) for relevant health states • Measures mapped to preference-based utility • Utilities and disutilities for AEs
Study design	Effectiveness and safety: • RCTs (phase 1–4) and open-label extensions • Single-arm trials • Observational (retrospective and prospective) studies (e.g., chart reviews, registries, surveys) • Pharmacodynamic and pharmacokinetic studies • Dose-finding/escalation studies Economic: • CEA, CUA, CBA, CMA, and cost-consequence analyses • Any study design for HCRU and cost HRQoL: • Any study design
Language restrictions	English language
Search dates	Original searches were conducted in June 2020, and updates were performed in April and August 2021

Exclusion criteria	
Population	Animal studies, in vitro studies, and studies in healthy populations
Interventions	Clinical studies: • Investigational therapies, including Oxabact® (Oxalobacter formigenes), nedosiran (DCR-PHXC), betaine, DCR-PH1, Diacomit® (stiripentol), and ALLN-177 Economic studies: NA HRQoL studies: NA
Outcomes	NA
Study design	Reviews, letters, comments, editorials, case reports, adherence studies, prognostic studies, epidemiological studies, studies of treatment prescribing patterns
Language restrictions	Records in languages other than English†
Search dates	Original searches were conducted in June 2020, and updates were performed in April and August 2021

*Publications reporting ECM but not specifying the treatment were included.
†Records in languages other than English were recorded for future reference.
AE=adverse event; AUC=area under the curve; CBA=cost-benefit analysis; CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis; DALY=disability-adjusted life-year; ECM=established clinical management; eGFR=estimated glomerular filtration rate; HCRU=healthcare resource utilisation; ICER=incremental cost-effectiveness ratio; LYG=life-years gained; NA=not applicable; PH1=primary hyperoxaluria type 1; PICOS=Population, Intervention, Comparison, Outcomes, and Study; QALY=quality-adjusted life-year; RCT=randomised controlled trial; SAE=serious adverse event; SF-36=36-Item Short Form Survey; TEAE=treatment-emergent adverse event; ULN=upper limit of normal

9.2.2 PRISMA diagrams

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for the SLR is shown in Figure C1.

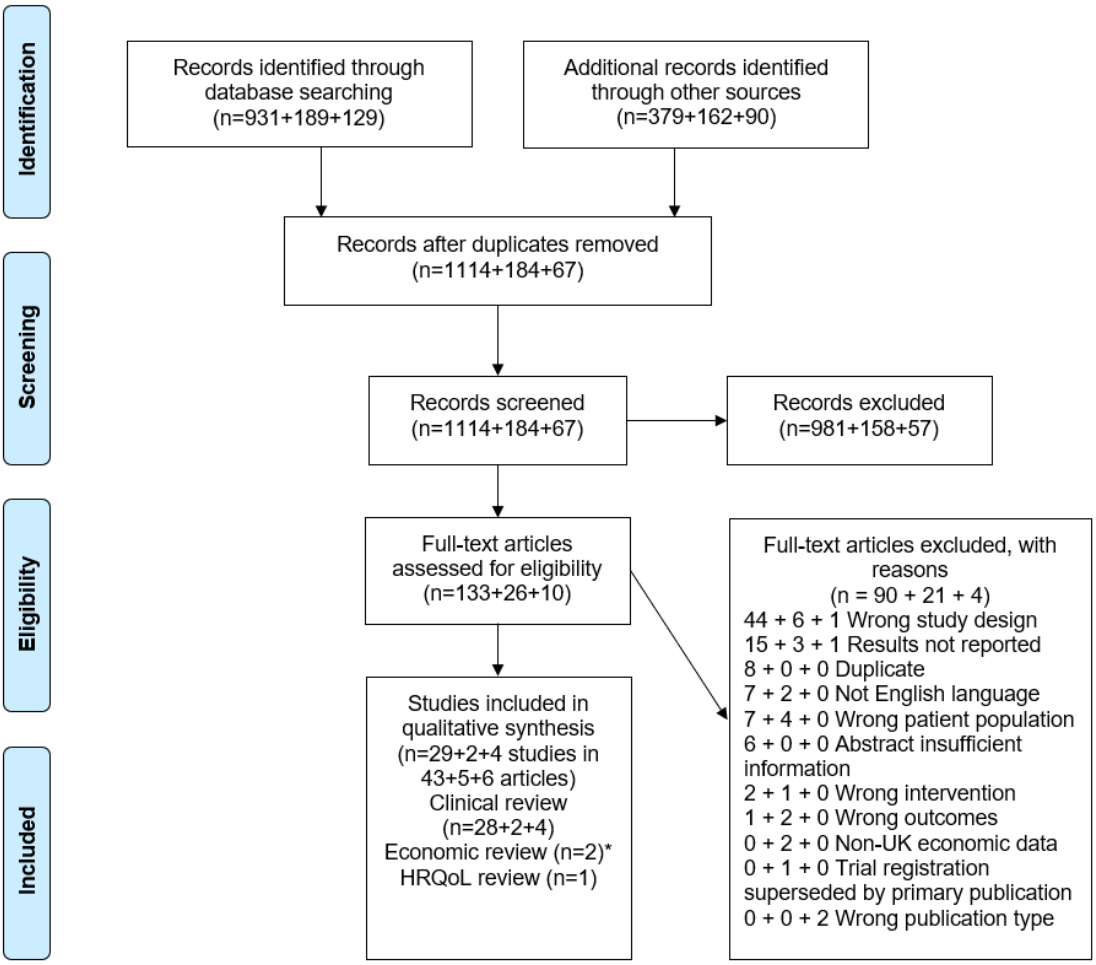

Figure C1. PRISMA flow diagram for clinical and non-clinical evidence in PH1
The original SLR searches were executed in June 2020, with updates in April and August 2021. Results are provided here for each execution of the searches (data are separated by "+" signs).
*Also included in clinical review.
HRQoL=health-related quality of life; SLR=systematic literature review; UK=United Kingdom

9.2.3 Unpublished studies

The search selection inclusion and exclusion criteria for unpublished studies were the same as the criteria for published studies (Table C1). The grey literature (unpublished) studies are included in the PRISMA diagram for the SLR (Figure C1).

9.3 Complete list of relevant studies

9.3.1 SLR results

Table C2 lists the 34 included studies of clinical evidence from the SLR. In cases where there were multiple references for a study, the most complete and/or the most recent publication of that study was selected as the primary study reference in this submission.

Lumasiran was evaluated in a phase 1/2, randomised, single-blind, placebo-controlled trial in 20 patients with PH1 (Part B),[91] an ongoing phase 2 OLE,[66] an ongoing phase 3 trial with a randomised placebo-controlled RCT period and associated extension phase (ILLUMINATE-A),[8] and an ongoing phase 3 single-arm interventional open-label study (ILLUMINATE-B[67]). Note that the phase 3 studies have reported results from their respective primary analysis periods.[8,67] At the time of writing the SLR report, the ILLUMINATE-C clinical study had yet to report data and had not been captured in the search results.

Conservative management, which involved the use of supportive measures such as increased fluid intake, crystallisation inhibitor use, and pyridoxine supplementation, was evaluated in eight observational studies, comprising two prospective[95,158] and six retrospective studies.[16,159-163] Renal replacement therapy, which involved the use of haemodialysis and/or peritoneal dialysis, was evaluated in two retrospective observational studies.[133,164] Transplantation was evaluated in 20 observational studies, of which 19 were retrospective[32,49,50,52,59,61,105,130,165-175] in design and one was a survey[176]. No RCTs were identified for studies on conservative management, renal replacement therapy, or transplantation.

There were no unpublished studies identified as being relevant by the SLR. Excluded studies are listed in Appendix 1.

Table C2. List of included published studies from the SLR

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Lumasiran trials				
Frishberg et al. (2021)[91]	ALN-GO1-001 Phase 1/2 NCT02706886	20 adults and children aged 6–64 years with diagnosis of PH1 and eGFR >45 mL/min/1.73m^2 (Part B) Randomised 3:1 to one of three doses of lumasiran, or placebo: Lumasiran, n=9 1 mg/kg SC QM (n=3) 3 mg/kg SC QM (n=3) 3 mg/kg SC Q3M (n=3) Placebo, n=3 (there was one patient for each lumasiran arm) Open-label expansion cohorts: Lumasiran 1 mg/kg SC QM (n=4) Lumasiran 3 mg/kg SC Q (n=4)	Lumasiran	Placebo
Frishberg et al. (2020)[66]	ALN-GO1-002 Phase 2 OLE NCT03350451	20 adults and children aged 6–64 years with diagnosis of PH1 who participated in the ALN-GO1-001 phase 2 multi-dose study of lumasiran (NCT02706886): 1 mg/kg SC QM (n=3) 3 mg/kg SC QM (n=7) 3 mg/kg SC Q3M (n=10)	Lumasiran	None
Garrelfs et al. 2021[8]	ALN-GO1-003 Phase 3 ILLUMINATE-A NCT03681184	39 adults and children aged ≥6 years with diagnosis of PH1 and relatively preserved renal function Randomised 2:1 in the 6-month double-blind period to: Lumasiran 3 mg/kg SC QM×3, then Q3M starting 1 month thereafter (i.e., at study month 3), n=26 Placebo SC QM×3, then Q3M, starting 1 month thereafter (i.e., at study month 3), n=13 Extension period (up to 54 months): Patients originally randomised to lumasiran received lumasiran 3 mg/kg SC Q3M Patients originally randomised to placebo received lumasiran 3 mg/kg SC QM×3, then Q3M starting 1 month thereafter	Lumasiran	Placebo

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Michael et al. 2020[67]	ALN-GO1-004 ILLUMINATE-B Phase 3 NCT03905694	18 children aged <6 years with diagnosis of PH1 and relatively preserved renal function Lumasiran loading and maintenance dose based on patient weight category (up to 60 months): <10 kg: 6 mg/kg QM×3, then 3 mg/kg QM ≥10 mg to <20 kg: 6 mg/kg QM×3, then 6 mg/kg Q3M starting 1 month thereafter (i.e., at study month 3) ≥20 kg: 3 mg/kg QM×3, then 3 mg/kg Q3M starting 1 month thereafter (i.e., at study month 3)	Lumasiran	None
Conservative management trials (all observational)				
Fargue et al. (2009)[16]	NA	• 27 patients with PH1, including four G170R heterozygotes • Age at diagnosis, median (range): 4.1 (0.1–12.3) years • Proportion with ESKD not reported	Conservative management	None
Gargah et al. (2012)[159]	NA	• 44 patients with PH1 • Age at diagnosis, median (range): 5.75 years (3 months to 14 years) • 12 (27%) with ESKD	Conservative management	None
Hoppe et al. (2005)[177]	NA	• 57 patients with PH, of which 42 had PH1 • Age at diagnosis not reported • Proportion with ESKD not reported	Conservative management	None
Hoyer-Kuhn et al. (2014)[160]	NA	• 12 patients with PH1, including three G170R homozygotes • Age at diagnosis not reported • Proportion with ESKD not reported	Conservative management	None
Milliner et al. (1998)[161]	NA	• 42 patients with PH, of which 22 had PH1 • Age at diagnosis, mean (range): 14.7 (<1–50) years • 10 (23.8%) with ESKD	Conservative management	None
Milliner et al. (1994)[160]	NA	• 25 patients with PH, of which 9 had PH1 • Age at diagnosis, median (range): 6 (0.4–29) years for PH; 13 years for PH1 • Proportion with ESKD not reported	Conservative management	None
Sanjad et al. (1999)[162]	NA	• 16 patients with PH1 • Age at diagnosis, median (range): 5 years (5 months to 14 years) • 4 (25%) with ESKD	Conservative management	None
van Woerden et al. (2003)[163]	NA	• 57 patients with PH1 • Age at diagnosis, median (range): 7.3 (0.1–57.3) years • 9 (33.3%) with ESKD	Conservative management	None
Renal replacement therapy studies (all observational)				
Fadel et al. (2021)[164]	NA	• 47 patients comprising: – 22 patients with PH1; n=10 PH1 patients with infantile onset (<1 year), n=9 PH1 patients with juvenile onset (1–10 years), n=3 PH1 patients with late onset (11–15 years) – 25 age/sex-matched controls • Age at development of ESKD in PH1 population, mean (SD): 4.83 (4.01) years • 47 (100%) with ESKD	Renal replacement therapy	None

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Sas et al. (2021)[133]	NA	• 17 patients with PH1, including one G170R homozygote • Age at diagnosis, median (range): 18.9 (0.3–74.0) years • 2 (11.8%) presented with ESKD (unclear what proportion of the study population had ESKD during the study period)	Renal replacement therapy	None
Transplantation studies (all observational)				
Bergstralh et al. (2010)[50]	NA	• 58 patients with PH, of which 56 had PH1 and underwent kidney or combined liver–kidney transplant • Age at diagnosis, median (range): 18 (0–74) years • Proportion with ESKD not reported	Transplantation	None
Calinescu et al. (2014)[59]	NA	• 56 patients with PH who underwent combined liver–kidney transplant • Baseline patient characteristics were not reported	Transplantation	None
Cibrik et al. (2002)[165]	NA	• 190 patients with PH, of which 134 received a kidney transplant and 56 received a liver–kidney transplant • Baseline patient characteristics were not reported	Transplantation	None
Cochat et al. (1999)[176]	NA	• 78 patients with PH1 who underwent kidney or combined liver–kidney transplant • Age at diagnosis not reported • 39 (50%) with ESKD	Transplantation	None
Compagnon et al. (2014)[52]	NA	• 54 patients with PH1, of which 21 received a kidney transplant and 33 received a combined liver–kidney transplant • Age at diagnosis not reported • 54 (100%) with ESKD	Transplantation	None
Cornell et al. (2021)[166]	NA	• 99 transplants, of which: – 37 transplants occurred in 36 PH patients; 35 transplants were in 34 PH1 patients (19 [54%] had an *AGXT G170R* mutation) – 62 transplants occurred in 62 non-PH patients • Transplants in PH patients were kidney transplant (n=8) and combined liver–kidney transplant (n=29) • Age at ESKD in PH patients, median (IQR): 30.8 (21.9–51.5) years • Unclear what proportion of PH patients had ESKD	Transplantation	None
Cussa et al. (2019)[167]	NA	• 13 patients with PH1 who underwent a combined liver–kidney transplant • Age at diagnosis and proportion with ESKD were not reported	Transplantation	None
Dehghani et al. (2020)[168]	NA	• 18 patients with PH who underwent a liver or combined liver–kidney transplant • Age at diagnosis not reported • 13 (72%) with ESKD	Transplantation	None
Guillaume et al. (2021)[169]	NA	• 7 patients with PH1, of which 6 patients had a liver–kidney transplant (combined in 1 patient and sequential in 5 patients) and 1 patient had a liver transplant alone • Age at liver transplantation, median (range): 25 (10–41) months • Age at kidney transplantation, median (range): 32.5 (26–75) months • 7 (100%) with ESKD	Transplantation	None

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Harambat et al. (2010)[32]	NA	• 155 patients with PH1, of which 36/140 patients had an *AGXT G170R* mutation, including 12 homozygotes; 72 patients received a transplant • Age at clinical diagnosis in the overall PH1 cohort, median (range): 7.7 (0.3–67.0) years • 66 (43%) with ESKD	Transplantation	None
Harambat et al. (2012)[49]	NA	• 100 patients with PH1 who received a kidney transplant • Age at diagnosis not reported • 100 (100%) with ESKD	Transplantation	None
Horoub et al. (2021)[170]	NA	• 24 patients with PH1, of which 8 underwent combined liver–kidney transplantation, 13 underwent sequential liver–kidney transplantation, and 3 underwent a pre-emptive liver transplantation • Age at diagnosis and proportion with ESKD were not reported	Transplantation	None
Jamieson et al. (1995)[61]	NA	• 61 patients with PH1 who underwent a combined liver–kidney transplant • Age at diagnosis not reported • 61 (100%) with ESKD	Transplantation	None
Khorsandi et al. (2016)[171]	NA	• 8 patients with PH1, of which 5 patients underwent sequential liver–kidney transplantation and 3 patients underwent pre-emptive liver transplantation • Age at clinical onset, median (range): 0.36 (0.17–1.25) years in sequential liver–kidney group and 5.18 (0.75–6.16) years in pre-emptive liver group • 5 (100%) of patients who underwent sequential liver–kidney transplantation had ESKD; none of the patients who underwent pre-emptive liver transplantation had ESKD	Transplantation	None
Lieske et al. (2005)[105]	NA	• 95 patients with PH, of which 75 (79%) had PH1; 28 patients underwent transplantation (type of transplant unclear) • Age at diagnosis in the PH cohort, median (mean [SD]): 10 (15.0 [15.2]) years • 19/93 (20.4%) with ESKD	Transplantation	None
Milan et al. (2003)[172]	NA	• 6 patients with PH1 who underwent a combined liver–kidney transplant • Age at diagnosis, mean (SD): 5.2 (3.3) years • Age at transplant, mean (SD): 14.8 (3.0) years • 6 (100%) with ESKD	Transplantation	None
Muller et al. (1998)[173]	NA	• 3 patients with PH1 who underwent a kidney transplant • Age at diagnosis, median (range): 16 (6–68) months • Age at transplant, median (range): 9.7 (8.9–13.2) months • 3 (100%) with ESKD	Transplantation	None
Perera et al. (2011)[175]	NA	• 4 patients with PH1 who underwent a pre-emptive liver transplant • Age at diagnosis, range: 6 months to 3 years at time of referral for management • Age at transplant, range: 10 months to 4.5 years • Proportion with ESKD not reported	Transplantation	None

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Perera et al. (2009)[174]	NA	• 9 patients with PH1 who underwent a combined liver–kidney transplant • Age at transplant, median (range): 8.6 (1.6–16.7) years • 9 (100%) with ESKD	Transplantation	None
Shasha-Iavsky et al. (2018)[130]	NA	• 36 patients with PH1, of which 7 patients underwent pre-emptive liver transplantation and 11 received conservative treatment • Baseline patient characteristics were not reported	Transplantation	None

eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; IQR=interquartile range; NA=not applicable; OLE=open-label extension; PH=primary hyperoxaluria; PH1=primary hyperoxaluria type 1; Q3M=once every 3 months; QM=once monthly; SC=subcutaneous

9.3.2 Study exclusion

None of the published studies listed in Table C2 were excluded.

9.4 Summary of methodology of relevant studies

9.4.1 Study design and methodology

The clinical development programme for lumasiran included:

- One RCT (ILLUMINATE-A) in patients aged ≥6 years with PH1 and relatively preserved renal function
- Two single-arm, interventional, open-label, phase 3 studies, one in paediatric patients aged <6 years with PH1 and relatively preserved renal function (ILLUMINATE-B) and the other in patients of any age with PH1 and advanced renal disease (ILLUMINATE-C)
- One phase 1/2 study (ALN-GO1-001) in healthy adult volunteers and patients aged ≥6 years with PH1
- One interventional, OLE, phase 2 study in patients aged ≥6 years with PH1 who participated in the phase 1/2 study noted above

Table C3. Summary of methodology for randomised controlled trials – ILLUMINATE-A

Study name	**ALN-GO1-003, NCT03681184, EudraCT 2018-001981-40** ILLUMINATE-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Extended Dosing Period to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1
Objectives	To evaluate the safety and efficacy of lumasiran (ALN-GO1) versus placebo in patients with PH1 and preserved renal function
Location	Sixteen study centres across eight countries (UK [3 sites], France [3], Germany [1], Israel [3], Netherlands [1], Switzerland [1], United Arab Emirates [1], US [3]) The three UK sites were: • Birmingham Women's and Children's Hospital, Birmingham • Great Ormond Street Hospital, London • Royal Free Hospital, London [redacted]
Design	International, multicentre, phase 3 study conducted in 2 parts: • Double-blind period: randomised, 6-month, placebo-controlled, double-blind treatment period • Extension period: 3-month blinded treatment extension and an OLE period of up to 51 months
Duration of study	November 2018 to May 2024; 60-month follow-up (6-month double-blind period, 54-month extension period)
Sample size	N=39 (Lumasiran=26, Placebo=13)

Inclusion criteria	• Age ≥6 years with documented or confirmed PH1 as determined by genetic analysis • Mean 24-h urinary oxalate excretion ≥0.70 mmol/24 h/1.73 m^2 (from first two valid 24-h urine collections) • Pyridoxine: allowed if patient was on a stable regimen for >90 days before randomisation and willing to remain on this stable regimen for 12 months from first study drug administration • Willing to comply with study requirements; written informed consent from patient or legal guardian(s) Note that all patients were required to continue their PH1 established clinical management (including hyperhydration, crystallisation inhibitors, and pyridoxine) through Month 12 of the study.
Exclusion criteria	• Clinical evidence of extrarenal systemic oxalosis • ALT or AST >2×ULN • Total bilirubin >1.5×ULN (patients with elevated total bilirubin that was secondary to documented Gilbert's syndrome were eligible if the total bilirubin was <2×ULN) • INR >1.5 (patients on oral anticoagulant [e.g., warfarin] with an INR <3.5 were allowed) • Known active human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection • eGFR <30 mL/min/1.73 m^2 at screening (calculated using the MDRD formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age) • Investigational agent within the last 30 days or 5 half-lives, whichever was longer, or are in follow-up of another clinical study prior to randomisation • History of renal or liver transplant • Other medical conditions or comorbidities, which in the opinion of the Investigator, would interfere with study compliance or data interpretation • History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc • History of intolerance to SC injection(s) • Unwilling to comply with the contraceptive requirements during the study period • Pregnant, planning a pregnancy, or breast-feeding • Unwilling or unable to limit alcohol consumption; alcohol intake of >2 units/day was excluded during the study (unit: 1 glass of wine [125 mL] = 1 measure of spirits [1 fluid ounce] = ½ pint of beer [284 mL]) • History of alcohol abuse within the last 12 months before screening
Method of randomisation	Conducted using an interactive response system; randomised 2:1 to lumasiran or placebo, stratified by mean urinary oxalate level (>1.70 vs. ≤1.70 mmol/24 h/1.73 m^2) calculated using the values obtained from the first two valid baseline 24-h urine collections
Method of blinding	Study personnel and patients including their families or caregivers were blinded to study drug treatment assignment until the last patient completed the assessments at the Month 9 visit. Selected site pharmacists were unblinded to study drug treatment only where required by documented pharmacy procedure.
Intervention(s) (n =) and comparator(s) (n =)	Lumasiran SC 3 mg/kg (n=26): • QM×3 followed by Q3M starting 1 month after the end of QM dosing (6-month double-blind period) • Q3M (3-month blinded extension that included two monthly doses of placebo after the first Q3M lumasiran dose to preserve the blind) • Q3M (51-month OLE) Placebo SC sterile normal saline (0.9% NaCl; n=13): • Placebo QM×3 followed by Q3M starting 1 month after the end of QM dosing (6-month double-blind period) • Lumasiran 3 mg/kg QM (3-month blinded extension) • Lumasiran 3 mg/kg Q3M starting 1 month after the end of QM dosing (51-month OLE)
Baseline differences	≥10% difference in distribution of race between groups Race, Lumasiran / Placebo, n (%) Asian: 3 (12) / 3 (23) White: 21 (81) / 9 (69) ≥10% difference in distribution of region between groups Region, Lumasiran / Placebo, n (%) Europe: 10 (38) / 8 (62) North America: 11 (42) / 2 (15)

Duration of follow-up, lost to follow-up information	60-month follow-up (6-month double-blind period, 54-month extension period) Treatment discontinuations (not based on full 60-month follow-up period): Lumasiran: n=2 (7.7%) AE: 1 (3.8%); the patient discontinued treatment after Month 3 but completed the double-blind period assessments Death: 0 Physician decision: 0 Protocol deviation: 0 Withdrawn by patient/guardian: 1 (3.8%) (See *Study withdrawals*) Placebo: n=0 Study withdrawals (not based on full 60-month follow-up period): Lumasiran: n=1 (3.8%); the parent/guardian stopped the patient's participation due to inability to comply with protocol-specific testing, and the patient did not complete the 6-month double-blind period Placebo: n=0
Statistical tests	MMRM approach for efficacy endpoints, except for binary endpoints that were analysed using a Cochran-Mantel-Haenszel test. • LSM treatment difference from baseline with SEMs, CIs, and p value for endpoints analysed via MMRM. • Number and associated percent of patients presented by treatment arm for binary endpoints. With the exception of change in eGFR (as a statistically significant treatment effect on this endpoint was not expected to emerge within 6 months) and the extension period endpoint, secondary endpoints were analysed in a prespecified hierarchical order as listed in this table to control for the overall type I error. It was determined that a sample size of approximately 24 patients provided 90% power to test a treatment difference of 37% in the mean percent reduction from baseline to Month 6 in 24-h urinary oxalate (corrected for BSA) with a two-sided $\alpha = 0.05$. The populations analysed included the: • Full analysis set, which comprised all patients who were randomised and received any amount of study drug • Plasma oxalate analysis set, which was used to evaluate the plasma oxalate endpoints and comprised all patients who received any amount of study drug and had a baseline plasma oxalate level ≥1.5×LLOQ (lower limit of quantitation), where LLOQ was 5.55 µmol/L. Patients with baseline plasma oxalate levels near the LLOQ (ie, <1.5×LLOQ) were excluded from the analysis to ensure that meaningful reductions in plasma oxalate could be evaluated for the study population • Safety analysis set, which comprised all patients who received any amount of study drug
Primary outcomes (including scoring methods and timings of assessments)	Percent change from baseline to Month 6 in 24-h urinary oxalate (corrected for BSA). • Estimated by an average percent change from baseline of 24-h urinary oxalate excretion across Months 3 through 6.

Secondary outcomes (including scoring methods and timings of assessments)	All secondary endpoints for the double-blind period were assessed at baseline (screening), Day 1, Months 1, 2, 3, 4, 5, and 6 except for eGFR, which was also assessed at Week 2. • Absolute change in 24-h urinary oxalate (corrected for BSA) from baseline to Month 6 • Percent change in 24-h urinary oxalate:creatinine ratio from baseline to Month 6 • Percent change in plasma oxalate from baseline to Month 6 • Proportion of patients with 24-h urinary oxalate level at or below 1.5×ULN at Month 6 • Proportion of patients with 24-h urinary oxalate level at or below ULN at Month 6 • Absolute change in plasma oxalate from baseline to Month 6 • Change in eGFR from baseline to Month 6 (mL/min/1.73 m^2); calculation based on the MDRD formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age at screening • *Extension Period endpoint* The *Extension Period* endpoint includes several individual endpoints assessed beyond Month 6 for the extension period: • Change from baseline (percent and absolute) in: 24-h urinary oxalate excretion, 24-h urinary oxalate:creatinine ratios, and eGFR • Percentage of time that 24-h urinary oxalate is ≤1.5×ULN Exploratory endpoints: • Change in KDQOL for patients ≥18 years of age at screening, and the PedsQL (generic and ESRD modules) for patients <18 years of age at screening. Assessed at baseline and every 6 months • Change in EQ-5D and EQ-5D VAS from baseline to Month 6. Questionnaire and VAS to be assessed at baseline and every 6 months • Change in rate of renal stone events, defined as an event that included ≥1 of the following: visit to healthcare provider (e.g., outpatient clinic, urgent care, emergency department, procedure) because of a renal stone; medication for renal colic; stone passage; or macroscopic haematuria due to a renal stone • Change from baseline in nephrocalcinosis as assessed by renal ultrasound at Months 6, 12, 24, 36, 48, and 60; graded (0–3) for each kidney, with a higher grade indicating greater severity • Change in urinary and plasma glycolate • Change in urinary oxalate:creatinine ratios as assessed in random spot urine collections • PK profile of lumasiran • Frequency of ADA, assessed at baseline and at any postbaseline visit • Change in patient resource use (e.g., work/school attendance, visits to doctor/hospital) as evaluated by a patient and caregiver impact questionnaire, and patient-reported information as collected in the eCRF assessed at baseline and every 6 months • Change in patient and caregiver experiences as evaluated by patient and caregiver experience surveys completed at baseline and every 6 months

ADA=antidrug antibody(ies); AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; BSA=body surface area; CI=confidence interval; eCRF=electronic case report form; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; GalNAc=*N*-acetylgalactosamine; INR=international normalised ratio; KDQOL=Kidney Disease Quality of Life Questionnaire; LLOQ=lower limit of quantitation; LSM=least squares mean; MDRD=Modification of Diet in Renal Disease; MMRM=mixed model for repeated measures; NaCl=sodium chloride; OLE=open-label extension; PedsQL=Pediatric Quality of Life Inventory; PH1=primary hyperoxaluria type 1; PK=pharmacokinetic; Q3M=every 3 months; QM×3=every month for three consecutive months; SEM=standard error of the mean; SC=subcutaneous; ULN=upper limit of normal; VAS=visual analogue scale

Source: Alnylam Data on File (ILLUMINATE-A [ALN-GO1-003] CSR[33]; ILLUMINATE-A [ALN-GO1-003] SAP[178]); Clinicaltrials.gov[87]; Garrelfs et al. (2021)[179]

Table C4. Summary of methodology for nonrandomised trials – ILLUMINATE-B

Study name	**ALN-GO1-004, NCT03905694, EudraCT 2018-004014-17** ILLUMINATE-B: An Open-Label Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Infants and Young Children with Primary Hyperoxaluria Type 1
Objectives	To evaluate the efficacy, safety, PK, and PD of lumasiran (ALN-GO1) in infants and young children (<6 years of age) with PH1 and relatively preserved renal function
Location	Nine study centres from across five countries (UK [1 site], France [2], Germany [1], Israel [3], US [2]) The one UK site was the Great Ormond Street Hospital, London. [redacted]
Design	International, multicentre, open-label, single-arm, phase 3 study

Duration of study	April 2019 to September 2024 60-month follow-up (six-month primary analysis, 54-month long-term extension period)
Sample size	N=18
Inclusion criteria	• Have reached at least 37 weeks estimated gestational age (full-term infant) but <6 years of age at consent • Documented PH1 as determined by genetic analysis • Urinary oxalate:creatinine ratio > ULN based on age on at least two of three single-void collections during screening • Pyridoxine: allowed if patient was on a stable regimen for >90 days before screening and able to remain on this stable regimen at least until Month 6 visit (dose adjustments for interval weight gain are acceptable) • Legal guardian(s) is (are) willing and able to comply with study requirements and provide written informed consent Note that all patients continued their PH1 established clinical management (including hyperhydration, crystallisation inhibitors, and pyridoxine) through Month 6 of the study, after which adjustments could be made according to the recommendations of the treating physician.
Exclusion criteria	• Clinical evidence of extrarenal systemic oxalosis • ALT or AST >2×ULN • Total bilirubin >1.5×ULN (patients with elevated total bilirubin that was secondary to documented Gilbert's syndrome were eligible if the total bilirubin was <2×ULN) • Known active human immunodeficiency virus infection, or evidence of current or chronic hepatitis C virus or hepatitis B virus infection • If ≥12 months old, has an eGFR ≤45 mL/min/1.73m^2 at screening (calculation was based on the Schwartz Bedside Formula); if <12 months old, has serum creatine value per the central laboratory above the ULN for age at screening • Investigational agent within the last 30 days or 5 half-lives, whichever was longer, or are in follow-up of another clinical study prior to randomisation • Has undergone renal or liver transplantation or a liver transplant is anticipated in the 6 months after the initial dose of lumasiran • Other medical conditions or comorbidities, which in the opinion of the Investigator, would interfere with study compliance or data interpretation • History of allergic reaction to an oligonucleotide or GalNAc • History of intolerance to SC injection(s) • For female patients who may achieve menarche during the study, is unwilling to comply with the contraceptive requirements during the study period
Method of randomisation	Not applicable
Method of blinding	Not applicable
Intervention(s) (n =)	Lumasiran SC (N=18) Loading dose (Day 1, Month 1, Month 2) based on weight: • <10 kg: 6.0 mg/kg QM×3 • ≥10 to <20 kg: 6.0 mg/kg QM×3 • ≥20 kg: 3.0 mg/kg QM×3 Maintenance dose (Month 3 and beyond) based on weight: • <10 kg: 3.0 mg/kg QM • ≥10 to <20 kg: 6.0 mg/kg Q3M • ≥20 kg: 3.0 mg/kg Q3M Patients did not switch back to lower-weight dosing schedules if their body weight decreased on trial

Baseline differences	≥10% difference in distribution of age between groups Age category (years), Lumasiran <10 kg / ≥10 to <20 kg / ≥20 kg, n (%) 0 to <1: 2 (66.7) / 0 / 0 1 to <2: 1 (33.3) / 1 (8.3) / 0 2 to <6: 0 / 11 (91.7) / 3 (100) ≥10% difference in distribution of race between groups Race, Lumasiran <10 kg / ≥10 to <20 kg / ≥20 kg, n (%) White: 1 (33.3) / 12 (100) / 3 (100) Other: 2 (66.7) / 0 / 0 ≥10% difference in distribution of region between groups Region, Lumasiran <10 kg / ≥10 to <20 kg / ≥20 kg, n (%) Europe: 2 (66.7) / 5 (41.7) / 1 (33.3) North America: 0 / 0 / 2 (66.7) Other: 1 (33.3) / 7 (58.3) / 0
Duration of follow-up, lost to follow-up information	60-month follow-up (6-month primary analysis, 54-month long-term extension period) Treatment discontinuations (not based on full 60-month follow-up period): Lumasiran: 0 Study withdrawals (not based on full 60-month follow-up period): Lumasiran: 0
Statistical tests	Restricted maximum likelihood–based MMRM approach for the primary efficacy endpoint and several secondary efficacy endpoints (absolute change in urinary oxalate excretion, percent and absolute change in plasma oxalate); descriptive statistics for remaining endpoints. • LSM treatment difference from baseline with SEMs, CIs, and p value for endpoints analysed via MMRM approach. • The number and associated percentage of patients who met each threshold at visits for binary endpoints. The planned enrolment for the study (20 patients) was determined based on feasibility considerations, rather than power calculations. The populations analysed included the: • Efficacy analysis set, which included all patients who received any amount of lumasiran and had at least one valid spot urinary oxalate:creatinine ratio value at baseline and at least one valid spot urinary oxalate:creatinine ratio value from assessment(s) at Month 3 to Month 6 • Safety analysis set, which comprised all patients who received any amount of study drug
Primary outcomes (including scoring methods and timings of assessments)	Percent change in urinary oxalate excretion from baseline to the average of Month 3 to Month 6, assessed with spot urinary oxalate:creatinine ratio measured at screening, Day 1, Month 1, 2, 3, 4, 5, and 6
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints assessed from Month 6 to end of study (assessed every 3 months until end of study): • Percent change in urinary oxalate excretion from baseline (monthly assessments between Months 7 and 18 were optional) • Percentage of time that spot urinary oxalate:creatinine ratio is at or below the near-normalisation threshold (≤1.5×ULN) Secondary endpoints assessed for the duration of study: • Absolute change in urinary oxalate excretion from baseline, assessed monthly until Month 6, every 3 months thereafter (optional monthly assessments between Months 7 and 18) • Proportion of patients with urinary oxalate excretion ≤ ULN and ≤1.5xULN, assessed monthly until Month 6, every 3 months thereafter (optional monthly assessments between Months 7 and 18) • Change (percent and absolute) in plasma oxalate from baseline, assessed monthly until Month 6, every 3 months thereafter (optional monthly assessments between Months 7 and 18) • Plasma PK parameters of lumasiran, assessed at Day 1, Month 6, 12, 18, and 24 • Change from baseline in eGFR, assessed monthly until Month 18, every 3 months thereafter

	Exploratory endpoints: • Change from baseline in nephrocalcinosis as assessed by renal ultrasound at Day 1, Month 6, 12, 24, 36, 48, and 60 • Change in frequency of renal stone events; continuous assessment through to end of study • Change in urinary glycolate and plasma glycolate; assessed during screening and at Day 1, Month 1, 3, 6, 9, 15, and every 6 months thereafter until end of study • Change in growth parameters (z-scores) from baseline over time; assessed monthly through Month 6, then monthly for body weight and every 3 months for height/length for patients weighing <10 kg or every 3 months for body weight and every 6 months for height/length for patients weighing ≥10 kg • Changes in developmental milestones over time; assessed using the Vineland Adaptive Behavior Scale during screening and every 6 months until end of study • Changes in patient and/or caregiver experience as evaluated by a patient/caregiver survey; assessed during screening and every 6 months until end of study • Frequency of ADA; assessed during screening period and at Month 1, 3, 6, 9, 12, and every 6 months until end of study

ADA=antidrug antibody(ies); AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; CI=confidence interval; eGFR=estimated glomerular filtration rate; GalNAc=*N*-acetylgalactosamine; MMRM=mixed model for repeated measures; PD=pharmacodynamic; PH1=primary hyperoxaluria type 1; PK=pharmacokinetic; Q3M=every 3 months; QM=monthly; QM×3=every month for three consecutive months; SC=subcutaneous; SEM=standard error of the mean; ULN=upper limit of normal

Source: Alnylam Data on File (ILLUMINATE-B [ALN-GO1-004] CSR 2[79]; ILLUMINATE-B [ALN-GO1-004] SAP[180]); Clinicaltrials.gov[88]; Frishberg et al. (2020)[66]; Sas et al. (2021)[9]

Table C5. Summary of methodology for nonrandomised trials – ILLUMINATE-C

Study name	**ALN-GO1-005, NCT04152200, EudraCT 2019-001346-17** ILLUMINATE-C: A Single-Arm Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1
Objectives	To evaluate the efficacy, safety, PK, and PD of lumasiran (ALN-GO1) in patients with PH1 and advanced renal disease
Location	15 study centres across 10 countries
Design	International, multicentre, open-label, single-arm, phase 3 study comprising two cohorts: • Cohort A: patients who do not yet require dialysis. Patients who experience progression of renal impairment over time and require dialysis therapy will cross over to Cohort B • Cohort B: patients who are on dialysis
Duration of study	January 2020 to August 2025 (estimated completion date) 60-month follow-up (6-month primary analysis, 54-month long-term extension period)
Sample size	N=21 (Cohort A=6, Cohort B=15)
Inclusion criteria	• Have reached at least 37 weeks estimated gestational age (full-term infant) at consent • Documented PH1 as determined by genetic analysis • eGFR ≤45 mL/min/1.73m^2 (calculated using the MDRD formula if ≥18 years or Schwartz Bedside Formula if ≥12 months to <18 years), or patients aged <12 months with serum creatinine that is considered elevated for age at consent • Mean plasma oxalate level from the first three collections at least 7 days apart during screening ≥20 µmol/L • Pyridoxine: allowed if patient is on a stable regimen for >90 days before consent and able to remain on this stable regimen at least until Month 6 visit (dose adjustments for interval weight gain are acceptable) • Willing to comply with study requirements; written informed consent from patient or legal guardian(s) • For patients who require dialysis [Cohort B]: on a stable haemodialysis regimen for >4 weeks prior to screening plasma oxalate assessment and able to maintain this regimen through Month 6, with changes permitted only when medically indicated

Exclusion criteria	• ALT or AST >2×ULN for age • Total bilirubin >1.5×ULN (patients with elevated total bilirubin that was secondary to documented Gilbert's syndrome were eligible if the total bilirubin was <2×ULN) • INR >1.5 (patients on oral anticoagulant [e.g., warfarin] with an INR <3.5 were allowed) • Known active human immunodeficiency virus infection, or evidence of current or chronic hepatitis C virus or hepatitis B virus infection • Investigational agent within the last 30 days or 5 half-lives, whichever was longer, or are in follow-up of another clinical study prior to randomisation • History of allergic reaction to an oligonucleotide or GalNAc • Conditions other than PH1 contributing to renal insufficiency (i.e., glomerulonephritis, nephrotic syndrome, or lupus nephritis) • Other medical conditions or comorbidities, which in the opinion of the Investigator, would interfere with study compliance or data interpretation, or prevent participation in at least 12 months of the study • Unwilling or unable to limit alcohol consumption; alcohol intake of >2 units/day was excluded during the study (unit: 1 glass of wine [125 mL] = 1 measure of spirits [1 fluid ounce] = ½ pint of beer [284 mL]) • History of alcohol abuse within the last 12 months before screening • Has undergone liver transplantation or a liver transplant is anticipated within 6 months • Has undergone renal transplant and is currently receiving immunosuppression to prevent transplant rejection • Maintained on a peritoneal dialysis regimen • Plans to start dialysis replacement therapy within 6 months • Unwilling to comply with the contraceptive requirements during the study period • Pregnant, planning a pregnancy, or breast-feeding
Method of randomisation	Not applicable
Method of blinding	Not applicable
Intervention(s) (n =)	Lumasiran SC (N=21) Loading dose (Day 1, Month 1, Month 2) based on weight: • <10 kg: 6.0 mg/kg QM×3 • ≥10 to <20 kg: 6.0 mg/kg QM×3 • ≥20 kg: 3.0 mg/kg QM×3 Maintenance dose (Month 3 and beyond) based on weight: • <10 kg: 3.0 mg/kg QM • ≥10 to <20 kg: 6.0 mg/kg Q3M • ≥20 kg: 3.0 mg/kg Q3M
Baseline differences	≥10% difference in distribution of age between Cohorts Age category (years), Lumasiran Cohort A / Lumasiran Cohort B, n (%) 2 to <6: [redacted] 6 to <18: [redacted] ≥10% difference in distribution of race between Cohorts Race, Lumasiran Cohort A / Lumasiran Cohort B, n (%) White: [redacted] Other: [redacted] ≥10% difference in distribution of region between Cohorts Region, Lumasiran Cohort A / Lumasiran Cohort B, n (%) Europe: [redacted] Middle East: [redacted] ≥10% difference in body weight between Cohorts Body weight, Lumasiran Cohort A / Lumasiran Cohort B, mean (SD), kg: [redacted]

Duration of follow-up, lost to follow-up information	60-month follow-up (6-month primary analysis, 54-month long-term extension period) Treatment discontinuation (not based on full 60-month follow-up period) shown by Cohort A / Cohort B / Overall, n (%): AE: [redacted] Death: 0 Physician decision: [redacted] Protocol deviation: [redacted] Withdrawn by patient/guardian: [redacted] (See *Study withdrawal*) Study withdrawal (not based on full 60-month follow-up period): Cohort A: [redacted] Cohort B: [redacted] Overall: [redacted]
Statistical tests	Restricted maximum likelihood–based MMRM approach for the primary efficacy endpoint and several secondary efficacy endpoints during the primary analysis period (absolute change in plasma oxalate, percent and absolute change in 24-h urinary oxalate corrected for BSA, percent and absolute change in spot urinary oxalate:creatinine ratio); descriptive statistics for remaining endpoints. • LSM treatment difference from baseline with SEMs, CIs, and p value for endpoints analysed via MMRM. • The number and percentages of patients in each category for binary endpoints. The planned enrolment for the study (16 patients) was determined based on feasibility considerations, rather than power calculations. The populations analysed by cohort included the: • Full analysis set, which included all patients in a given cohort who received any amount of lumasiran and had at least one evaluable plasma oxalate value (predialysis in Cohort B) at baseline and at least one plasma oxalate value from assessment(s) at Month 3 to Month 6 • Safety analysis set, which comprised all patients who received any amount of study drug • PK analysis set, which comprised all patients who received any amount of lumasiran, had at least one postdose blood sample for PK parameters, and had evaluable PK data
Primary outcomes (including scoring methods and timings of assessments)	Primary endpoints: • Cohort A: percent change from baseline to Month 6 in plasma oxalate • Cohort B: percent change from baseline to Month 6 in predialysis plasma oxalate Plasma oxalate levels assessed via blood samples collected at baseline (3 assessments during screening), Day 1, Month 1, 2, 3, 4, 5, and 6.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints assessed from baseline to Month 6: • Percent change in plasma oxalate AUC between dialysis sessions (Cohort B); assessed with up to eight blood samples withdrawn over a 24-h period at baseline (screening), Month 3, and Month 6 • Absolute change in plasma oxalate; assessed at baseline, Day 1, Month 1, and monthly thereafter • Change in urinary oxalate; assessed from 24-h urine samples at baseline, Month 3, and Month 6 (or single-void urine samples collected monthly for anuric patients) • Change in HRQoL, assessed by the PedsQL Total Score for patients aged ≥2 to <18 years at consent and by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales and SF-12 Physical Component Summary and Mental Component Summary in patients aged ≥18 years at consent; assessed at baseline and at Month 6 • Plasma PK parameters of lumasiran; assessed from blood samples collected at Day 1 and Month 6

	Secondary endpoints assessed from Month 6 to the end of the study: • Percent change in plasma oxalate AUC between dialysis sessions; assessed every 6 months (Cohort B) • Percent and absolute change in plasma oxalate; assessed every 3 months • Change in nephrocalcinosis; assessed by renal ultrasound at baseline, Month 6, 12, and annually thereafter • Change in frequency and mode of dialysis (Cohort B); assessed at baseline, Month 6, and every 3 months thereafter • Change in frequency of renal stone events; assessed continuously throughout study • Change in urinary oxalate; assessed from 24-h urine samples collected every 6 months (or single-void urine samples collected every 3 months for anuric patients) • Change in renal function as assessed by eGFR from blood samples drawn at baseline, Day 1, monthly to Month 15, and every 3 months thereafter (Cohort A) • Change in measures of systemic oxalosis in cardiac, dermatologic, skeletal, and ocular systems; assessed at baseline, Month 6, 12, and annually thereafter • Change in HRQoL, assessed by the PedsQL Total Score for patients aged ≥2 to <18 years at consent and by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales and SF-12 Physical Component Summary and Mental Component Summary in patients aged ≥18 years at consent; assessed every 6 months Exploratory endpoints: • Growth parameters in patients aged <6 years at consent; body weight assessed monthly through to Month 6 and height/length assessed monthly to Month 6 if aged <6 years (otherwise every 3 months); beyond Month 6, body weight assessed monthly to end of study and height/length assessed monthly to Month 15 and every 3 months thereafter for patients weighing <10 kg or body weight assessed every 3 months and height/length assessed every 6 months to end of study for patients weighing ≥10 kg • In patients aged ≥2 to <18 years at consent: change in HRQoL as assessed by EQ-5D-Y and PedsQL (individual subscales of the generic and ESRD modules, and ESRD module total score); assessed every 6 months • In patients aged ≥18 years at consent: change in HRQoL as assessed by EQ-5D-5L and KDQOL Symptoms and Problems of Kidney Disease subscale; assessed every 6 months • Change in patient and caregiver experiences as evaluated by patient experience and caregiver experience questionnaires; assessed at baseline and every 6 months thereafter • Frequency of ADA; assessed at baseline/Day 1, Month 1, 3, 6, and every 6 months thereafter • Change in urinary and plasma glycolate; assessed at the same time as oxalate sample collection

ADA=antidrug antibody(ies); AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; AUC=area under the curve; BSA=body surface area; CI=confidence interval; eGFR=estimated glomerular filtration rate; EQ-5D-5L=EQ-5D, Five-Level Questionnaire; EQ-5D-Y=EQ-5D, Youth version; ESRD=end-stage renal disease; GalNAc=*N*-acetylgalactosamine; HRQoL=health-related quality of life; INR=international normalised ratio; KDQOL=Kidney Disease Quality of Life; MDRD=Modification of Diet in Renal Disease; PD=pharmacodynamic; PedsQL=Pediatric Quality of Life Inventory; PH1=primary hyperoxaluria type 1; PK=pharmacokinetic; Q3M=every 3 months; QM=monthly; QM×3=every month for three consecutive months; SC=subcutaneous; SEM=standard error of the mean; SF-12=12-Item Short Form Health Survey; ULN=upper limit of normal

Source: Alnylam Data on File (ILLUMINATE-C [ALN-GO1-005] CSR 1[64]; ILLUMINATE-C [ALN-GO1-005] Protocol[181]; ILLUMINATE-C [ALN-GO1-005] SAP[182]); Clinicaltrials.gov[89]

ILLUMINATE-A (ALN-GO1-003)

The lumasiran phase 3 trial ILLUMINATE-A is an international, multicentre, randomised, double-blind, placebo-controlled trial with an ongoing extension phase to evaluate the efficacy and safety of lumasiran in patients with PH1 and relatively preserved renal function. Study criteria are listed in Table C3.[8,33]

The 6-month double-blind study duration was chosen based on the sustained reduction of urinary oxalate levels in PH1 patients in the phase 2 multi-dose study, together with advice received from health authorities (EMA and US FDA) at the end of phase 2.[33,183] Specifically, the US FDA agreed with the primary endpoint and placebo-controlled primary analysis period[71] followed by long-term follow-up for patients.

Given the lack of approved therapies for patients with PH1 and the small population available for the study, use of a placebo comparator and limiting the duration of placebo exposure to the 6-month double-blind period

were considered appropriate for estimating the treatment effect and gaining an understanding of the safety profile of lumasiran.[33] In addition, change in oxalate was regarded as a clinically relevant endpoint that maximised the power of this clinical study in a disease state in which trial population size is fundamentally limited by the extreme rarity of the condition.[33]

The primary objective of the study was to determine the efficacy of lumasiran in patients with PH1 by evaluating the difference between the lumasiran and placebo groups in the percent change in 24-h urinary oxalate excretion from baseline to Month 6 (corrected for BSA).[8] The primary objective was chosen based on the pathophysiology of PH1, which is driven by excessive oxalate production by the liver and subsequent renal elimination of oxalate. The mechanism of action of lumasiran—a reduction in hepatic oxalate production (which is reflected in decreased oxalate levels[27])—is expected to confer clinical benefit in this population because overproduction of oxalate for subsequent elimination by the kidneys drives disease progression (toxic calcium oxalate crystal formation, nephrocalcinosis, acute kidney injury, obstructive stones, and systemic oxalosis).[4,5,17,18,30,31] The amount of oxalate excreted in the urine serves as one indicator of the level of hepatic oxalate overproduction.[20] In ILLUMINATE-A, urinary oxalate was assessed as a continuous variable because increasing levels of urinary oxalate excretion have been associated with a graded increase in risk of progression to renal failure. Furthermore, employing change in urinary oxalate as a continuous variable maximised the power of this small study in a rare disease.[33]

The EMA agreed that a primary endpoint based on urinary oxalate was supported by the small population available for the study, epidemiological data, and the plausibility of urinary oxalate levels to predict long-term outcomes.[70] The choice of primary endpoint in patients with PH1 and preserved renal function in ILLUMINATE-A aligns with the recent critical evaluation of literature on clinical outcomes and endpoints for the approval of new therapies for PH1, as published by Milliner et al. (2020)[27]. According to Milliner et al., representing the Kidney Health Initiative (KHI) and Oxalosis and Hyperoxaluria Foundation (OHF) in the US, urinary oxalate, plasma oxalate, and change in slope of eGFR are the strongest markers of PH1 disease progression. The KHI/OHF recommendations state that a substantial change (i.e., near-normalisation) in urinary oxalate is considered a reasonable basis for traditional regulatory approval for the treatment of PH1 in patients with preserved renal function (eGFR ≥45 mL/min/1.73 m^2).[27] Since these recommendations were published, data have emerged showing that like urinary oxalate, plasma oxalate is also predictive of ESKD and positively correlates with renal decline starting from the early stages of the disease.[28,104] Percent and absolute change in plasma oxalate from baseline were secondary endpoints in the ILLUMINATE-A study.[8]

ILLUMINATE-B (ALN-GO1-004)

The lumasiran phase 3 trial ILLUMINATE-B is an ongoing, international, multicentre, open-label study to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of lumasiran in infants and young children. Study criteria are listed in Table C4. The primary objective of the study was to evaluate the effect of lumasiran on percent change in urinary oxalate excretion as measured by spot urinary oxalate:creatinine ratio from baseline to Month 6 (average of Month 3–6).[9] The primary endpoint was measured from spot urine samples, since the young patients in this study population could not always comply with 24-h urine collections (the standard method for measuring urinary oxalate excretion).[9,79] Secondary endpoints included percent and absolute change in plasma oxalate from baseline.[9]

ILLUMINATE-C (ALN-GO1-005)

The lumasiran phase 3 trial ILLUMINATE-C is an ongoing, international, multicentre, open-label study to evaluate the efficacy, safety, PK, and PD of lumasiran in patients with PH1 and advanced renal disease (eGFR ≤45 mL/min/1.73 m^2), including patients requiring haemodialysis. Study criteria are listed in Table C5.[181]

ILLUMINATE-C included a cohort of patients who did not yet require dialysis (Cohort A) and a cohort of patients who were on dialysis (Cohort B). The study design specified inclusion of at least 6 patients in each cohort at baseline, with patients in Cohort A who experienced progression of renal impairment and required

dialysis therapy able to cross over to Cohort B.[181] Twenty-one patients enrolled in ILLUMINATE-C, 6 patients in Cohort A and 15 patients in Cohort B.

The primary endpoint in ILLUMINATE-C was percent change in plasma oxalate from baseline to Month 6, which was measured as predialysis plasma oxalate in Cohort B.[181]

The choice of primary endpoint aligns with the critical evaluation of endpoints for PH1 performed by the KHI and OHF. Since elevated plasma oxalate is linked to systemic oxalosis in patients with PH1 and advanced renal disease (eGFR ≤45 mL/min/1.73 m^2), a substantial decrease in markedly elevated plasma oxalate is a strong indicator of clinical efficacy and could support accelerated approval in patients with advanced disease. Furthermore, patients with low eGFR have reduced ability to excrete oxalate in sufficient quantities for urinary oxalate assessments to be used as a meaningful indicator of hepatic oxalate production.[27]

Phase 1/2 trial (ALN-GO1-001 Part B)

ALN-GO1-001 Part B (ALN-GO1-001B) was a phase 1/2, randomised, placebo-controlled, single-blind, multi-dose study to evaluate lumasiran in patients aged ≥6 years with PH1 with urinary oxalate ≥0.7 mmol/1.73m^2/day and eGFR >45 mL/min/1.73m^2 (N=20). Lumasiran was administered as three monthly doses of 1 mg/kg (Cohort 1) or 3 mg/kg (Cohort 2), or as two quarterly doses of 3 mg/kg (Cohort 3).[183]

The primary study endpoint was safety; secondary study endpoints included change in 24-h urinary oxalate.[183] All patients who completed the study enrolled in the phase 2 OLE (ALN-GO1-002).[90,184]

Phase 2 trial

ALN-GO1-002 was a phase 2 multicentre OLE study to evaluate the long-term administration of lumasiran in patients with PH1 aged 6 to 64 years who were previously enrolled in ALN-GO1-001B (N=20).[66,184,185] Patients initiated dosing with SC lumasiran at the same dosing regimen as they received in ALN-GO1-001B (1 mg/kg monthly [n=8], 3 mg/kg monthly [n=7], or 3 mg/kg every 3 months [n=5]).[66,184] Patients who received 1 mg/kg monthly were subsequently transitioned to 3 mg/kg every 3 months to align with the intended phase 3 maintenance dose.[185]

The primary study objective was to evaluate the long-term safety of multiple doses of lumasiran. Secondary objectives included the assessment of changes in 24-h urinary oxalate (corrected for BSA), 24-h urinary oxalate:creatinine ratio, and eGFR.[185]

9.4.2 Sources for studies reported in more than one reference

Details for the ILLUMINATE-A trial were drawn from the published phase 3 trial (Garrelfs et al. 2021[8]), published abstracts (Sas et al. 2021[68]; Saland et al. 2020[63]), the published clinical trial protocol,[87] and unpublished data.[33,178] Details for the ILLUMINATE-B trial were drawn from the published phase 3 trial (Sas et al. 2021[9]), the published clinical trial protocol[88] and abstract (Michael et al., 2020[67]), and unpublished data.[79,180] Details for the ILLUMINATE-C trial were obtained from the published clinical trial protocol[89] and abstract (Michael et al. 2021[11]), and unpublished data.[64,181,182] Data on the lumasiran phase 2 OLE were drawn from published abstracts (Hulton et al. 2019[184]; Frishberg et al. 2020[66]) and unpublished data.[182,185]

9.4.3 Baseline characteristics

Table C6 and Table C7 summarise the differences between patient populations and methodology in all included lumasiran studies.

Table C6. Baseline demographics for lumasiran studies

Baseline demographics	Study name						
	ILLUMINATE-A[8] (ALN-GO1-003)		ILLUMINATE-B[9,79] (ALN-GO1-004)	ILLUMINATE-C[11,64] (ALN-GO1-005)			Phase 2 OLE[66,185] (ALN-GO1-002)
	Phase 3 RCT		Phase 3 Open-label	Phase 3 Open-label			Phase 2 OLE
	Lumasiran, n=26	Placebo, n=13	Lumasiran, N=18	Lumasiran Cohort A, n=6	Lumasiran Cohort B, n=15	Overall, N=21	Lumasiran, N=20
Age, median (range), years*	16.5 (6–47)	11.0 (6–60)	NR	9.0 (0–40)	6.0 (1–59)	8.0 (0–59)	11.5 (6–43)
Age, median (range), months	NR	NR	50.1 (3–72)	NR	NR	NR	NR
Age by category (in years), n (%)*							
0 to <1	NA	NA	2 (11)	[redacted]	[redacted]	[redacted]	NA
1 to <2	NA	NA	2 (11)				NA
2 to <6	NA	NA	14 (78)	[redacted]	[redacted]	[redacted]	NA
6 to <18	14 (54)	8 (62)	NA	[redacted]	[redacted]	[redacted]	16 (80.0)
18 to <65	12 (46)	5 (38)	NA	[redacted]	[redacted]	[redacted]	4 (20.0)
Age at diagnosis, median (range), years	3 (−1 to 59)†	8 (0–36)	NR	NR	NR	NR	3.8 (−0 to 13)†
Age at diagnosis, mean (SD), months	NR	NR	16.3	[redacted]	[redacted]	[redacted]	NR
Female, n (%)	8 (31)	5 (38)	10 (56)	3 (50)	6 (40)	9 (42.9)	7 (35)
Weight, median (range) or mean (SD), kg	NR	NR	14.5 (6.2–24.3)	[redacted]	[redacted]	[redacted]	42.8 (21.3–112.5)
Race, n (%)							
Asian	3 (12)	3 (23)	NA	[redacted]	[redacted]	[redacted]	4 (20.0)
White	21 (81)	9 (69)	16 (89)	[redacted]	[redacted]	[redacted]	15 (75.0)
Other	2 (8)	1 (8)	2 (11)	[redacted]	[redacted]	[redacted]	1 (5.0)
Region, n (%)							
Europe	10 (38)	8 (62)	8 (44)	[redacted]	[redacted]	[redacted]	NR
Middle East	5 (19)	3 (23)	NA	[redacted]	[redacted]	[redacted]	NR
North America	11 (42)	2 (15)	2 (11)	[redacted]	[redacted]	[redacted]	NR
Other‡	NR	NR	8 (44)	[redacted]	[redacted]	[redacted]	NR

*In ILLUMINATE-C, this demographic represents the age at consent.
†Minimum reflects one patient with a prebirth diagnosis (−0.4 years in phase 2 OLE).
‡In ILLUMINATE-C, Other includes Australia, Israel, Jordan, Lebanon, Turkey, and the United Arab Emirates.
BSA=body surface area; NA=not applicable; NR=not reported; RCT=randomised control trial; SD=standard deviation

Source: Alnylam Data on File (ILLUMINATE-B [ALN-GO1-004] CSR 2[79]; ILLUMINATE-C [ALN-GO1-005] CSR 1[64]; Phase 2 OLE [ALN-GO1-002 CSR][185]); Frishberg et al. (2020)[66]; Garrelfs et al. (2021)[8]; Michael et al. (2021)[11]; Sas et al. (2021)[9]

Table C7. Baseline disease characteristics for lumasiran studies

Baseline disease characteristic	Study name						
	ILLUMINATE-A[8] (ALN-GO1-003)		ILLUMINATE-B[9,79] (ALN-GO1-004)	ILLUMINATE-C[11,64] (ALN-GO1-005)			Phase 2 OLE[66,185] (ALN-GO1-002)
	RCT		Phase 3 Open-label	Phase 3 Open-label			Phase 2 OLE
	Lumasiran, n=26	Placebo, n=13	Lumasiran, N=18	Lumasiran Cohort A, n=6	Lumasiran Cohort B, n=15	Overall, N=21	Lumasiran, N=20*
24-h urinary oxalate excretion (corrected for BSA), mean (SD), mmol/24 h/1.73 m²	1.84 (0.60)	1.79 (0.68)	2.083 (0.7087)†	[redacted]‡	[redacted]†	[redacted]‡	2.242 (0.9956)
24-h urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	0.209 (0.101)	0.237 (0.110)	0.3406 (0.10929)†	[redacted]‡	[redacted]†	[redacted]‡	0.2793 (0.12977)
Spot urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	0.225 (0.110)	0.236 (0.140)	0.631 (0.426)	[redacted]	[redacted]	[redacted]	NR
Plasma oxalate, mean (SD), µmol/L	14.8 (7.6)§	15.5 (7.3)§	13.24 (6.500)	[redacted]	[redacted]	[redacted]	NR
eGFR, mean (SD), mL/min/1.73 m²	83.0 (25.5)	78.9 (26.8)	112.802 (27.6270)	[redacted]	[redacted]	[redacted]	77.341 (22.1113)
CKD stage by eGFR, n (%), mL/min/1.73 m²							
≥90	9 (35)	4 (31)	NR	NR	NR	NR	NR
60 to <90	13 (50)	6 (46)	NR	NR	NR	NR	NR
30 to <60	4 (15)	3 (23)	NR	NR	NR	NR	NR
Patient-reported history of the following, n (%)							
Renal stone events	23 (89)¶	10 (77)¶	3 (17)‖	[redacted]	[redacted]	[redacted]	NR
Lithotripsy/stone removal procedures in the 12 months prior to consent	4 (15.4)	3 (23.1)	2 (11.1)	NR	NR	NR	NR
Pyridoxine use at baseline	13 (50)	9 (69)	11 (61)	[redacted]	[redacted]	[redacted]	13 (65.0)
Pyelonephritis	5 (19)	5 (39)	2 (11)	[redacted]	[redacted]	[redacted]	NR
Urinary tract infections	11 (42)	5 (39)	4 (22)	[redacted]	[redacted]	[redacted]	NR
Nephrocalcinosis	12 (46)	9 (69)	14 (78)	[redacted]	[redacted]	[redacted]	NR
Symptomatic renal stone events in the 12 months prior to consent, n (%)							
1 to 5	8 (31)	4 (31)	NR	NR	NR	NR	NR
6 to 10	2 (8)	0	NR	NR	NR	NR	NR
>10	1 (4)	0	NR	NR	NR	NR	NR
Presenting symptoms/PH1 complications, n (%)**							
Asymptomatic (familial screening)	2 (8)	3 (23)	5 (28)	[redacted]	[redacted]	[redacted]	NR
Renal stone	21 (81)	7 (54)	5 (28)	[redacted]	[redacted]	[redacted]	14 (77.8)
ESKD	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA
Nephrocalcinosis	10 (39)	7 (54)	8 (44)	[redacted]	[redacted]	[redacted]	10 (55.6)
Other	4 (15)	3 (23)	5 (28)	[redacted]	[redacted]	[redacted]	5 (27.8)

Baseline disease characteristic	Study name						
	ILLUMINATE-A[8] (ALN-GO1-003)		ILLUMINATE-B[9,79] (ALN-GO1-004)	ILLUMINATE-C[11,64] (ALN-GO1-005)			Phase 2 OLE[66,185] (ALN-GO1-002)
	RCT		Phase 3 Open-label	Phase 3 Open-label			Phase 2 OLE
	Lumasiran, n=26	Placebo, n=13	Lumasiran, N=18	Lumasiran Cohort A, n=6	Lumasiran Cohort B, n=15	Overall, N=21	Lumasiran, N=20*
Genotype							
PR/any genotype of PR, M, or N	11 (42)	6 (46)	3 (17)	[redacted]	[redacted]	[redacted]	NR
M/M or M/N	6 (23)	4 (31)	10 (56)	[redacted]	[redacted]	[redacted]	NR
N/N	9 (35)	3 (23)	5 (28)	[redacted]	[redacted]	[redacted]	NR

*Baseline characteristics were derived from baseline in the parent phase 1/2 study.
†24-h urinary oxalate was performed in a limited subset of patients who were able to complete a 24-h urine collection (n=5 for 24-h urinary oxalate excretion and n=6 for 24-h urinary oxalate:creatinine ratio).
‡24-h urinary oxalate was performed in 5/6 patients in Cohort A and in 1/15 patients in Cohort B of ILLUMINATE-C.
§Based on the plasma oxalate analysis set of ILLUMINATE-A comprising 23 patients in the lumasiran arm and 10 patients in the placebo arm
¶Symptomatic renal stone events.
‖History of renal stone events in the 12 months prior to the study.
**Includes all symptoms that a patient had experienced prior to diagnosis. A patient may check more than one category; therefore, percentages may exceed 100%.

BSA=body surface area; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; M=missense; N=nonsense; PR=pyridoxine responsive; SD=standard deviation

Source: Alnylam Data on File (ILLUMINATE-B [ALN-GO1-004] CSR 2[79]; ILLUMINATE-C [ALN-GO1-005] CSR 1[64]; Phase 2 OLE [ALN-GO1-002 CSR][185]); Frishberg et al. (2020)[66]; Garrelfs et al. (2021)[8]; Michael et al. (2021)[11] ; Sas et al. (2021)[9]

9.4.4 Subgroup and sensitivity analyses

ILLUMINATE-A

Prespecified subgroup analyses were performed for the primary endpoint using the full analysis set (FAS) population in the following subgroups:[33]

- Age at screening (6 to <12, versus 12 to <18, versus ≥18 years)
- Gender (Male or Female)
- Race (White or Non-white)
- Baseline 24-h urinary oxalate corrected for BSA (≤1.70 versus >1.70 mmol/24 h/1.73m^2)
- Baseline eGFR (<60 versus ≥60 mL/min/1.73m^2)
- History of renal stones (Yes or No)
- Baseline vitamin B6 use (Yes or No)
- Region 1: North America (including US and Canada) versus Other (outside North America)
- Region 2: Europe versus Other (outside Europe)

Two prespecified sensitivity analyses were performed to evaluate the estimated treatment effect on the primary endpoint of percent change in 24h urinary oxalate (corrected for BSA) from baseline to Month 6.[8] The primary analysis assumed that the treatment effect reached steady state at Month 3 and was maintained through Month 6.[33] Both sensitivity analyses estimated the treatment effect of the primary endpoint without assuming equal treatment effect from Month 3 through Month 6. Sensitivity Analysis 1 added the interaction of visit and treatment to the primary MMRM model, when Month 3 through Month 6 data were used. In contrast, Sensitivity Analysis 2 included all postbaseline data (including percent change from baseline at Months 1 and 2).[33]

ILLUMINATE-B

Prespecified subgroup analyses were performed for the primary endpoint in the following subgroups:[79]

- Age group: 0 to <1 year, 1 to <6 years
- Weight-based dosing category: 0 to <10 kg, ≥10 to <20 kg, and ≥20 kg

Three prespecified sensitivity analyses were performed to support the primary endpoint and included percent change from baseline for the:[79]

- Spot urinary oxalate:creatinine ratio by visit for the efficacy analysis set
- Spot urinary oxalate:creatinine ratio from Month 3 to Month 6 for the safety analysis set
- Ratio of measured spot urinary oxalate:creatinine to ULN from Month 3 to Month 6 for the efficacy analysis set

ILLUMINATE-C

Prespecified subgroup analyses were performed for the primary endpoint in the following subgroups:[182]

- Age group: 0 to <2 years, 2 to <6 years, 6 to <18 years, ≥18 years
- Weight-based dosing category: 0 to <10 kg, ≥10 to <20 kg, and ≥20 kg

The following sensitivity analysis was performed in ILLUMINATE-C:

- Percent change in plasma oxalate (Cohort A) or predialysis plasma oxalate (Cohort B) from baseline to Month 6 for the safety analysis sets

9.4.5 Patient disposition

ILLUMINATE-A

Figure C2 shows the CONSORT flow diagram for the ILLUMINATE-A study. Patients (N=39) were randomised 2:1 to the lumasiran arm (n=26) or placebo (n=13).[8,33] A total of 24 of 26 patients initially randomised to receive lumasiran in the double-blind period continued to receive lumasiran in the extended-dosing period. All patients initially randomised to receive placebo crossed over to receive lumasiran.[10]

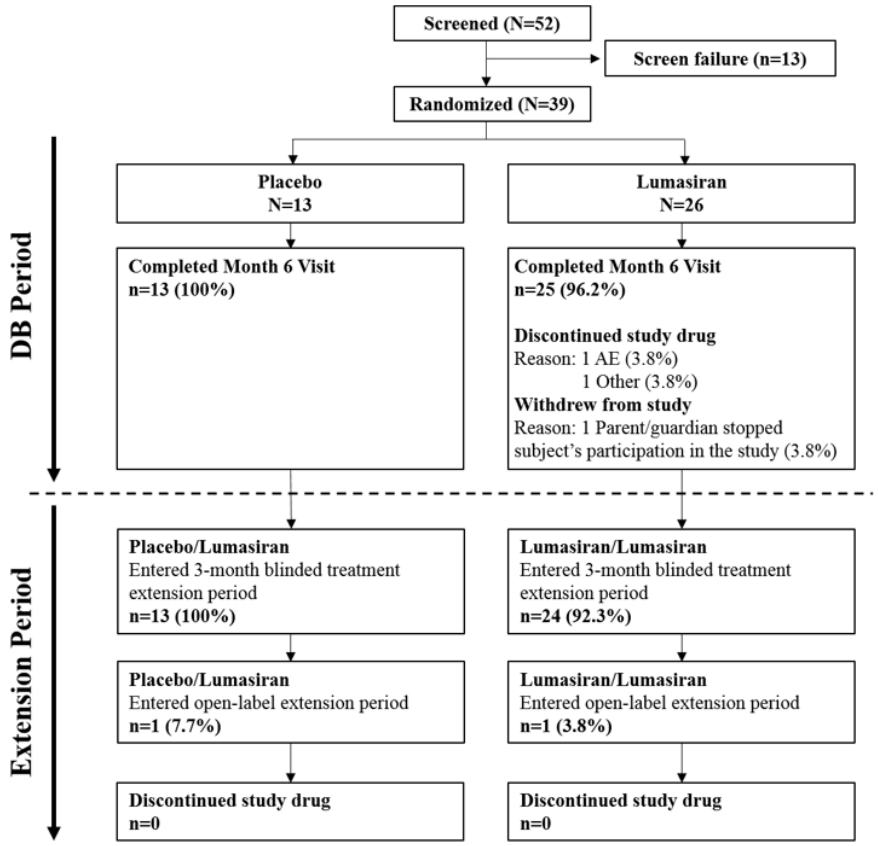

Figure C2. CONSORT flow diagram for ILLUMINATE-A
AE=adverse event; DB=double-blind.

Source: Alnylam Data on File (ILLUMINATE-A [ALN-GO1-003] CSR)[33]; Garrelfs et al. (2021)[8]

ILLUMINATE-B

The lumasiran phase 3 ILLUMINATE-B study enrolled a total of 18 patients. All patients completed the 6-month primary analysis period.[9]

ILLUMINATE-C

The lumasiran phase 3 ILLUMINATE-C study enrolled a total of 21 patients, six patients in Cohort A (patients not yet on dialysis) and 15 patients in Cohort B (patients on dialysis). All patients completed the 6-month primary analysis period.[11]

Phase 2 OLE

The lumasiran phase 2 OLE study enrolled 20 patients (all eligible patients from the phase 1/2 multi-dose study).[183,184]

9.4.6 Discontinuations and loss to follow-up

ILLUMINATE-A

Of the 26 patients randomised to the lumasiran arm in ILLUMINATE-A, 25 completed the double-blind treatment and two patients discontinued (one patient discontinued after the end of the double-blind period). The reasons for discontinuation included AEs (n=1; fatigue and disturbance in attention, considered unrelated to the study drug) and withdrawal of parent/caregiver consent (n=1). None of the 13 placebo-treated patients withdrew from the study during the primary analysis period.[8,33]

ILLUMINATE-B

There were no discontinuations from study treatment in ILLUMINATE-B.[9,79]

ILLUMINATE-C

Of the 21 patients in the ILLUMINATE-C study, [redacted].[64]

Phase 2 OLE

There were no discontinuations from study treatment in the phase 2 OLE.[184]

9.5 Critical appraisal of relevant studies

9.5.1 Quality assessment tables

Quality assessment of studies in the SLR was performed by two independent researchers. A 7-item qualitative tool adapted from the CRD[157] was used for the randomised studies. A 7-item qualitative tool adapted from the Critical Appraisal Skills Programme (CASP) was used for nonrandomised studies retrieved in the SLR search. The quality assessment analyses for ILLUMINATE-A and ILLUMINATE-B are summarised in Table C8 and Table C9, respectively. The quality assessment analysis for the phase 1/2 randomised trial and phase 2 OLE are summarised in Appendix 1: Search strategy for clinical evidence.

Table C8. Critical appraisal of randomised control trials – ILLUMINATE-A

Reference:	**ALN-GO1-003**	
Study name	**ILLUMINATE-A,[8,63] NCT03681184, EudraCT 2018-001981-40**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomised 2:1 to lumasiran or placebo, stratified by mean baseline urinary oxalate level
Was the concealment of treatment allocation adequate?	Yes	By Interactive Response System
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Not clear	Study reports groups were similar, however, some differences in median and ranges of age, proportion female and proportions in the categories of race
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes (first 6-month period) Not clear (extension period)	Participants and study personnel were blinded until primary analysis (month 6) and then for the first 3 months of the extension. Some unblinding was permitted in the protocol but not reported that this occurred. The method of masking was not reported Results reported in Saland (12 months) presumably include data from both blinded and unblinded periods Main outcome measures were objective Some concerns regarding detection and performance bias
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No imbalance in drop-outs
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	Exploratory outcomes were not listed in the published protocol to check, HRQoL and Patient and Carer Impact questionnaires were stated in the protocol but not specifically stated to be outcomes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods	Not clear	Analysis was a modified ITT analysis (all those undergoing randomisation and received at least one dose of treatment)

used to account for missing data?		
Adapted from Centre for Reviews and Dissemination (2008) *Systematic reviews. CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination		

HRQoL=health-related quality of life; ITT=intent to treat

Table C9. Critical appraisal of nonrandomised trials – ILLUMINATE-B

Reference	**ALN-GO1-004**	
Study name	**ILLUMINATE-B,[67] NCT03905694, EudraCT 2018-004014-17**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Minimal details reported of eligibility to the study
Was the exposure accurately measured to minimise bias?	Not clear	No details of doses given
Was the outcome accurately measured to minimise bias?	Not clear	Minimal safety outcomes only reported in abstract
Have the authors identified all important confounding factors?	No	No discussion of confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	No	No discussion of confounding factors
Was the follow-up of patients complete?	No	Interim analysis only
How precise (for example, in terms of confidence interval and p values) are the results?	No	No precision estimates provided
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence: 12 questions to help you make sense of a cohort study		

Critical appraisal was performed with the evidence identified using the SLR Population, Intervention, Comparison, Outcomes, and Study (PICOS) criteria. For ILLUMINATE-B, the only relevant source was an abstract reporting an interim analysis. The study is ongoing and full details are expected to be provided in the primary publication. The uncertainties noted above are resolved upon consideration of internal manufacturer data.

9.6 Results of the relevant studies

9.6.1 Results table

ILLUMINATE-A: Primary Analysis Period

The clinical efficacy of lumasiran in PH1 patients ≥6 years of age was evaluated in the ILLUMINATE-A RCT. Table C10 summarises the clinical efficacy outcomes. The endpoints in the ILLUMINATE-A trial were chosen to measure the effects of lumasiran on a broad range of clinically important and patient-relevant outcomes, including the impact of lumasiran on oxalate excretion, plasma oxalate levels, renal function, and nephrocalcinosis and renal stones.[8,33]

Table C10. Outcomes from published and unpublished studies – ILLUMINATE-A

Reference	ALN-GO1-003						
Study name	ILLUMINATE-A, NCT03681184, EudraCT 2018-001981-40						
Size of study groups	Lumasiran (n=26) Placebo (n=13)						
Study duration	60 months						
Outcome Name (unit)	**Treatment effect (95% CI)**		**Effect Size**		**Statistical test**		Comments
	Lumasiran	**Placebo**	**Value**	**95% CI**	**Type**	**p value**	
Percent change in 24-h urinary oxalate excretion from baseline to Month 6, %, LSM*†	−65.4 (−71.3, −59.5)	−11.8 (−19.5, −4.1)	−53.5	(−62.3, −44.8)	MMRM	1.685×10^{-14}	Primary endpoint; FAS; using two sensitivity analyses, a clinically meaningful and statistically significant change was demonstrated with lumasiran compared to placebo
Absolute change in 24-h urinary oxalate from baseline to Month 6, mmol/24 h/1.73 m^2, LSM*†	−1.24 (−1.37, −1.12)	−0.27 (−0.44, −0.10)	−0.98	(−1.18, −0.77)	MMRM	1.225×10^{-11}	Secondary endpoint; FAS
Percent change in 24-h urinary oxalate:creatinine ratio from baseline to Month 6, %, LSM†	−62.5 (−70.7, −54.4)	−10.8 (−21.6, −0.0)	−51.8	(−64.3, −39.2)	MMRM	5.032×10^{-10}	Secondary endpoint; FAS
Percent change in plasma oxalate from baseline to Month 6, %, LSM†‡	−39.8 (−45.8, −33.8)	−0.3 (−9.1, 8.5)	−39.5	(−50.1, −28.9)	MMRM	2.862×10^{-8}	Secondary endpoint; plasma oxalate analysis set
Proportion of patients with 24-h urinary oxalate ≤1.5×ULN at Month 6, %*§	84	0	84	(55, 94)	CMH	8.341×10^{-7}	Secondary endpoint; FAS
Proportion of patients with 24-h urinary oxalate ≤ULN at Month 6, %*§	52	0	52	(23, 70)	CMH	0.0010	Secondary endpoint; FAS
Absolute change in plasma oxalate from baseline to Month 6, µmol/L, LSM†‡	−7.5 (−9.0, −5.9)	1.3 (−1.0, 3.5)	−8.7	(−11.5, −6.0)	MMRM	3.893×10^{-7}	Secondary endpoint; plasma oxalate analysis set

*Corrected for BSA.
†Calculated as the mean change or mean percent change during Months 3–6.
‡Plasma oxalate analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group.
§Data were available for 25 patients in the lumasiran group and 13 patients in the placebo group. ULN was 0.514 mmol/24 h/1.73 m^2.
BSA=body surface area; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; FAS=full analysis set; LSM=least squares mean; MMRM=mixed model for repeated measures; SEM=standard error of the mean; ULN=upper limit of normal
Source: Alnylam, Data on File (ILLUMINATE-A [ALN-GO1-003] CSR[33]); Garrelfs et al. (2021)[8]

The primary endpoint was the difference between lumasiran and placebo treatment in the percent change from baseline in 24-h urinary oxalate (corrected for BSA, mmol/24 h/1.73 m^2) during the double-blind period, analysed using the MMRM method in the FAS.[8,33] A decrease from baseline in urinary oxalate is indicative of a reduction in risk of progression to renal failure, whereas an increase in urinary oxalate excretion is associated with an increase in risk of progression to renal failure.[56]

Lumasiran met the primary endpoint in ILLUMINATE-A: the reduction from baseline in 24-h urinary oxalate (average of Months 3–6 and corrected for BSA) was significantly greater in the lumasiran group than in the placebo group.[8] At 6 months, the LSM (95% CI) change in 24-h urinary oxalate from baseline was −65.4% (−71.3%, −59.5%) in the lumasiran group and −11.8% (−19.5%, −4.1%) in the placebo group (LSM [95% CI] difference: −53.5% (−62.3%, −44.8%); $p=1.685\times10^{-14}$; Figure C3).[8,33]

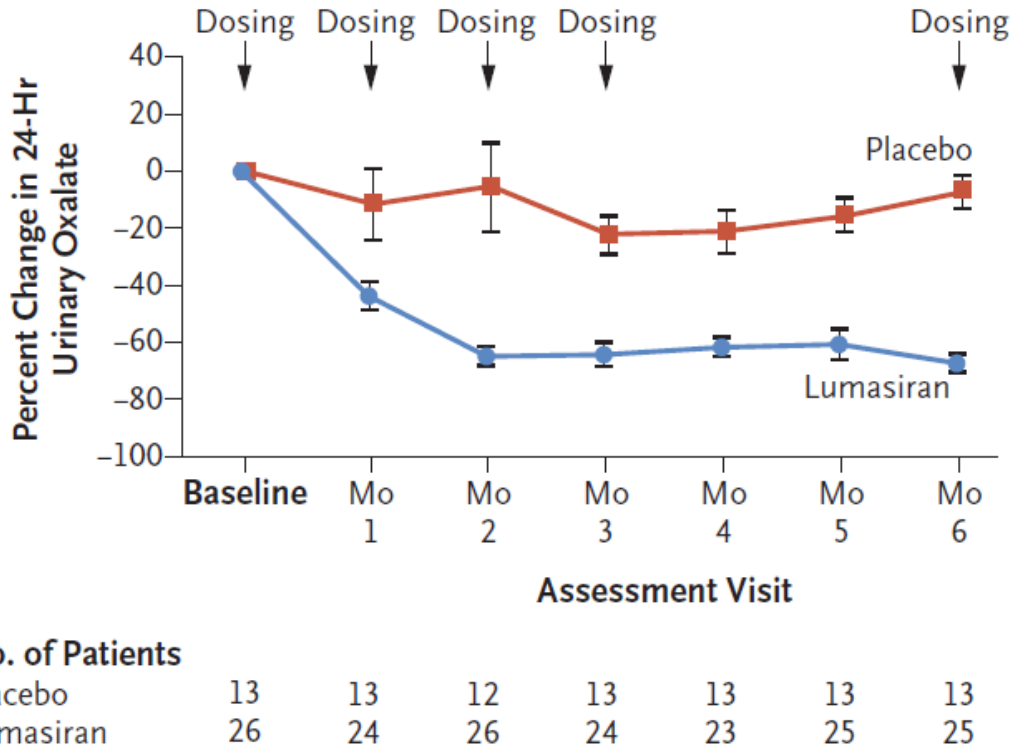

Figure C3. ILLUMINATE-A primary analysis: percent change from baseline in 24-h urinary oxalate (corrected for BSA) to Month 6
BSA=body surface area; Mo=month
Source: Garrelfs et al. (2021)[8]

Additional prespecified sensitivity analyses (involving the use of varied assumptions in the MMRM model) on the primary endpoint resulted in a consistent estimate of the treatment effect of lumasiran compared to placebo on percent change in 24-h urinary oxalate, confirming the robustness of the primary analysis.[8]

The robust improvement from baseline in 24-h urinary oxalate with lumasiran was present across subgroups, including subgroups defined by baseline urinary oxalate levels (24-h urinary oxalate [corrected for BSA] of ≤1.70 versus >1.70 mmol/24 h/1.73 m^2), baseline pyridoxine use, and baseline renal function categories (Figure C4).[8]

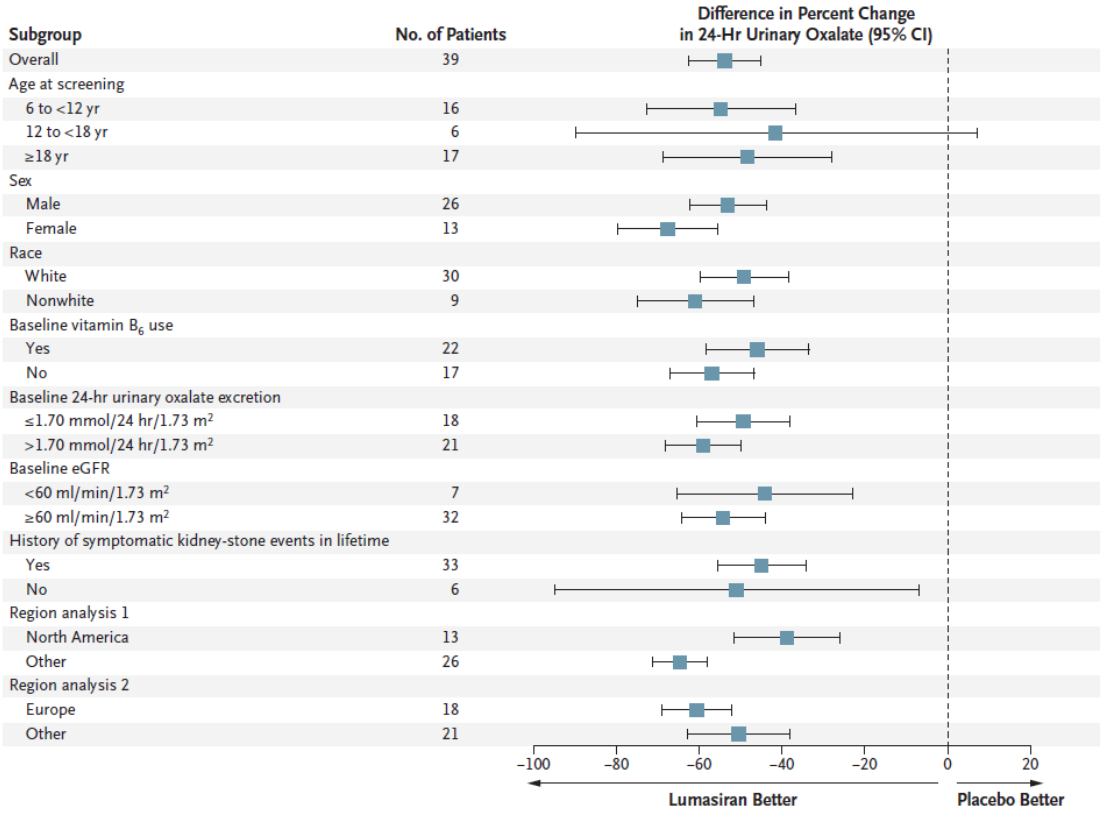

Figure C4. ILLUMINATE-A primary analysis: percent change from baseline in 24-h urinary oxalate in patient subgroups
CI=confidence interval; eGFR=estimated glomerular filtration rate
Source: Garrelfs et al. (2021)[8]

The secondary endpoint of change in absolute 24-h urinary oxalate (corrected for BSA) from baseline to Month 6 was analysed using the same MMRM model as specified for the primary endpoint.[33]

A clinically meaningful and statistically significant absolute reduction in 24-h urinary oxalate was demonstrated with lumasiran compared to placebo from baseline to Month 6 (average of Months 3–6). The LSM (95% CI) absolute change from baseline was −1.24 mmol/24 h/1.73m^2 (−1.37, −1.12) in the lumasiran group and −0.27 mmol/24 h/1.73m^2 (−0.44, −0.10) in the placebo group (LSM [95% CI] difference: −0.98 mmol/24 h/1.73m^2 [−1.18, −0.77]; p=1.225×10^{-11}). Patients treated with lumasiran had a sustained decrease in absolute 24-h urinary oxalate corrected for BSA (Figure C5).[8,33]

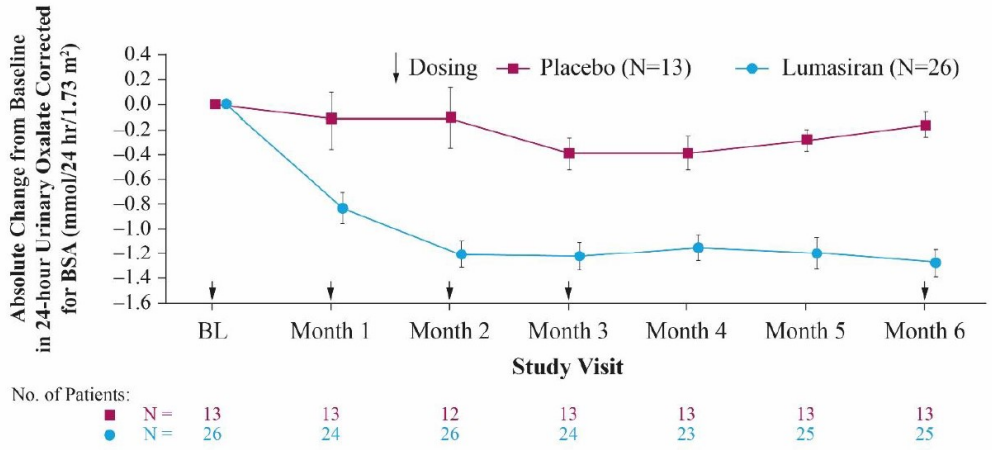

Figure C5. ILLUMINATE-A primary analysis: absolute change from baseline in 24-h urinary oxalate (corrected for BSA) to Month 6
BL=baseline; BSA=body surface area
Source: Garrelfs et al. (2021)[8]

Patients treated with lumasiran demonstrated a sustained decrease in 24-h urinary oxalate:creatinine ratio (another key PD parameter indicative of hepatic oxalate production) from baseline to Month 6 (Figure C6). The LSM (95% CI) percent change across Months 3–6 was −62.5% (−70.7, −54.4) in the lumasiran group and −10.8% (−21.6, −0.0) in the placebo group (LSM [95% CI] difference: −51.8% [−64.3, −39.3]; $p=5.032\times10^{-10}$).[8,33]

Plasma oxalate endpoints were evaluated using the prespecified plasma oxalate analysis set, which included patients who received study drug and had a baseline plasma oxalate level ≥1.5×LLOQ (lower limit of quantitation). This ensured that meaningful reductions in plasma oxalate could be evaluated for the study population without confounding from a floor effect due to the sensitivity of the plasma oxalate assay.[33]

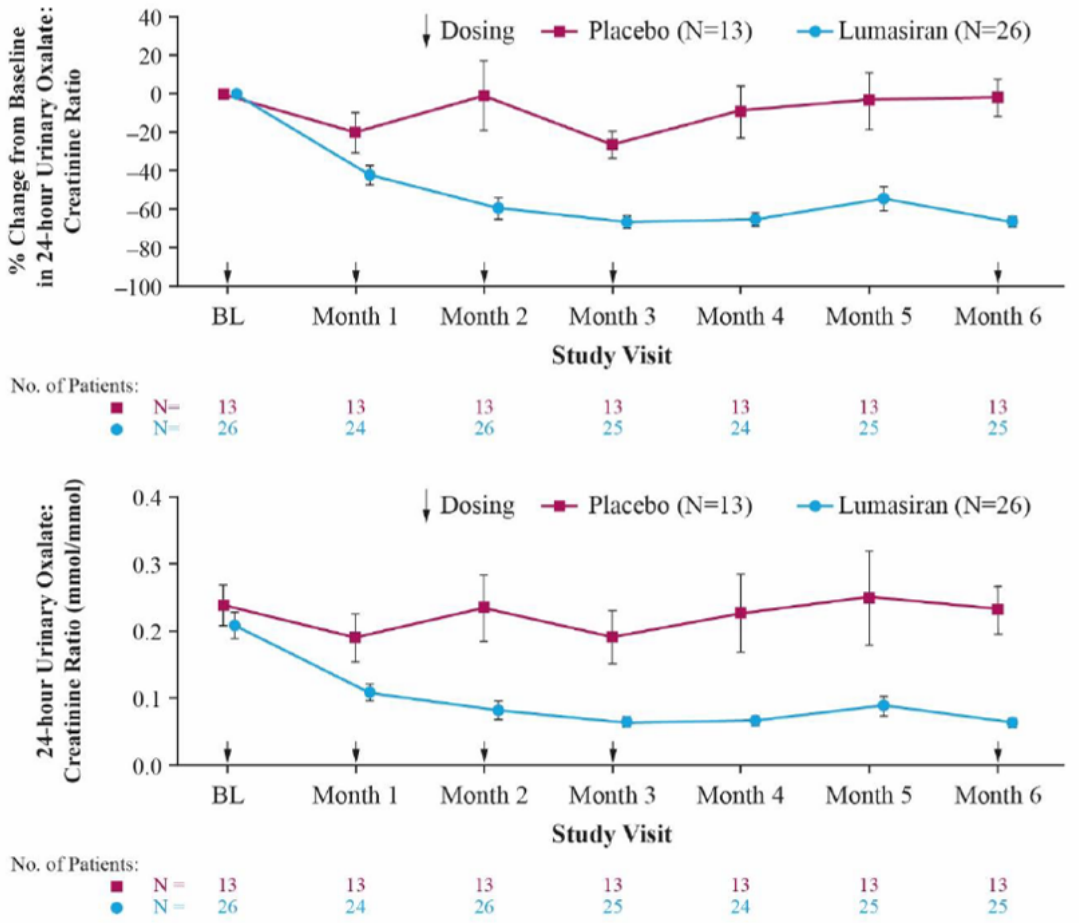

Figure C6. ILLUMINATE-A primary analysis: percent and absolute change from baseline in 24-h urinary oxalate:creatinine ratio (mmol/mmol) to Month 6
BL=baseline
Source: Garrelfs et al. (2021)[8]

Patients in the plasma oxalate analysis set treated with lumasiran demonstrated a statistically significant percent reduction from baseline to Month 6 (average of Months 3–6) in plasma oxalate compared to placebo. The LSM (95% CI) percent change averaged across Months 3–6 was −39.8% (−45.8%, −33.8%) in the lumasiran group and −0.3% (−9.1%, 8.5%) in the placebo group. The LSM (95% CI) difference in percent change was −39.5% (−50.1%, −28.9%; $p=2.862\times10^{-8}$).[8,33]

Patients treated with lumasiran demonstrated a statistically significant reduction from baseline to Month 6 in absolute plasma oxalate compared to placebo. The LSM (95% CI) absolute change in plasma oxalate averaged across Months 3–6 was −7.5 µmol/L (−9.0, −5.9) in the lumasiran group and 1.3 µmol/L (−1.0, 3.5) in the placebo group. The LSM (95% CI) difference in absolute change was −8.7 µmol/L (−11.5, −6.0;

p=3.893×10^{-7}).[8,33] Steady state was achieved at the end of the loading-dose phase in patients treated with lumasiran (Figure C7). The true treatment effect may be underestimated because 14 of 23 (60.9%) lumasiran-treated patients had at least one value that was below LLOQ (and was thus imputed to be equal to LLOQ) at Months 3 through 6. In contrast, none of the placebo-treated patients had a value below LLOQ at Months 3 through 6.[33]

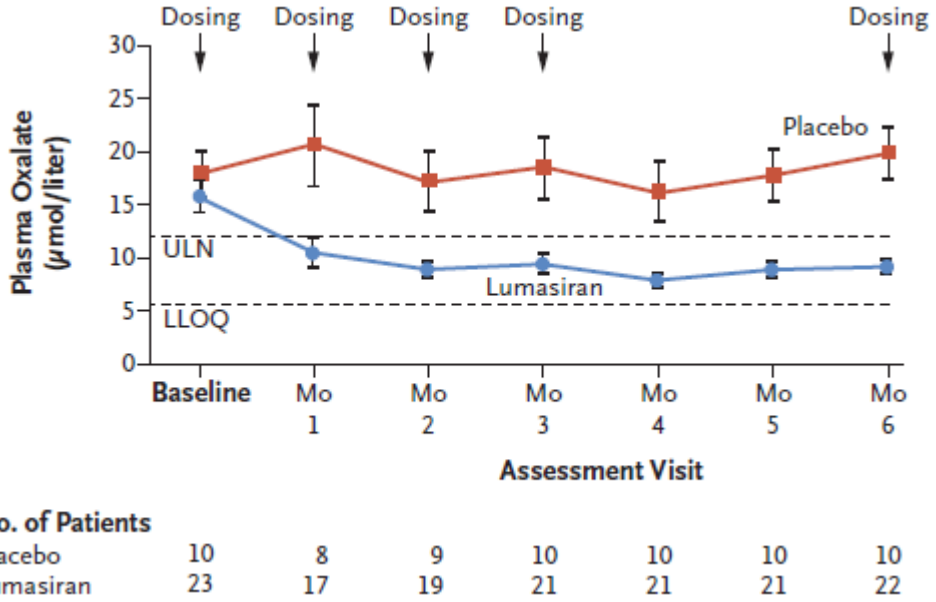

Figure C7. ILLUMINATE-A primary analysis: absolute change from baseline in plasma oxalate (μmol/L) to Month 6

The plasma oxalate analysis set was defined as patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ was 5.55 μmol/L. ULN was 12.11 μmol/L.
LLOQ=lower limit of quantification; Mo=month; ULN=upper limit of normal
Source: Garrelfs et al. (2021)[8]

Significant between-group differences in favour of lumasiran were observed for additional secondary endpoints; for most endpoints these differences were seen starting at the end of the loading-dose phase.[33]

- A higher proportion of lumasiran-treated patients achieved normalisation or near-normalisation (≤1.5×ULN) at Month 6 in 24-h urinary oxalate levels versus placebo-treated patients, which was considered clinically meaningful and statistically significant (p=8.341×10^{-7}). Specifically, 21 of 25 patients (84%) in the lumasiran group achieved normalisation or near-normalisation versus no patients (0%) in the placebo group. Furthermore, in the lumasiran group, this goal was achieved by 100% and 71.4% of patients with lower and higher baseline urinary oxalate levels (≤1.70 and >1.70 mmol/24 h/1.73 m^2), respectively.[8,33]

Similarly, a higher proportion of lumasiran-treated patients achieved normalisation (≤ ULN) at Month 6 in 24-h urinary oxalate levels versus placebo-treated patients, which was considered clinically meaningful and statistically significant (p=0.001). Specifically, 13 of 25 patients (52%) in the lumasiran group achieved normalisation versus no patients (0%) in the placebo group. Furthermore, in the lumasiran group, this goal was achieved by 72.7% and 35.7% of patients with lower and higher baseline urinary oxalate levels (≤1.70 and >1.70 mmol/24 h/1.73 m^2), respectively.[8,33] As expected based on the natural course of the disease, eGFR remained relatively stable for both treatment groups during the 6-month double-blind treatment period (Figure C8). eGFR was not included in the hierarchical testing of secondary endpoints at Month 6 because of this expectation.[8,17]

Exploratory endpoint results were provided for patients with evaluable data after Month 6.

- A sustained decrease was observed from baseline in urinary oxalate:creatinine ratio as assessed by random spot urine collections. Furthermore, steady state in terms of this measure was achieved by the end of the loading-dose phase in patients treated with lumasiran (Figure C9). The timing and magnitude of reduction were consistent with that observed for the primary endpoint (percent change in 24-h urinary oxalate [corrected for BSA]; Figure C3).[8]

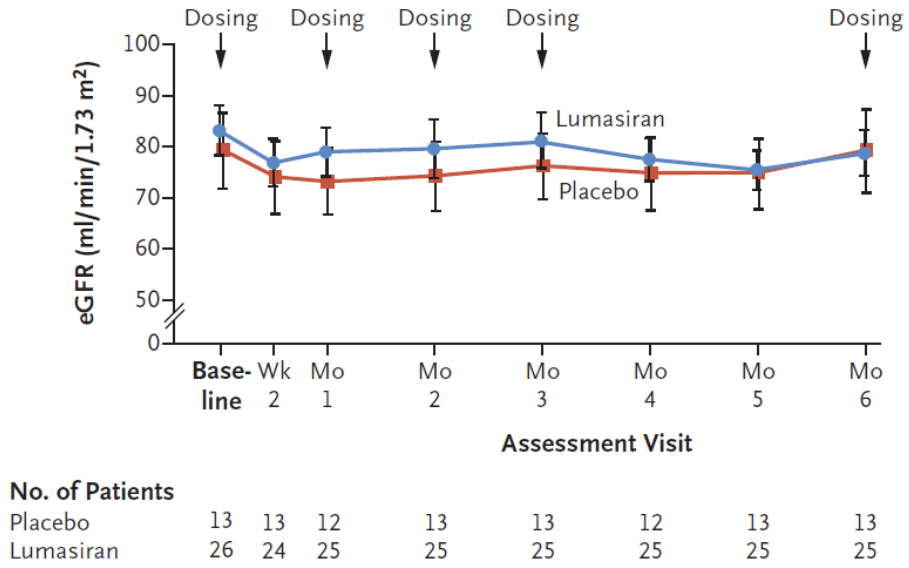

Figure C8. ILLUMINATE-A primary analysis: observed values for eGFR (mL/min/1.73 m²) from baseline to Month 6
eGFR=estimated glomerular filtration rate; Mo=month
Source: Garrelfs et al. (2021)[8]

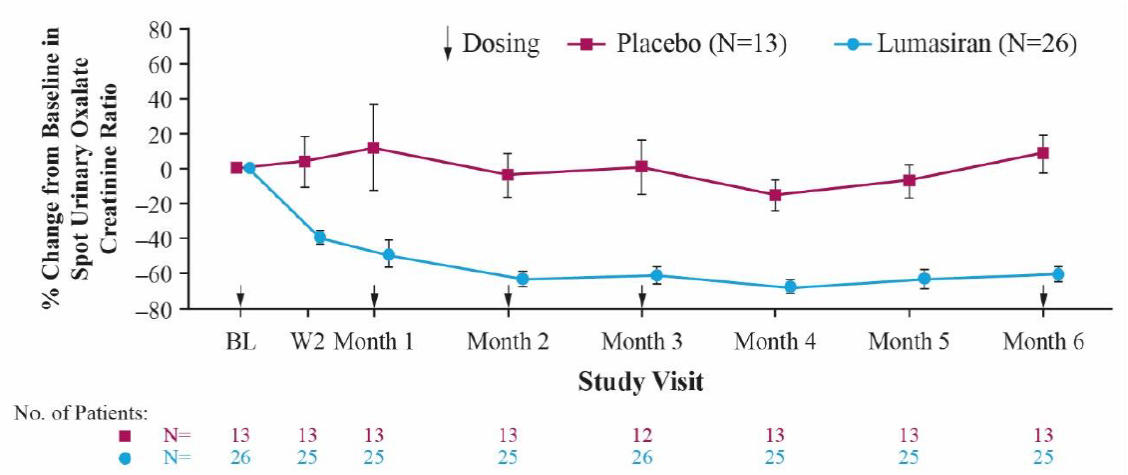

Figure C9. ILLUMINATE-A primary analysis: percent change from baseline in random spot urinary oxalate:creatinine ratio (mmol/mmol) to Month 6
BL=baseline ; W=week
Source: Garrelfs et al. (2021)[8]

- In the lumasiran group, the rate of renal stone events decreased from a calculated rate of 3.19 per person-year (95% CI: 2.57, 3.96) in the 12 months prior to the trial to an observed rate of 1.09 per person-year (95% CI: 0.63, 1.87) during the 6-month double-blind period. In the placebo group, the rates of renal stone events were 0.54 per person-year (95% CI: 0.26, 1.13) in the 12 months prior to the trial and 0.66 per person-year (95% CI: 0.25, 1.76) over the 6-month treatment period.[8]

- Nephrocalcinosis grade improved in three of 22 lumasiran-treated patients compared with none of 12 placebo-treated patients. The nephrocalcinosis grade worsened in no patients in the lumasiran group and in one patient in the placebo group.[8]
- Levels of plasma glycolate and 24-h urinary glycolate:creatinine ratios initially increased and then reached a plateau for patients in the lumasiran group.[8] At Month 6, the mean (standard error of the mean [SEM]) absolute change from baseline in plasma glycolate was 100.4 (12.63) µmol/L in the lumasiran group and 13.8 (13.37) µmol/L in the placebo group. At Month 6, the mean (SEM) absolute change from baseline in 24-h urinary glycolate:creatinine ratio was 0.1903 (0.05786) µmol/L in the lumasiran group and −0.0616 (0.05378) µmol/L in the placebo group.[33] Glycolate level is an additional PD measure that indicates reduction of glycolate oxidase activity, but is less clinically relevant than urinary and plasma oxalate measures as indicators of disease activity.[27]
- The mean (SD) change from baseline to Month 6 in the EQ-5D VAS was [redacted] for the lumasiran group and [redacted] for the placebo group, with higher scores indicating better health status.[33]

None of the study participants tested positive for ADA at baseline. Overall, 1 of 29 (3%) of lumasiran-treated patients (including patients initially randomised to placebo who received lumasiran in the extension period) had a postdose ADA sample during the study that tested positive for ADA. This patient had tested negative for ADA prior to dosing and at Months 1 and 3, and then tested ADA positive at Month 6 (titre of 50). No further ADA samples were collected from this patient prior to data cut-off.[33]

The presence of this low-titre ADA did not impact PK (4-h postdose lumasiran concentrations were similar to those for patients testing negative for ADA) or the magnitude or duration of reduction in 24-h urinary oxalate, and no AEs were reported for this patient during the study.[33]

- The patient had a 66.2% reduction from baseline to Month 6 in 24-h urinary oxalate (baseline vs. Month 6: 1.72 vs. 0.58 mmol/24 h/1.73 m^2).[33]
- Percent change from baseline for 24-h urinary oxalate was maintained at −53.1% to −66.8% for all assessments at or after Month 2.[33]
- Reduction of 24-h urinary oxalate was consistent with results in the overall lumasiran-treated population.[33]

<u>ILLUMINATE-A: Extension Period</u>

Interim results from the ILLUMINATE-A extension period provided a further 6 months of efficacy and safety data for lumasiran in PH1 (i.e., through 12 months of lumasiran treatment for patients originally randomised to lumasiran [lumasiran/lumasiran group] and through 6 months of lumasiran treatment for patients originally randomised to placebo [placebo/lumasiran group]; Figure C10).[10]

Patients initially randomised to lumasiran and who remained on lumasiran had a sustained reduction in 24-h urinary oxalate (corrected for BSA) through Month 12. The mean reduction from baseline to Month 12 in this lumasiran/lumasiran group was 64.1%[10] (vs. 65.4% observed to Month 6 in the primary analysis[8]). Patients initially randomised to placebo and who crossed over to lumasiran (i.e., placebo/lumasiran group) demonstrated a similar time course and magnitude of 24-h urinary oxalate reduction following 6 months of lumasiran treatment; the mean reduction relative to the first dose of lumasiran was 57.3%.[10]

Figure C10. ILLUMINATE-A extension period: percent change from baseline to Month 12 in 24-h urinary oxalate (corrected for BSA)
BL=baseline; BSA=body surface area; M=month; UOx=urinary oxalate
Source: Hulton et al. (2021)[10]

A [redacted] reduction in 24-h urinary oxalate (corrected for BSA) was observed to Month 12 in patients continuing treatment with lumasiran (i.e., patients originally randomised to lumasiran). In these patients, the LSM (SEM) absolute change from baseline was [redacted] at Month 6 and [redacted] at Month 12. In patients in the placebo/lumasiran group, the LSM (SEM) absolute change from baseline was [redacted] at Month 6 and [redacted] at Month 12 following 6 months of lumasiran treatment (Figure C11; Alnylam, Data on File[186]).

Continued treatment with lumasiran maintained the proportion of patients achieving near-normalisation or normalisation (≤1.5×ULN) of 24-h urinary oxalate. A total of 84.0% and 87.5% in the lumasiran/lumasiran group achieved near-normalisation or normalisation at Months 6 and 12, respectively. Similarly, 76.9% in the placebo/lumasiran group achieved near-normalisation or normalisation at Month 12, after 6 months of treatment with lumasiran[10] (compared to 0% at the time of crossover from placebo to lumasiran at Month 6[8,10]).

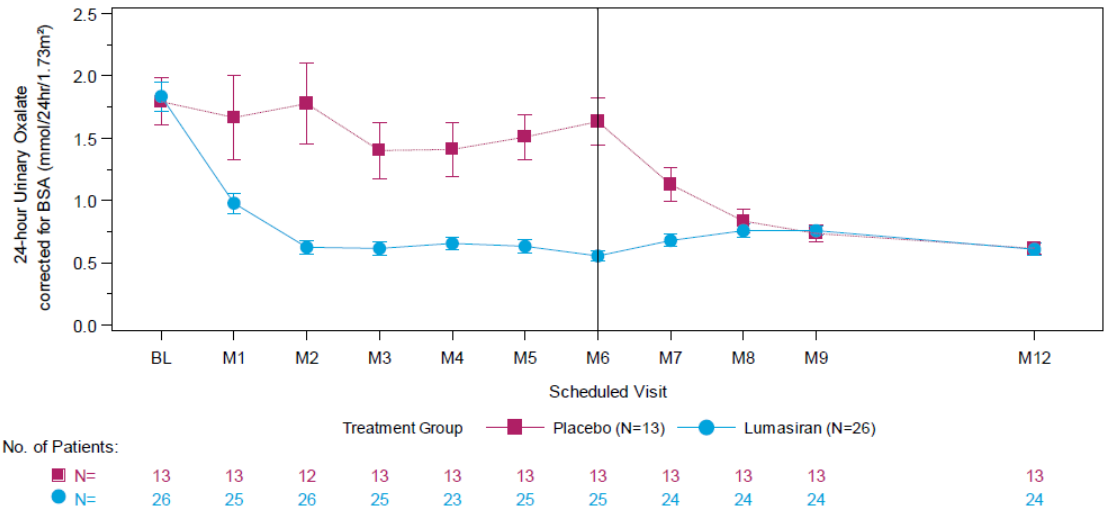

Figure C11. ILLUMINATE-A extension period: absolute change from baseline to Month 12 in 24-h urinary oxalate (corrected for BSA)
BL=baseline; BSA=body surface area; M=month
Source: Hulton et al. (2021)[10]

Continued treatment with lumasiran during the extension period maintained the reduction in 24-h urinary oxalate:creatinine ratio observed at Month 6 (sensitivity analysis excluding urine creatinine samples that were inadequately processed; Figure C12). The LSM (SEM) percent change from baseline was −66.2% (2.8%) at Month 6 and −62.9% (3.1%) at Month 12 in the lumasiran/lumasiran group. Placebo-crossover patients exhibited a sustained decrease in 24-h urinary oxalate:creatinine ratio following 6 months of lumasiran treatment. The LSM (SEM) percent change from baseline was −54.3% (4.7%) at Month 12, after 6 months of lumasiran treatment, in the placebo/lumasiran group.[10]

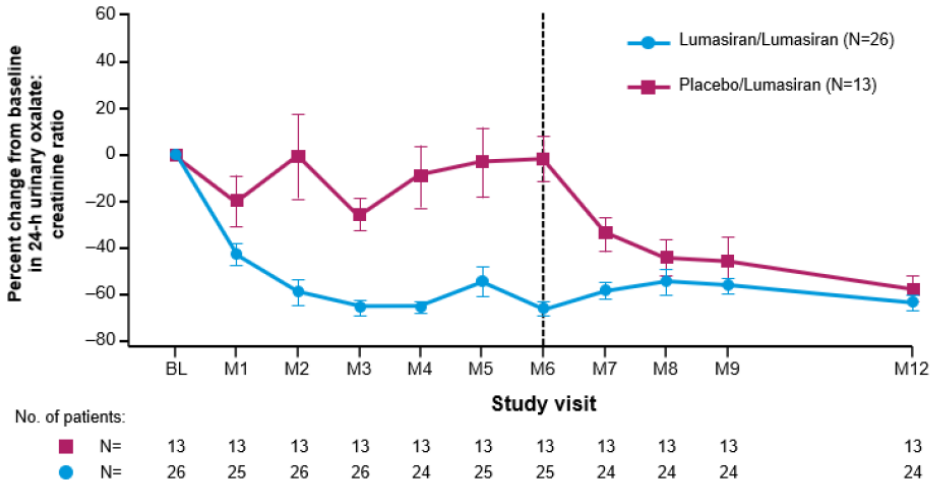

Figure C12. ILLUMINATE-A extension period: percent change from baseline to Month 12 in 24-h urinary oxalate:creatinine ratio (mmol/mmol)
Results of a sensitivity analysis excluding urine creatinine samples that were inadequately processed.
BL=baseline; M=month
Source: Hulton et al. (2021)[10]

Sustained percent and absolute reductions in plasma oxalate were maintained to Month 12 in patients continuing treatment with lumasiran. The LSM (SEM) percent change from baseline was −36.9% (4.9%) at Month 6 and −35.0% (6.1%) at Month 12 in the lumasiran/lumasiran group (Figure C13).[10] The LSM (SEM) absolute change from baseline was [redacted] at Month 6 and [redacted] at Month 12 (Figure C14) (Alnylam, Data on File[186]).

Reduction in plasma oxalate was replicated by placebo/lumasiran crossover patients after 6 months of lumasiran treatment, at study Month 12 (Figure C13 and Figure C14). The LSM (SEM) percent and absolute changes from baseline were −48.9% (5.1%)[10] and [redacted], respectively, at Month 12 (compared with [redacted] and [redacted], respectively, at Month 6, upon completion of placebo treatment; Alnylam, Data on File[186,187]). Note that these differences from baseline are calculated based on actual values at the prespecified timepoints, whereas the primary analysis averaged values over a 3-month period (Months 3–6).

[redacted]

Figure C13. ILLUMINATE-A extension period: percent change from baseline to Month 12 in plasma oxalate levels (µmol/L)
The plasma oxalate analysis set was defined as patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ was 5.55 µmol/L. ULN was 12.11 µmol/L.
BL=baseline; LLOQ=lower limit of quantification; M=month
Source: Alnylam, Data on File[186]

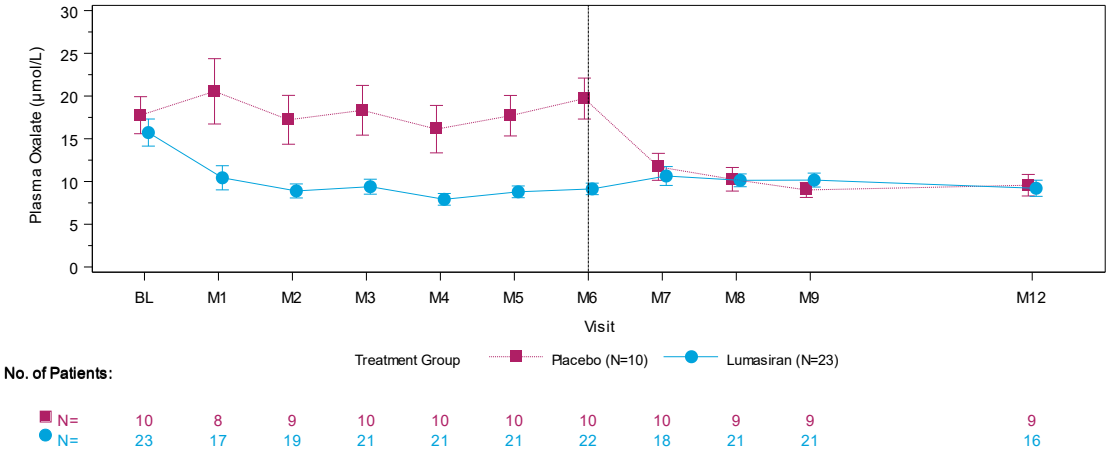

Figure C14. ILLUMINATE-A extension period: absolute change from baseline to Month 12 in plasma oxalate levels (µmol/L)
The plasma oxalate analysis set was defined as patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ was 5.55 µmol/L. ULN was 12.11 µmol/L.
BL=baseline; BSA=body surface area; LLOQ=lower limit of quantification; M=month; ULN=upper limit of normal
Source: Hulton et al. (2021)[10]

eGFR remained stable in all patients through Month 12, as shown in Figure C15.[10]

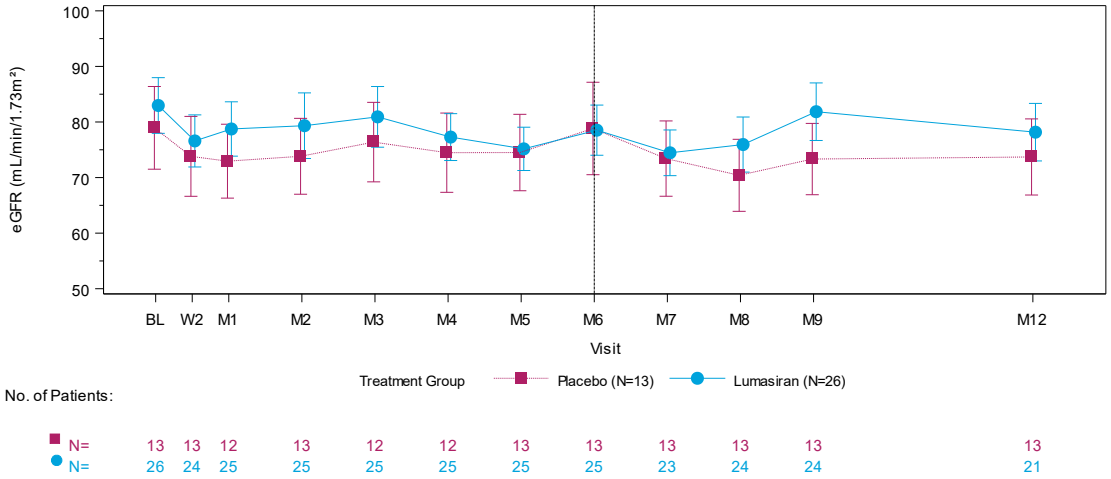

Figure C15. ILLUMINATE-A extension period: observed values for eGFR (mL/min/1.73 m²) from baseline to Month 12
BL=baseline; eGFR=estimated glomerular filtration rate; M=month; W=week
Source: Hulton et al. (2021)[10]

Renal stone event data continue to be collected during the ILLUMINATE-A extension period. In the lumasiran/lumasiran group, the reduction in renal stone frequency observed in the double-blind period was maintained with a further 6 months of lumasiran treatment. The renal stone event rates were 3.19 events per person-year in the 12 months prior to the study, 1.09 events from baseline to Month 6, and 0.85 events from Month 6 to Month 12. In the placebo/lumasiran group, the renal stone event rates were 0.54 events per person-year in the 12 months prior to the study, 0.66 events during the 6-month placebo-treatment period, and 0.17 events during the ensuing 6 months of lumasiran treatment (Figure C16).[10]

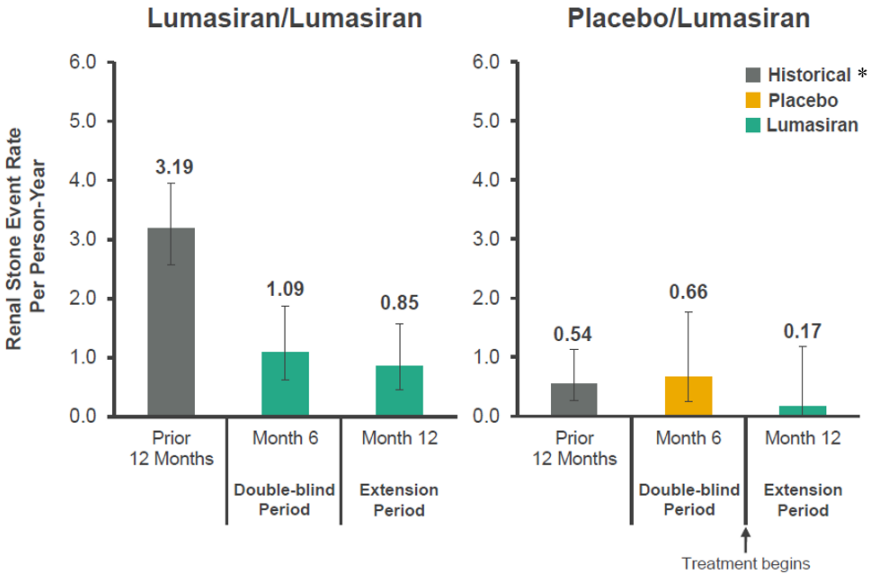

Figure C16. ILLUMINATE-A extension period: renal stone events following 6–12 months of treatment
*Patient-reported history of renal stone events.
Source: Hulton et al. (2021)[10]

Following 6 months of placebo treatment (N=13), nephrocalcinosis grade improved in 0% of patients, remained stable in 85%, and worsened in 8%, relative to baseline (data were unavailable for 8%). In contrast, in patients initially randomised to receive lumasiran for 6 months (n=24), nephrocalcinosis grade improved in 13%, remained stable in 83%, and worsened in 0%, relative to baseline (data were unavailable for 4%). Continued treatment with lumasiran for a further 6 months resulted in an increase in the proportion of patients

experiencing improvement in nephrocalcinosis. In patients who received lumasiran for 12 months (n=24), nephrocalcinosis grade improved in 46%, remained stable in 17%, and worsened in 13%, relative to baseline (data were unavailable for 25%).[10] Of those who improved, 73% (8/11) improved in both kidneys after 12 months of lumasiran treatment (Figure C17).[68]

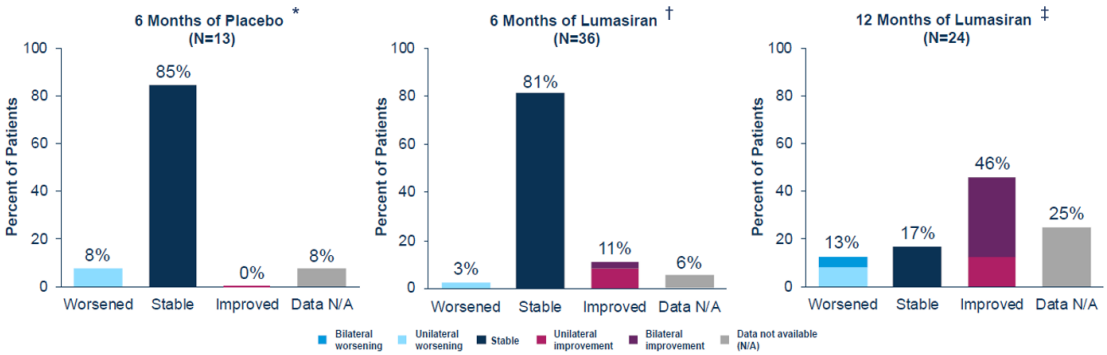

Figure C17. ILLUMINATE-A extension period: nephrocalcinosis change from baseline during placebo, or 6 or 12 months lumasiran treatment

*Patients originally randomised to placebo.
†Includes first 6 months of treatment for patients originally randomised to lumasiran (worsened 0%, stable 83%, improved 13%, unavailable 4%) and the first 6 months of lumasiran treatment for patients originally randomised to placebo (shown in the figure).
‡Includes 12 months of treatment for patients originally randomised to lumasiran.
N/A=not available
Source: Hulton et al. (2021)[10]; Sas et al. (2021)[68]

ILLUMINATE-B: Primary Analysis Period

The clinical efficacy of lumasiran was evaluated in the single-arm ILLUMINATE-B trial in patients <6 years of age with PH1 and relatively intact renal function. ILLUMINATE-B assessed the efficacy of lumasiran on several clinically meaningful and patient-relevant outcomes, including the impact of lumasiran on urinary and plasma oxalate, renal function, nephrocalcinosis, and the frequency of renal stone events.

Table C11 summarises the ILLUMINATE-B efficacy results for the 18 patients who completed the 6-month primary analysis period.[9,67]

Table C11. Outcomes from published and unpublished studies – ILLUMINATE-B

Reference	ALN-GO1-004				
Study name	ILLUMINATE-B, NCT03905694, EudraCT 2018-004014-17				
Size of study groups	Lumasiran (n=18)				
Study duration	60 months				
Outcome Name (unit)	**Effect Size**		**Statistical test**		Comments
	Value	**95% CI**	**Type**	**p value**	
Percent change in spot urinary oxalate: creatinine ratio from baseline to Month 6, LSM	–72.0	(–77.5, –66.4)	MMRM	4.256×10^{-21}	Primary endpoint; EAS; using three sensitivity analyses, a clinically meaningful and statistically significant change was demonstrated with lumasiran from baseline
Absolute change in spot urinary oxalate:creatinine ratio from baseline to Month 6, mmol/mmol, LSM	–0.49	(–0.52, –0.46)	MMRM	NR	Secondary endpoint; EAS; statistical analysis was performed similarly to the primary endpoint
Percent change in plasma oxalate from baseline to Month 6, %, LSM*	–31.7	(–39.5, –23.9)	MMRM	NR	Secondary endpoint; EAS; statistical analysis was performed similarly to the primary endpoint
Absolute change in plasma oxalate from baseline to Month 6, µmol/L, LSM*	–5.2	(–6.2, –4.2)	MMRM	NR	Secondary endpoint; EAS; statistical analysis was performed similarly to the primary endpoint
Proportion of patients with spot urinary oxalate excretion ≤ULN at Month 6, %‡	6	NR	NA	NA	Secondary endpoint; EAS; descriptive statistics
Proportion of patients with spot urinary oxalate excretion ≤1.5×ULN at Month 6, %‡	50	NR	NA	NA	Secondary endpoint; EAS; descriptive statistics
Change from baseline in eGFR (ml/min/1.73m^2), mean (SD) *	−0.3 (15)	NR	NA	NA	Secondary endpoint; EAS; descriptive statistics

*In patients with baseline plasma oxalate ≥1.5× lower limit of quantitation (n=13; mean, 15.6; range, 8.7–30.6 µmol/L at baseline), LSM reduction from the average of Month 3 to Month 6 was 39.4% (95% CI, 29.3%, 49.4%) or 6.9 µmol/L (95% CI, 5.5, 8.3 µmol/L).
†Age-dependent ULN
‡N=16. eGFR was only calculated in patients ≥12 months of age at baseline.
CI=confidence interval; EAS=efficacy analysis set; eGFR=estimated glomerular filtration rate; LSM=least squares mean; MMRM=mixed model for repeated measures; NA=not applicable; NR=not reported; PK=pharmacokinetic; SD=standard deviation; SEM=standard error of the mean; ULN=upper limit of normal
Source: Alnylam Data on File (ILLUMINATE-B [ALN-GO1-004] CSR 2[79]; ILLUMINATE-B [ALN-GO1-004] SAP[180]); Sas et al. (2021)[9]

For the primary endpoint, a clinically meaningful percent change from baseline to Month 6 (average of Months 3–6) was observed in the spot urinary oxalate:creatinine ratio (Figure C18). The LSM (95% CI) percent change in spot urinary oxalate:creatinine ratio was −72.0% (−77.5%, −66.4%); $p=4.256\times10^{-21}$.[9,79]

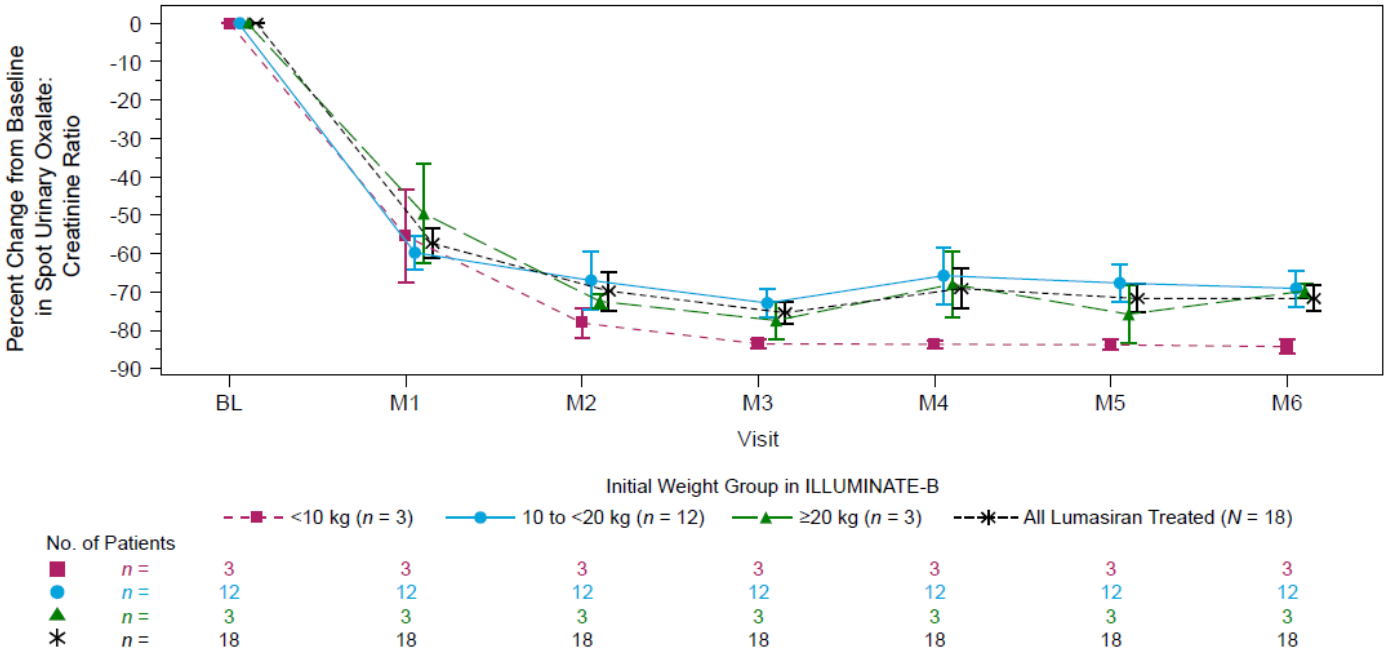

Figure C18. ILLUMINATE-B primary analysis: percent change from baseline to Month 6 in spot urinary oxalate:creatinine ratio
BL=baseline; M=month; SEM=standard error of the mean
Source: Sas et al. (2021)[9,67]

There was a sustained reduction in spot urinary oxalate:creatinine ratio across all weight groups. Mean observed percent change from baseline to Month 6 in spot urinary oxalate:creatinine ratio was −71.7%. Patients weighing <10 kg [n=3], 10 to <20 kg [n=12], and ≥20 kg [n=3] demonstrated changes of −84.2%, −69.1%, and −69.7%, respectively, from baseline to Month 6.[67,79]

The robustness of the reduction in spot urinary oxalate:creatinine ratio was confirmed via:[9]

- Sensitivity analyses, which focused on the percent change from baseline in age-dependent ULN ratio (defined as spot urinary oxalate:creatinine ÷ age-specific ULN). The LSM (95% CI) change in ULN ratio from baseline to Month 6 (average from Month 3 to Month 6) was −70.2% (−75.6%, −64.8%). The magnitude of reduction was similar to that seen in the primary analysis, indicating that the impact of natural decline in spot urinary oxalate:creatinine ratio with age was minimal compared to the lumasiran treatment effect
- 24-h urinary analyses:
  - 24-h urinary oxalate (corrected for BSA) was available for two patients. The percent changes from baseline to Month 6 were −74.0% and −62.8%, respectively, for these two patients
  - 24-h urinary oxalate:creatinine ratio was available for three patients. The mean percent change from baseline was −69.0% for these patients

Secondary endpoints in ILLUMINATE-B (from baseline to Month 6) included absolute change in spot urinary oxalate:creatinine ratio (mmol/mmol), percent and absolute change in plasma oxalate, and change from baseline in eGFR. The proportion of patients achieving near-normalisation and normalisation of urinary oxalate excretion was also reported.[9]

Treatment with lumasiran resulted in a sustained absolute reduction in oxalate:creatinine ratio from baseline to Month 6 (average of Months 3–6; Figure C19). The LSM (95% CI) absolute change in spot urinary oxalate:creatinine ratio was −0.49 mmol/mmol (−0.52, −0.46).[9] Mean changes of −1.1474, −0.3684, and −0.3066 mmol/mmol from baseline to Month 6 were demonstrated in patients weighing <10 kg, 10 to <20 kg, and ≥20 kg, respectively.[79]

Nine of 18 patients (50%) achieved near-normalisation (≤1.5×ULN) in spot oxalate:creatinine ratio at Month 6, including one patient (6%) who achieved normalisation (≤ULN).[9]

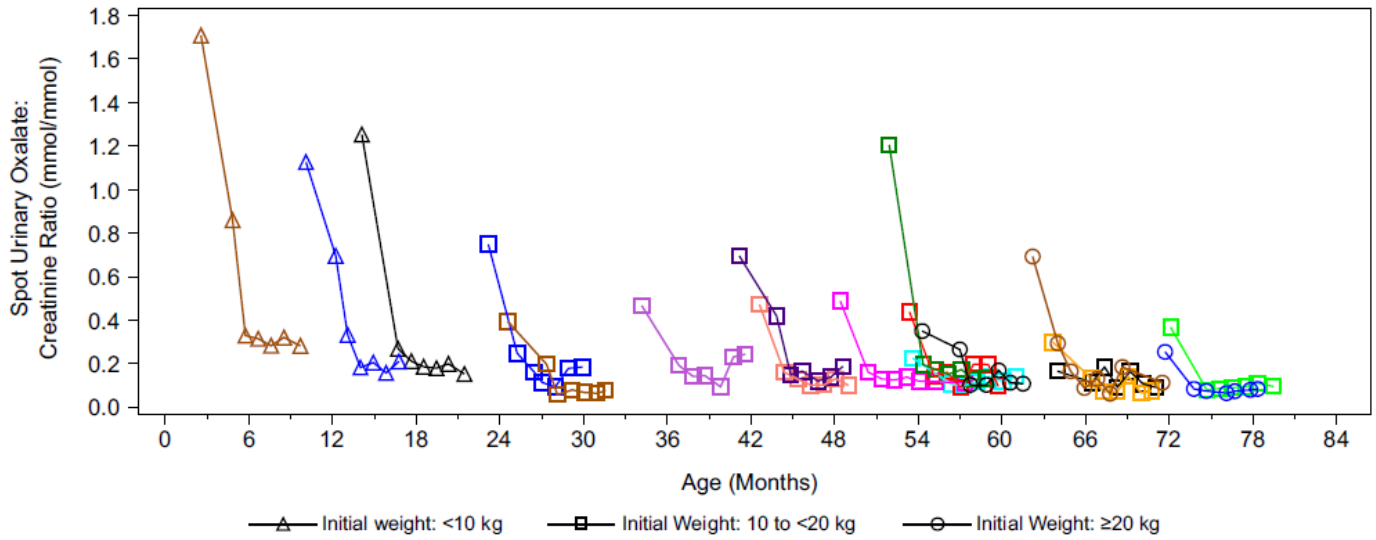

Figure C19. ILLUMINATE-B primary analysis: absolute change in spot urinary oxalate:creatinine ratio (mmol/mmol) by age
Actual values for spot urinary oxalate:creatinine ratio are displayed by patient age for baseline and for each available timepoint during the primary analysis period.
Source: Sas et al. (2021)[9]

The LSM (95% CI) percent change in plasma oxalate from baseline to Month 6 (average of Months 3–6) was −31.7% (−39.5%, −23.9%), while the absolute change was −5.2 µmol/L (−6.2, −4.2). In patients with a plasma oxalate level of ≥1.5×LLOQ [n=13] at baseline, the LSM (95% CI) percent change to Month 6 (average of Months 3–6) was −39.4% (−49.4%, −29.3%), while the absolute change was −6.9 µmol/L (−8.3, −5.5).[9]

Renal function in the youngest patients generally followed the expected trajectory for healthy children of similar ages. The mean (SD) change from baseline to Month 6 was −0.3 (15) mL/min/1.73 m^2.[9]

Low rates of renal stone events in ILLUMINATE-B patients were unchanged between the 12-month historical recall and the first 6 months of treatment. A total of four renal stone events were reported by three patients in the 12 months prior to providing informed consent (0.24 event rate per person-year). Two patients each had a single postbaseline mild renal stone event within the 6-month treatment period (0.24 event rate per person-year).[9,67]

Treatment with lumasiran resulted in reversal of nephrocalcinosis in some patients. In ILLUMINATE-B, 78% (14/18) of patients had nephrocalcinosis at baseline. Nephrocalcinosis grade improved in 44% (8/18) after 6 months of lumasiran treatment; three patients had bilateral improvement and five patients had unilateral improvement. No patients worsened, while the nephrocalcinosis grade remained unchanged in 56% (10/18) (Figure C20).[9,67,68]

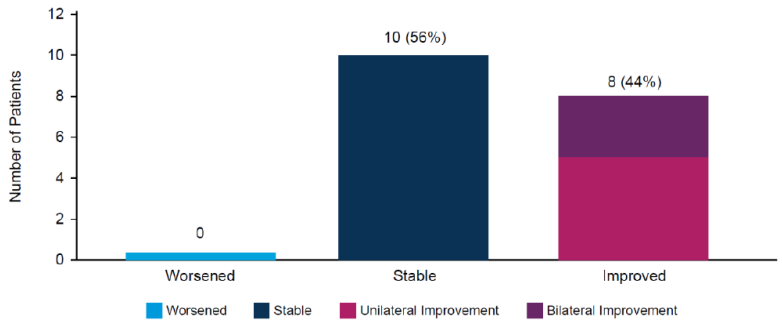

Figure C20. ILLUMINATE-B primary analysis: nephrocalcinosis change from baseline to Month 6
N/A=not available
Source: Sas et al. (2021)[9]

Lumasiran led to clinically meaningful and sustained reductions in urinary oxalate excretion across all weight ranges in infants and young children enrolled in ILLUMINATE-B.[9,79] Overall, the treatment effect observed for urinary oxalate and plasma oxalate is consistent with that seen in the placebo-controlled ILLUMINATE-A RCT, indicating similar efficacy and suitable dosing regimens across all ages of patients with PH1. The clinical benefit of oxalate reduction is further supported by the low incidence of renal stone events and reversal of nephrocalcinosis.[8,9]

ILLUMINATE-B: Extension Period

Interim results from the ILLUMINATE-B extension period demonstrated that a clinically meaningful percent change in spot urinary oxalate:creatinine ratio was maintained through 12 months of treatment with lumasiran. The mean percent reduction from baseline at Month 12 was [redacted]. The mean absolute reduction was [redacted] (Figure C21) (Alnylam, Data on File[188]).

[redacted]

Figure C21. ILLUMINATE-B extension period: percent change from baseline spot urinary oxalate:creatinine ratio (mmol/mmol)
BL=baseline; M=month
Source: Alnylam, Data on File[188]

The proportion of patients achieving near-normalisation (≤1.5×ULN) and normalisation (≤ULN) in spot urinary oxalate:creatinine ratio observed at Month 6 was [redacted]. At Month 12, [redacted] patients achieved near-normalisation and normalisation, respectively (compared with 9/18 [50%] and 1/18 [6%], respectively, at Month 6[67]) (Alnylam, Data on File[188]).

Plasma oxalate reductions observed at Month 6 were also [redacted] with continued lumasiran treatment (Figure C22). At Month 12, the mean (SD) percent change from baseline plasma oxalate was [redacted] vs. LS mean [95% CI] percent change of –31.7% [–39.5%, –23.9%] at Month 6[67]). At Month 12, the mean (SD) absolute change from baseline plasma oxalate was [redacted] (vs. mean [SD] absolute change of [redacted] at Month 6) (Alnylam, Data on File[188]).

Figure C22 ILLUMINATE-B extension period: percent change from baseline plasma oxalate
Data are expressed as mean (SEM).
BL=baseline; M=month; SEM=standard error of the mean
Source: Alnylam, Data on File[188]

The eGFR [redacted] of continued treatment with lumasiran. [redacted] patients experienced at least one renal stone event. The rate of renal stone events was [redacted] between Month 6 and Month 12 (vs. 0.24 events from baseline to Month 6 and 0.24 events in the 12 months prior to providing informed consent[67,68]). Of the [redacted] patients with renal ultrasound at baseline and Month 12, [redacted] patients had bilateral improvement, [redacted] patients had unilateral improvement, and [redacted] patients remained unchanged relative to baseline nephrocalcinosis grade (Alnylam, Data on File[188]). This compared with bilateral improvement in three patients, unilateral improvement in five patients, and no change in 10 patients at Month 6 relative to baseline nephrocalcinosis grade (in 18 patients with ultrasound at baseline and Month 6).[68]

ILLUMINATE-C: Primary Analysis Period

The clinical efficacy of lumasiran in patients of all ages with advanced renal disease and genetically confirmed PH1 diagnosis was evaluated in the ILLUMINATE-C single-arm, open-label study.[11,64] Table C12 summarises the clinical efficacy outcomes in patients not yet on dialysis (Cohort A) and patients on dialysis (Cohort B).

Table C12. Outcomes from published and unpublished studies – ILLUMINATE-C

Reference	ALN-GO1-005						
Study name	ILLUMINATE-C, NCT04152200, EudraCT 2019-001346-17						
Size of study groups	Lumasiran Cohort A—patients not yet on dialysis (n=6) Lumasiran Cohort B—patients on dialysis (n=15)						
Study duration	60 months (6-month primary analysis period plus 54-month extension)						
Outcome name (unit)	**Effect size Cohort A**		**Effect size Cohort B**		**Statistical test**		Comments
	Value	**95% CI**	**Value**	**95% CI**	**Type**	**p value**	
Percent change in plasma oxalate from baseline to Month 6, %*	–33.33	(–81.82, 15.16)	–42.43	(–50.71, –34.15)	MMRM	Cohort A: [redacted] Cohort B: [redacted]	Primary endpoint; FAS; statistical analyses were primarily descriptive
Absolute change in plasma oxalate from baseline to Month 6, µmol/L*	–35.28	(–56.32, –14.24)	–48.33	(–55.85, –40.80)	MMRM	NA	Secondary endpoint; FAS; statistical analyses were primarily descriptive
Percent change in plasma oxalate AUC (0–24 h) between dialysis sessions from baseline to Month 6, %	NA	NA	–41.4	(–51.0, –31.8)	MMRM	NA	Secondary endpoint; Cohort B FAS
Percent change in BSA-corrected 24-h urinary oxalate from baseline to Month 6, %†	–10.557	(–31.986, 10.871)	NA	NA	MMRM	NA	Secondary endpoint; Cohort A FAS
Absolute change in BSA-corrected 24-h urinary oxalate from baseline to Month 6, mmol/24 h/1.73 m^2 †	–0.533	(–0.888, –0.179)	NA	NA	MMRM	NA	Secondary endpoint; Cohort A FAS
Percent change in spot urinary oxalate:creatinine ratio from baseline to Month 6, %	–39.51	(–64.13, –14.90)	NA	NA	MMRM	NA	Secondary endpoint; Cohort A FAS
Absolute change in spot urinary oxalate:creatinine ratio from baseline to Month 6, mmol/mmol	–0.188	(–0.229, –0.147)	NA	NA	MMRM	NA	Secondary endpoint; Cohort A FAS

*Predialysis plasma oxalate in Cohort B.
†Based on a subgroup of urine-producing patients in Cohort A (n=5).
AUC=area under the curve; BSA=body surface area; CI=confidence interval; FAS=full analysis set; MMRM=mixed model for repeated measures; NA=not applicable
Source: Alnylam, Data on File (ILLUMINATE-C [ALN-GO1-005] CSR 1[64]; Michael et al. (2021)[11]

The primary endpoint was percent change in plasma oxalate from baseline to Month 6, which was measured as predialysis plasma oxalate in Cohort B. At 6 months, the LSM (95% CI) change in plasma oxalate from baseline was −33.33% (−81.82%, 15.16%) in Cohort A. The LSM (95% CI) change in predialysis plasma oxalate from baseline was −42.43% (−50.71%, −34.15%) in Cohort B. A clinically meaningful magnitude of percent plasma oxalate reduction from baseline to Month 6 was observed in both cohorts, as shown in Figure C23.[11]

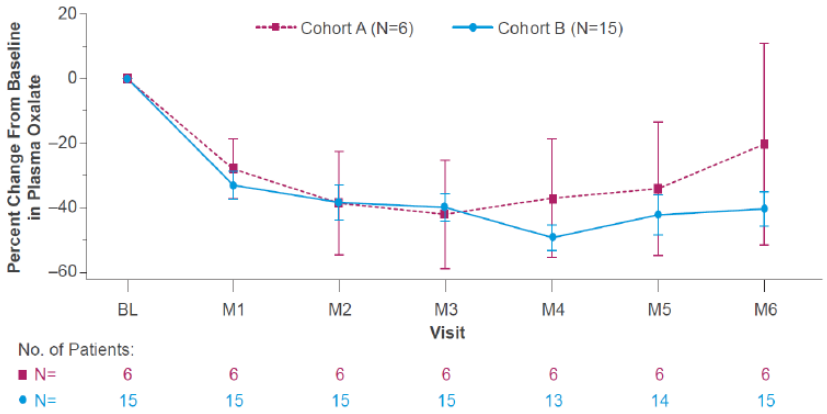

Figure C23. ILLUMINATE-C primary analysis: percent change in plasma oxalate from baseline to Month 6
Data are expressed as least squares mean (SEM), estimated by MMRM.
BL=baseline; M=month; MMRM=mixed model for repeated measure; SEM=standard error of the mean
Source: Alnylam Pharmaceuticals[189]

A robust reduction in plasma oxalate was observed irrespective of patients' baseline characteristics in the larger Cohort B, as demonstrated by the subgroup analysis of the primary endpoint (Figure C24). Note that baseline plasma oxalate values were higher in Cohort B; median (range) values were 57.9 (22.7–134.0) µmol/L in Cohort A and 103.7 (56.3–167.0) µmol/L in Cohort B (Table C7).[11]

Cohort A (N=6)

Cohort B (N=15)

Figure C24. ILLUMINATE-C primary analysis: Forest plots of percent change in plasma oxalate from baseline to Month 6 in patient subgroups

Estimated by MMRM.
CI=confidence interval; LS=least squares; MMRM=mixed model for repeated measure
Source: Alnylam Data on File (ILLUMINATE-C [ALN-GO1-005] CSR 1)[64]

The secondary endpoint of absolute change in plasma oxalate from baseline to Month 6 (average of Months 3–6) was analysed in both cohorts. The LSM (95% CI) absolute change from baseline was −35.28 µmol/L (−56.32, −14.24) in Cohort A and −48.33 µmol/L (−55.85, −40.80) in Cohort B.[11]

The secondary endpoint of percent change from baseline to Month 6 (average of Months 3–6) in plasma oxalate $AUC_{(0–24\ h)}$ measured between dialysis sessions was assessed in patients receiving dialysis (i.e., Cohort B). This endpoint is used to evaluate the effect of lumasiran on patients' systemic exposure to plasma oxalate between dialysis sessions. The LSM (95% CI) percent change from baseline was −41.4% (−51.0%, −31.8%).[11]

The remaining secondary efficacy endpoints were assessed in Cohort A. With regard to these endpoints, treatment with lumasiran was associated with a reduction in:[11]

- BSA-corrected 24-h urinary oxalate from baseline to Month 6 (average of Months 3–6). The LSM (95% CI) percent change from baseline was −10.557% (−31.986%, 10.871%). The LSM (95% CI) absolute change from baseline was −0.533 mmol/24 h/1.73 m^2 (−0.888, −0.179)

- Spot urinary oxalate:creatinine ratio from baseline to Month 6 (average of Months 3–6). The LSM (95% CI) percent change from baseline was −39.51% (−64.13%, −14.90%). The LSM (95% CI) absolute change from baseline was −0.188 mmol/mmol (−0.229, −0.147)

Echocardiograms were performed to assess the effect of lumasiran on cardiac outcomes driven by systemic oxalosis (exploratory endpoint). Parameters assessed included those associated with cardiac structure and function (e.g., left ventricular ejection fraction [LVEF] and global longitudinal strain [GLS]). In Cohort A, [redacted] who had an abnormal (<55%) LVEF at baseline subsequently experienced an important improvement (defined as ≥5% increase if <55% at baseline) following 6 months of lumasiran treatment. In Cohort B, [redacted] had an abnormal LVEF at baseline, of which [redacted] subsequently experienced an important improvement by Month 6.[64]

In Cohort A, [redacted] who had an abnormal (<15%) GLS as measured by echocardiogram at baseline subsequently experienced an important improvement (defined as ≥2% increase in absolute value from baseline) following 6 months of lumasiran treatment. In Cohort B, [redacted] had an abnormal GLS at baseline and [redacted] subsequently experienced an important improvement by Month 6.[64]

In Cohort A, [redacted] reported at least one renal stone event in the year prior to consent, and [redacted] patients reported at least one renal stone event during 6 months of treatment with lumasiran. The per-patient-year rate of renal stone events was [redacted] following 6 months of lumasiran, compared with [redacted] in the year prior to consent. In Cohort B, [redacted] reported at least one renal stone event in the year prior to consent and [redacted] reported events following 6 months of lumasiran. The per-patient-year rate of renal stone events was [redacted] prior to consent and [redacted] while on study drug, which is as expected given that patients were on haemodialysis therapy.[64]

Of the [redacted] patients in Cohort A with available renal ultrasound data at baseline and Month 6, [redacted] patients had unilateral improvement, [redacted] had bilateral improvement, [redacted] had bilateral worsening, and [redacted] had no change in nephrocalcinosis grade following 6 months of lumasiran treatment. Of the [redacted] patients in Cohort B with available renal ultrasound data at baseline at Month 6, [redacted] patient had unilateral improvement, [redacted] had bilateral improvement, and [redacted] patients had no change in nephrocalcinosis grade following 6 months of lumasiran treatment.[64]

9.6.2 Justification of the inclusion of outcomes from any analyses other than intention-to-treat

In ILLUMINATE-A, the primary analysis was predominantly conducted using the FAS. The FAS and intent-to-treat (ITT) populations are identical, as no patients are excluded from the analysis due to study drop-out. The plasma oxalate set was used to evaluate plasma oxalate endpoints (see Table C3 for a full description of the analysis sets). In ILLUMINATE-B, the primary analysis was conducted using the efficacy analysis set (Table C4). In ILLUMINATE-C, the primary analysis was conducted using the FAS (Table C5).

9.7 Adverse events

9.7.1 Included studies reporting adverse events

Details of the study selection, study methodology, and critical appraisal and results of the studies are reviewed in Section 9.2 through Section 9.6 and in Appendix 1. Safety data from the ILLUMINATE-A RCT and ILLUMINATE-B interventional phase 3 studies are presented, together with long-term safety of lumasiran treatment from the phase 2 OLE.[8,33,63,66,67,79,184]

9.7.2 Adverse events reported

ILLUMINATE-A

The safety and tolerability of lumasiran as reported in the double-blind period of the ILLUMINATE-A trial are summarised in Table C13. All safety analyses reported were performed on the safety analysis set

(i.e., patients who received any amount of study drug; n=39).[33] Overall, 85% (n=22/26) of patients in the lumasiran group and 69% (n=9/13) of patients in the placebo group reported at least one AE. No serious adverse events (SAEs) and no severe AEs were reported. There were no patient deaths during the study. Two patients discontinued lumasiran. In one case, the parent/guardian withdrew consent due to the patient's inability to comply with protocol-specific testing; the patient did not complete the 6-month double-blind period. In the other case, the patient discontinued treatment after 3 months due to AEs of fatigue and disturbance in attention that were considered unrelated to the study drug; the patient completed the study evaluations for the 6-month double-blind period. No patients in the placebo group had treatment interrupted or discontinued due to an AE. No patients in either group withdrew from the study due to an AE.[8,33]

Injection-site reactions (ISRs) occurred at a greater frequency in the lumasiran group versus the placebo group (38% vs. 0%).[8] As lumasiran is administered subcutaneously, the frequency of injection-site reactions was evaluated by performing an analysis of AEs mapping to the MedDRA high-level term of Injection Site Reactions.[33] All ISRs were transient and mild in severity. The most frequently reported symptoms of ISR were erythema, pain, pruritus, and discomfort. Headache (12% vs. 23%), rhinitis (8% vs. 15%), and upper respiratory infection (8% vs. 15%) were reported at a higher frequency in the placebo group versus the lumasiran group (Table C13).[8]

The proportion of patients experiencing treatment-related AEs was 42.3% (n=11/26) in the lumasiran group and 7.7% (n=1/13) in the placebo group. AEs related to lumasiran were injection-site reaction (n=6/26 [23.1%)], injection-site erythema (n=3/26 [11.5%)], and injection-site pain (n=3/26 [11.5%)]; no treatment-related AE was reported by ≥10% patients in the placebo group.[33]

As lumasiran is directed to the liver, the frequency of hepatic events was evaluated by performing an analysis of AEs mapping to the standardised MedDRA query (SMQ) Drug Related Hepatic Disorders.[33] No hepatic events mapping to this SMQ were reported in either treatment group. No clinically significant laboratory abnormalities were observed in liver function test (LFT) parameters in the lumasiran group.[8] The majority of patients had alanine transaminase (ALT) and aspartate transaminase (AST) values within the normal range (≤ ULN); ALT: 80.8% (n=21/26) in the lumasiran group and 84.6% (n=11/13) in the placebo group; AST: 96.2% (n=25/26) in the lumasiran group and 84.6% (n=11/13) in the placebo group. No patient in either treatment group had an ALT or AST level >3×ULN. Total bilirubin values were within the normal range (≤ ULN) in 88.5% of patients (n=23/26) in the lumasiran group and in 92.3% (n=12/13) in the placebo group. No patient in either treatment group had a total bilirubin >2×ULN.[8,33]

At the data cut-off of 26 April 2021, patients had been exposed to lumasiran for a median of [redacted] (range, [redacted]), with [redacted] cumulative doses of lumasiran administered. AEs were reported in [redacted]. The most common AEs occurring in ≥10% of patients were [redacted]. AEs related to lumasiran treatment occurred in [redacted]. [redacted] reported SAEs, which included [redacted]. [redacted] were related to lumasiran, and [redacted] resolved. [redacted], which occurred during the extension period and were unrelated to lumasiran. There was one discontinuation from study treatment, which was described above, in the primary analysis period. There were [redacted] deaths (Alnylam, Data on File[190]).

Table C13. Adverse events across patient groups – ILLUMINATE-A primary analysis

AE, n (%)	Lumasiran (n=26)	Placebo (n=13)
Any AE*	22 (85)	9 (69)
AE occurring in ≥10% of patients in either group		
Injection-site reactions†	10 (38)	0
Headache	3 (12)	3 (23)
Rhinitis	2 (8)	2 (15)
Upper respiratory infection	2 (8)	2 (15)
AE leading to discontinuation of lumasiran or placebo	1 (4)	0
AE leading to withdrawal from the trial	0	0
Any SAE	0	0
Any severe AE	0	0
Death	0	0

*All AEs were mild or moderate in severity.
†Includes AEs of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort.
AE=adverse event; SAE=serious adverse event
Source: Garrelfs et al. (2021)[8]

ILLUMINATE-B

All 18 patients (100%) reported at least one AE during the primary analysis period of ILLUMINATE-B. All AEs were mild or moderate in severity. The most common AE was pyrexia (Table C14). Three patients (17%) experienced treatment-related AEs, which were mild, transient ISRs in two patients and headache in one patient.[9]

One patient (6%) had an SAE of viral infection that was considered moderate in severity and unrelated to the study drug. There were no deaths, severe AEs, or AEs leading to treatment discontinuation,[9] nor were there AEs that mapped to the Drug Related Hepatic Disorders SMQ. No patients had ALT or AST values >3×ULN.[79]

Table C14. Adverse events across patient groups – ILLUMINATE-B primary analysis

AE, n (%)	<10 kg (n=3)	10 to <20 kg (n=12)	≥20 kg (n=3)	All lumasiran-treated (N=18)
AE	3 (100)	12 (100)	3 (100)	18 (100)
AEs occurring in ≥3 patients overall				
Pyrexia	1 (33)	4 (33)	1 (33)	6 (33)
Rhinitis	1 (33)	3 (25)	0	4 (22)
URTI	0	2 (17)	1 (33)	3 (17)
Vomiting	1 (33)	2 (17)	0	3 (17)
AEs leading to discontinuation of study treatment	0	0	0	0
AEs leading to withdrawal from the trial	0	0	0	0
Death	0	0	0	0
Serious AE	0	0	1 (33)†	1 (6)†
Severe AE	0	0	0	0

*Includes AEs of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort.
†Viral infection, considered unrelated to the study drug by the Investigator.
AE=adverse event; UTRI=upper respiratory tract infection
Source: [9]; Sas et al. (2021)[9]

[redacted] patients completed at least 12 months of lumasiran treatment and experienced at least one AE, of which [redacted] were related to lumasiran. The most common AEs occurring in ≥10% of patients were [redacted]. There was [redacted] in patients receiving lumasiran for 12 months (Alnylam, Data on File[190]).

Overall, the ILLUMINATE-B data demonstrate efficacy and safety in a population of young children, supporting a positive benefit/risk determination for lumasiran in PH1 patients under 6 years of age.

ILLUMINATE-C

AEs considered related to lumasiran were reported in six patients (28.6%) in the primary analysis period of ILLUMINATE-C (Table C15).[64] All treatment-related AEs were mild or moderate in severity. The most common treatment-related AEs were pyrexia (n=6 [28.6%]) and ISR (n=5 [23.8%]). All ISR events were mild in severity and transient. There were no lumasiran-related SAEs or severe AEs. As described in Section 9.4.6, [redacted].[11,64]

Overall, [redacted] experienced treatment-emergent SAEs. The most common treatment-emergent SAEs in Cohort A were [redacted]. The most common in Cohort B were [redacted]. Most patients [redacted] in ALT or AST, as measured by worst postbaseline liver function tests during the 6 month primary analysis period. Overall, [redacted] had ALT or AST values ≤ULN, [redacted] patients who were in Cohort B [redacted] had values >ULN and ≤3×ULN, and [redacted] patients also in Cohort B [redacted] had values between 3 and 5×ULN.[64] There were [redacted] postbaseline deaths during the study.[11,64]

Overall, the ILLUMINATE-C data demonstrate an AE profile consistent with PH1 and advanced renal disease.[64]

Table C15. Adverse events across patient groups – ILLUMINATE-C primary analysis

AE, n (%)	Lumasiran Cohort A (n=6)	Lumasiran Cohort B (n=15)	Overall (N=21)
Any AE*	5 (83.3)	12 (80.0)	17 (81.0)
Any AE occurring in ≥10% of either cohort			
Pyrexia	1 (16.7)	5 (33.3)	6 (28.6)
Injection-site reactions*	1 (16.7)	4 (26.7)	5 (23.8)
Device-related infection	0	2 (13.3)	2 (9.5)
Diarrhoea	0	2 (13.3)	2 (9.5)
Lumasiran-related AEs leading to lumasiran discontinuation	0	0	0
Lumasiran-related AEs leading to study withdrawal	0	0	0
Death	0	0	0
Any serious AE	1 (16.7)	5 (33.3)	6 (28.6)
Any severe AE	0	3 (20.0)	3 (14.3)

*Includes AEs of injection-site discoloration, erythema, and haematoma.
AE=adverse event
Source: Michael et al. (2021)[11]

Phase 2 OLE

Patients with PH1 who completed the phase 1/2 lumasiran multi-dose study and met eligibility criteria were able to enrol in the phase 2 OLE and to continue receiving lumasiran 1.0 mg/kg SC monthly, 3.0 mg/kg SC monthly, or 3.0 mg/kg SC quarterly (depending on their original regimen in the parent phase 1/2 study) for up to 1600 days.[66,90,184] Patients who received 1 mg/kg monthly were subsequently transitioned to 3 mg/kg every 3 months to align with the intended phase 3 maintenance dose.[185] All patients enrolled in ALN-GO1-001B (the parent phase 1/2 trial) completed this parent trial and subsequently enrolled in the phase 2 OLE (N=20).[184]

At the data cut-off of 1 March 2021, patients had been on study for a median of [redacted] (range, [redacted]). AEs were reported in all 20 patients (100%). The most common AEs occurring in ≥10% of patients were [redacted]

[redacted]. AEs related to lumasiran treatment occurred in [redacted]. [redacted] reported SAEs, which included [redacted]. [redacted] were related to lumasiran, and [redacted] resolved. There were [redacted] (Alnylam, Data on File[190]).

9.7.3 Summary of safety profile

The safety profile of lumasiran in patients with PH1 has been well characterised in both placebo-controlled and open-label interventional studies.[8,33,63,66,79,184,191]

In the double-blind period of the ILLUMINATE-A trial, 85% of patients in the lumasiran group and 69% patients in the placebo group reported at least one AE. All AEs were considered mild or moderate in severity. No severe AEs, SAEs, or deaths were reported. ISR was the most common AE that occurred more frequently with lumasiran (38% vs. 0%). The most reported ISR signs and symptoms were erythema, pain, pruritus, and discomfort. All ISRs were transient and considered mild in severity. One patient in the lumasiran group discontinued study drug due to AEs (fatigue and disturbance in attention), which were not considered to be related to the drug by the investigator; no patients in the placebo group discontinued study drug due to AEs. There were no clinically relevant changes in laboratory measures.[8]

During the extension period of ILLUMINATE-A, the safety profile of lumasiran was consistent with that of the double-blind period; no new safety signals were noted.[10] [redacted] discontinued study drug due to an AE (up to a cut-off date of 26 April 2021; Alnylam, Data on File[190]).

In the primary analysis of ILLUMINATE-B, AEs considered related to lumasiran were observed in three patients (17%), comprising mild, transient, and self-limiting ISRs in two patients and headache in one patient. There were no deaths, severe AEs, or AEs leading to treatment discontinuation.[9,79]

ILLUMINATE-C provides safety data for patients of all ages with PH1 and advanced renal disease. In the primary analysis of ILLUMINATE-C, AEs considered related to lumasiran were observed in six patients (28.6%) and were mild or moderate in severity. The most common treatment-related AE was ISR (23.8%); all events were mild in severity and transient. There were no treatment-related SAEs or severe AEs, and there were no deaths on the study. [redacted].[11,64]

The phase 2 OLE provides safety data for a median of [redacted] of lumasiran treatment. AEs were reported in all 20 patients. The most common drug-related AE was [redacted]. [redacted] (Alnylam, Data on File[190]).

9.8 Evidence synthesis and meta-analysis

9.8.1 Evidence synthesis

No meta-analyses or indirect comparisons were feasible due to the lack of RCTs for any comparator to lumasiran.

9.8.2 Rationale for exclusion

As described in Section 9.3.1, only one phase 3 RCT on lumasiran was included in the submission and no other RCTs for comparators that could be used in an indirect treatment comparison were identified.

9.9 Interpretation of clinical evidence

9.9.1 Statement of principal findings

Lumasiran is a novel, subcutaneously administered RNAi therapeutic specifically designed to address the underlying cause of PH1. Studies across a range of ages and levels of disease severity have shown that lumasiran is efficacious in lowering oxalate production. Among patients with preserved renal function,

lumasiran has demonstrated the ability to reduce oxalate to normal or near-normal levels in the majority of treated patients, regardless of age.[8,33,63,67,68,79] Among patients with advanced renal disease, lumasiran treatment leads to meaningful reductions in plasma oxalate in all patients, regardless of age and whether or not the patient is receiving dialysis.[11,64]

- Six months of lumasiran treatment lowered urinary oxalate excretion by 65% from baseline (or 1.24 mmol/24 h/1.73 m^2) in patients ≥6 years of age with relatively intact renal function (ILLUMINATE-A). This treatment effect is significantly greater than the 12% (or 0.27 mmol/24 h/1.73 m^2) reduction from baseline observed in the placebo group (mean difference in percent reduction: $p=1.685\times10^{-14}$; mean difference in absolute reduction: $p=1.225\times10^{-11}$).[8,33]
- Lumasiran has a consistent treatment effect on urinary oxalate excretion across all prespecified subgroups, including those defined by baseline urinary oxalate level, concomitant pyridoxine use, and across baseline renal function categories.[179]
- More lumasiran-treated than placebo-treated patients achieved near-normalisation (defined as ≤1.5×ULN, 84% vs. 0%) or normalisation (defined as ≤ULN, 52% vs. 0%) of urinary oxalate excretion within 6 months.[8] Furthermore, 77% of patients who crossed over from placebo to lumasiran achieved near-normalisation or normalisation of urinary oxalate excretion within 6 months of lumasiran treatment (ILLUMINATE-A).[10]
- Six months of lumasiran treatment lowered urinary oxalate excretion by 72% in patients <6 years of age with relatively intact renal function (ILLUMINATE-B; percent change from baseline).[9] This was maintained through 12 months of treatment (Alnylam, Data on File[188]).
- Ongoing phase 3 trials demonstrate that the oxalate-lowering efficacy of lumasiran is maintained for at least 12 months (ILLUMINATE-A[10] and ILLUMINATE-B [Alnylam, Data on File[188]]).
- Six months of lumasiran treatment significantly lowered plasma oxalate from baseline versus placebo (percent change: −39.8% vs. −0.3%; absolute change: −7.5 vs. 1.3 µmol/L; $p<0.001$ for both comparisons) in PH1 patients aged ≥6 years with relatively preserved renal function (ILLUMINATE-A).[8] Treatment with lumasiran resulted in substantial reductions in plasma oxalate (−31.7%) from baseline in patients aged <6 years with PH1 and relatively preserved renal function (ILLUMINATE-B).[9] Plasma oxalate reductions observed after 6 months were maintained through 12 months with continued lumasiran treatment (Alnylam, Data on File[188]).[10]
- In patients of all ages with advanced renal impairment (ILLUMINATE-C), treatment with lumasiran resulted in a reduction of 33.3% in plasma oxalate from baseline to Month 6 for patients not yet on dialysis (Cohort A) and a reduction of 42.4% in predialysis plasma oxalate from baseline to Month 6 for patients on dialysis (Cohort B).[11]
- The oxalate-lowering efficacy of lumasiran has been shown to translate to clinical benefit, including reduction of renal stone events and reversal of nephrocalcinosis.[8,10]
- Renal stone events, a key driver of morbidity in the early stages of PH1, occur less frequently upon initiation of oxalate-lowering treatment with lumasiran.[17,27,63,68]
- Nephrocalcinosis, an indicator of kidney damage and a strong risk factor for ESKD, was improved in 0% of placebo-treated patients and in 13% and 46% of patients following 6 and 12 months of lumasiran treatment, respectively in ILLUMINATE-A.[8] In ILLUMINATE-B, nephrocalcinosis grade improved in 44%[9] and [redacted] (Alnylam, Data on File[188]) of patients after 6 and 12 months of lumasiran treatment, respectively. These findings can be attributed to the oxalate-lowering efficacy of lumasiran, as spontaneous improvements in nephrocalcinosis are not expected to be observed in patients with PH1 over short time frames.[8,10]

Lumasiran met the primary endpoint in the ILLUMINATE-A trial by demonstrating a significantly greater reduction in 24-h urinary oxalate versus placebo. Lumasiran also significantly lowered plasma oxalate from

baseline versus placebo (secondary endpoint).[8] These findings were supported by the significant reduction from baseline in 24-h urinary oxalate and plasma oxalate demonstrated in the phase 3 ILLUMINATE-B trial.[9] The oxalate-lowering efficacy of lumasiran is maintained with further treatment, as demonstrated by the 12-month analyses of these phase 3 trials[10] (Alnylam, Data on File[188]) and the phase 2 OLE.[63,66] Primary analysis data from the ILLUMINATE-C trial indicate a reduction in plasma oxalate in patients with impaired renal function that is consistent with that seen in patients with intact renal function in ILLUMINATE-A and ILLUMINATE-B.[8,9,11]

Lumasiran has been well tolerated in clinical trials to date, with no deaths, drug-related severe, or drug-related serious AEs reported in ILLUMINATE-A, ILLUMINATE-B, ILLUMINATE-C, and the phase 2 OLE. Most AEs were mild or moderate in severity. While drug-related ISRs can occur, they tend to be mild in severity and transient.[8-11,66] One SAE was reported in ILLUMINATE-B, but it was not considered drug-related.[9] In ILLUMINATE-C, the proportion of patients experiencing SAEs that were unrelated to lumasiran is consistent with the clinical profile of patients with advanced renal disease.[11,64] No discontinuations or withdrawals associated with ongoing lumasiran treatment were reported in the abovementioned trials.[8-11,63,66]

9.9.2 Strengths and limitations

Lumasiran has been studied across a range of ages and levels of disease severity in several phase 3 clinical trials, with ongoing extension periods.[8-11,63] ILLUMINATE-A is a global, randomised, placebo-controlled, double-blind trial with long-term extension. It demonstrated the safety and efficacy of lumasiran in PH1 patients ≥6 years of age with relatively intact renal function.[8] The disease characteristics of the study population were consistent with the epidemiology of the disease and representative of the general population of patients with PH1 eligible for this study.[33] While the randomised treatment period was limited to 6 months, this duration was sufficient to capture clinically meaningful treatment effects on urinary oxalate excretion and plasma oxalate levels.[8] To date, the long-term extension period of the ILLUMINATE-A trial, together with the ongoing phase 2 OLE, confirms the consistent and maintained efficacy and safety of lumasiran over time. The ongoing ILLUMINATE-A extension period will continue to provide data relating to improvements on endpoints, such as renal stone events and nephrocalcinosis, that are anticipated over the longer term.

[redacted]

[20]

Lumasiran has also been evaluated in a study population that reflects the potential for PH1 to affect very young children.[9,34,125] In particular, ILLUMINATE-B and ILLUMINATE have provided and will continue to provide important evidence of lumasiran efficacy in younger patients (≤6 years of age) with PH1.

Lumasiran has been evaluated on efficacy endpoints that are inherently biological, highly relevant to PH1, and supported by regulatory agencies[70,71] and disease experts.[27] According to KHI/OHF expert recommendations, oxalate and change in slope of eGFR are the strongest markers of PH1 disease progression. Timed 24-h urine collections provide the most accurate measurement of urinary oxalate excretion and a substantial change (i.e., near-normalisation) in urinary oxalate is considered a basis for approval for the treatment of PH1. Furthermore, a reduction in hepatic oxalate production is reflected in decreased plasma oxalate levels.[27] Since oxalate is a biological endpoint, the ILLUMINATE-B and ILLUMINATE-C trials are unlikely to be affected by biases that inherently influence open-label trials. A patient's feelings and thoughts cannot influence their oxalate values; nor can knowledge of what treatment they are receiving.

Lumasiran has been evaluated across a wide range of renal function/impairment levels.[8,9,11,63] Lumasiran was evaluated in patients with PH1 and relatively preserved renal function in the ILLUMINATE-A and ILLUMINATE-B studies, although the renal function threshold for inclusion in ILLUMINATE-A was relatively low (eGFR ≥30 mL/min/1.73 m^2). Evidence of treatment efficacy in patients with PH1 and advanced renal disease, as defined by eGFR ≤45 mL/min/1.73 m^2 (or serum creatinine elevated for age, in patients <12 months of age) has been gathered in the ILLUMINATE-C interventional, single-arm, open-label phase 3 study.[11,64] The oxalate-lowering efficacy of lumasiran is being assessed by measuring changes in plasma oxalate, a contributing factor to renal decline and systemic oxalosis.[27] In ILLUMINATE-C, lumasiran treatment has been shown to substantially reduce plasma oxalate levels in patients with advanced PH1, including those with disease that is sufficiently advanced to require dialysis (primary analysis of ILLUMINATE-C).[11,64]

Across studies and subgroups, the effectiveness of lumasiran has been evident in patients permitted to continue their stable ECM (hyperhydration, crystallisation inhibitors, and/or pyridoxine), which reflects well the reality of patients with PH1 in the UK.[33,192,193]

9.9.3 Relevance to the scope

The evidence base comprised patients who participated in the randomised phase 3 ILLUMINATE-A study,[8,10] the interventional, single-arm, open-label phase 3 ILLUMINATE-B[9] and ILLUMINATE-C studies,[11] and the phase 2 OLE.[66,184]

Population

The phase 3 ILLUMINATE trials were directly relevant to the patient population in the UK because: 1) the majority of patients in the trials were from Europe and the Middle East, and 2) by permitting patients to continue ECM, including in many cases pyridoxine, the study populations reflect well the reality of patients with PH1 in the UK. Furthermore, [redacted].

Outcomes

The outcomes listed in the NICE scope were measured in the ILLUMINATE trials, including PD parameters such as urinary oxalate, urinary oxalate:creatinine ratio (a key PD measure that correlates with 24-h urinary oxalate)[97], and plasma oxalate (an indicator of hepatic oxalate production)[27].

Clinical effectiveness

ILLUMINATE-A, ILLUMINATE-B, and the phase 2 OLE demonstrate very strong evidence of clinical efficacy (Section 9.6) and safety (Section 9.7) for patients with relatively preserved renal function.[8,10,66,67,79] ILLUMINATE-C has demonstrated a substantial reduction in plasma oxalate in patients with PH1 and advanced renal decline, including renal decline that is sufficiently advanced to require dialysis. The overall magnitude of health benefits to patients reported in the evidence base is likely to be achieved in clinical practice in the UK, as the study populations reflect well the real-world situation of PH1 patients in the UK and the recommended dosage is based on the dosage used in the ILLUMINATE trials.

Impact of the technology beyond direct health benefits

As discussed in detail in Section 7, the use of lumasiran is anticipated to result in significant societal economic benefits due to increased independence and productivity of patients and correspondingly reduced burden on caregivers.

9.9.4 External validity

External validity of the lumasiran study results in PH1 is likely to be high since ILLUMINATE-A was a randomised trial with a double-blind, placebo-controlled period that enrolled a substantial number of patients with this rare disease. ILLUMINATE-B extends the external validity by expanding the age range of the population from which the evidence is generated. The ILLUMINATE-C trial provides further evidence in

patients with advanced renal disease, including those requiring dialysis. The evidence base included:[8,33,63,67,79]

1. Adult and paediatric patients with PH1
2. A broad range of CKD stages (determined by eGFR)
3. Diverse symptoms reflecting the wide spectrum of the disease
4. A range of patient experience with ongoing therapies, including those most relevant to the UK[192]

Therefore, ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C captured the heterogeneity of the patient population expected to be encountered in UK clinical practice.

9.9.5 Criteria for suitability

Lumasiran is suitable for all patients indicated. Use of lumasiran in earlier stages of PH1 is anticipated to result in an avoidance of disease progression and the need for transplantation. Use of lumasiran in later stages of disease is anticipated to stabilise disease, potentially reverse systemic oxalosis, reduce dialysis frequency and/or intensity, and enable more patients to reach and/or increase eligibility for transplantation and achieve better outcomes post transplantation.

10 Measurement and valuation of health effects

- Excess oxalate is the driver of PH1 morbidity and mortality—its accumulation leads to severe damage to the kidney and other organs.
- PH1 progresses in severity over time, such that HRQoL deteriorates over time without treatment.
- Symptomatic renal stones negatively impact HRQoL through symptoms including renal or uteric colic (abdominal pain), blood in the urine, painful urination, the urge to urinate often, blockage of the urinary tract, and repeated urinary tract infections.
- Utility results from health-state vignettes highlight the considerable impact of PH1 on HRQoL, particularly once patients reach the need for dialysis.

10.1 Patient experience

10.1.1 Aspects of the condition that most affect patients' quality of life

A comprehensive discussion of the effects of PH1 on patients' HRQoL can be found in Section 7.1. PH1 is a rare, chronic, autosomal recessive, genetic metabolic disorder that results in hepatic overproduction of oxalate.[4,30,32] The primary clinical manifestations of PH1 are caused by the formation of toxic calcium oxalate crystals in the kidney, which trigger a significant inflammatory response implicated in tissue damage.[4,5,17,18] Nephrocalcinosis (chronic deposition of calcium salts in the kidney) leads to progressive loss of renal function and may result in acute kidney injury.[4,17] Oxalate can also cause acute kidney injury via aggregation into obstructive stones and resultant obstruction of urinary outflow.[17,18] Renal stones may also cause symptoms that negatively impact HRQoL, which is further negatively impacted by associated urologic interventions and procedures aimed at managing renal stones.[45,46]

The frequency of renal stone events is an outcome measured in the ILLUMINATE trials[8,33,67,79,181] that the KHI/OHF recommendations have identified as relevant, given the effect these events have on how patients with PH feel and function.[27] Throughout the disease course, excretion of excess oxalate puts patients at risk for formation of calcium oxalate renal stones, which can cause pain and thereby impair HRQoL, as well as necessitate emergency care visits and invasive stone removal procedures, thus increasing the healthcare resource utilisation (HCRU) and cost burden of PH1.[20,45]

As kidney damage from oxalate accumulates, the kidneys' ability to clear oxalate is impaired and oxalate levels in plasma rise, creating a feedback loop that results in further kidney damage (due to increased oxalate exposure) and further oxalate accumulation (due to worsening kidney damage resulting in impaired ability to clear oxalate), along with systemic oxalate deposition that damages organs beyond the kidneys.[26-28,30,31] Due to this feedback loop, oxalate accumulation and renal decline are understood to accelerate as the disease progresses, such that a patient's rate of renal decline is nonlinear.[29] Systemic oxalosis causes severe complications that can lead to significant morbidity and disability (e.g., vision loss, pathologic fractures, cardiac insufficiency, skeletal pain, skin ulcers, arrhythmias, and peripheral neuropathy).[20,31,47,48] Beyond systemic oxalosis, oxalate-related renal decline in PH1 ultimately leads to ESKD. Nephrocalcinosis, oxalate excretion in urine, and plasma oxalate levels are significantly associated with risk of progression to ESKD in patients with PH1.[17,28,56,104]

The disease course of PH1 may vary from patient to patient, even within a family, and disease progression can be rapid and unpredictable.[30,48,103] PH1 has particularly devastating consequences for children, with rapid progression to ESKD and significant excess mortality in those with infantile onset of disease.[20,31-37]

Hospitalisations, school and work interruptions, and the psychological effect and emotional stress of a PH1 diagnosis and the necessary disease management also place substantial burden on patients and their caregivers (Section 7.1).[45]

10.1.2 How a patient's HRQoL is likely to change over the course of the condition

PH1 is a serious condition that is fatal in most patients if not adequately treated, due to its ability to cause severe damage to the kidneys and other organs.[18,30,31] Historically available disease management measures exert a heavy burden on patients and caregivers.[45] Testimonials from patients with PH1 also highlight the burden and anxiety associated with dialysis, systemic oxalosis, and renal stone events together with their removal (Section 7.1.4).[45]

Renal decline is the central manifestation of clinical progression in PH1 and clinical practice guidelines for PH1 largely stratify management on the basis of CKD stage.[20] The defined stages of CKD relate to renal function and are stage 1 (normal), stage 2 (mildly decreased), stage 3a (mildly to moderately decreased), stage 3b (moderately to severely decrease), stage 4 (severely decreased), and stage 5 (ESKD, kidney failure).[194] HRQoL and/or disease-related complications in PH1 may vary across CKD stages.[195]

In a study commissioned by Alnylam Pharmaceuticals, ranking of health-state vignettes by the public revealed that the impact of PH1 on HRQoL worsened with renal decline, with a significant decrease for the health states describing dialysis and ESKD (Section 10.1.6). This may reflect the burden of undergoing dialysis and the restrictions it places on patients' time and ability to carry out daily activities. It may also reflect progressive worsening of PH1 symptoms due to systemic oxalosis. This worsening of HRQoL with renal decline was followed by a large improvement in HRQoL following transplantation, reflecting improved health.[44]

10.1.3 HRQoL data derived from clinical trials

At the time of this submission, HRQoL data analyses were available from ILLUMINATE-A, but not ILLUMINATE-C. Table C16 summarises the data derived from ILLUMINATE-A (refer to Table C3 for full details on data collection). Note that changes in patient and/or caregiver experience, as opposed to HRQoL data, were captured in the ILLUMINATE-B study, given the unreliability of self-reporting in young patients.

Table C16. HRQoL data derived from the ILLUMINATE-A clinical trial

Study name NCT number	Instrument	Method of valuation	Measurement points	Appropriate for CEA	Results with CIs*
Alnylam Data on File (ILLUMINATE-A [ALN-GO1-003] CSR)[33] NCT03681184	KDQOL (for patients ≥18 years)	Domain scores	Baseline Every 6 months	No	[redacted]*
	PedsQL (for patients <18 years)	Individual domain, total summary, and composite scores for Generic and ESKD modules	Baseline Every 6 months	No	[redacted]
	EQ-5D including VAS	Pooled result based on EQ-5D-5L (for patients ≥18 years) and EQ-5D-Y (for patients <18 years)	Baseline Every 6 months	Yes	EQ-5D VAS (pooled for EQ-5D-5L and EQ-5D-Y) mean change from baseline (SD) at 6 months: Lumasiran: [redacted] Placebo: [redacted] EQ-5D-5L index score, mean (SD) Lumasiran, N=[redacted] Baseline: [redacted] Month 6: [redacted] Change from baseline to Month 6: [redacted] Placebo, N=[redacted] Baseline: [redacted] Month 6: [redacted] Change from baseline to Month 6: [redacted] EQ-5D-Y index score: [redacted] [redacted]* [redacted]

Consistency with the reference case is included in the scope.
*Based on the natural history of PH1 and the protocol restrictions (e.g., maintenance of a stable hydration regimen, where easing of hyperhydration requirements upon observation of effective oxalate lowering could have positively impacted HRQoL).
CEA=cost-effectiveness analysis; CI=confidence interval; EQ-5D-5L=EQ-5D, Five-Level Questionnaire; EQ-5D-Y=EQ-5D, Youth version; ESKD=end-stage kidney disease; HRQoL=health-related quality of life; KDQOL=Kidney Disease Quality of Life; NR=not reported; PedsQL=Pediatric Quality of Life Inventory; SD=standard deviation; VAS=visual analogue scale

Additional source: Alnylam Data on File (ILLUMINATE-A [ALN-GO1-003] SAP)[196]

10.1.4 Mapping HRQoL

EQ-5D-5L data collected during the ILLUMINATE-A trial were mapped to the EQ-5D 3-level version (EQ-5D-3L) to derive utility values, using UK tariffs, according to the mapping function developed by van Hout et al. (2012).[197] EQ-5D-3L tariffs were used for EQ-5D-Y; no mapping was required as the EQ-5D-Y instrument is based on the EQ-5D-3L.

10.1.5 HRQoL studies

The search strategy for economic evidence was identical to that outlined for clinical evidence in Section 9.1. HRQoL studies identified by the SLR are described in Section 10.1.6. HRQoL studies that are excluded due to being out of scope are listed in Appendix 1: Search strategy for clinical evidence.

10.1.6 Details of the studies in which HRQoL is measured

The SLR only identified one study describing HRQoL evidence for PH1. Modersitzki et al. (2019)[198] published a conference abstract of their non-interventional study comparing HRQoL by time since last stone event at multiple timepoints in 56 pretransplantation adults with PH enrolled in the RKSC registry (Table C17).

HRQoL data from original research commissioned for lumasiran include ILLUMINATE-A, which is relevant for PH1 patients with CKD 1–3b (Table C16), and a health-state vignette study that was conducted given the paucity of suitable HRQoL data related to PH1 in the literature. Health-state vignettes were developed in accordance with recommendations published by the NICE Decision Support Unit,[199] to describe the HRQoL of adults and children with PH1 and different stages of CKD. Use of vignette-derived EQ-5D estimates is a well-recognised and recommended approach in the absence of suitable EQ-5D data obtained directly from patients.[199]

[redacted][44]

Table C17 shows the HRQoL data collected during the health-state vignette study. The EQ-5D-5L data used in the cost-effectiveness analysis (CEA) were mapped using the method described for ILLUMINATE-A EQ-5D-5L data in Section 10.1.4.

Table C17. HRQoL data derived from the SLR search and health-state vignettes

Instrument	Method of valuation	Measurement points	Consistency with reference case	Appropriate for CEA	Results
Modersitzki et al. (2019)[198]					
SF-36 v2 (no mapping)	Domain score	HRQoL by last stone event: ≤30 days 31–365 days ≥366 days n=56 participants with surveys at multiple timepoints	Yes	Yes	≤30 days before survey: Physical functioning: 50 Role physical: 48 Bodily pain: 43 General health: 49 Vitality: 49 Social functioning: 47 Role emotional: 53 Mental health: 48 Physical component score: 48 Mental component score: 50 31–365 days before survey: Physical functioning: 54 Role physical: 53 Bodily pain: 47 General health: 46 Vitality: 50 Social functioning: 48 Role emotional: 51 Mental health: 51 Physical component score: 50 Mental component score: 49 ≥366 days before survey: Physical functioning: 56 Role physical: 57 Bodily pain: 56 General health: 54 Vitality: 53 Social functioning: 58 Role emotional: 57 Mental health: 54 Physical component score: 55 Mental component score: 55 *Values indicated are mean domain scores derived from a figure in the abstract, which also showed confidence intervals. Group means <47 indicate the presence of impaired functioning.*

Instrument	Method of valuation	Measurement points	Consistency with reference case	Appropriate for CEA	Results
Health-state vignettes[44]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]

CEA=cost-effectiveness analysis; CKD=chronic kidney disease; cLKT=combined liver–kidney transplant; EQ-5D-5L=EQ-5D, Five-Level Questionnaire; ESKD=end-stage kidney disease; HRQoL=health-related quality of life; SF-36=36-Item Short Form Health Survey; SLR=systematic literature review; VAS=visual analogue scale

10.1.7 Key differences between the values derived from the literature search and those reported or mapped from clinical trials

The SLR highlighted a fundamental lack of HRQoL data relating to PH1 in the literature. The one study (Modersitzki et al. 2019[198]) that was retrieved specifically described the burden of renal stone events and was used in the CEA to model utility decrement due to renal stone events (Section 10.1.6).

In the CEA, utility values for patients in early-stage disease (CKD 1–3b) were obtained from pooled patient-level EQ-5D data collected at [redacted] in the ILLUMINATE-A study. Use of the ILLUMINATE-A trial data is appropriate because confounding factors, such as hyperhydration and use of pyridoxine, are controlled. Importantly, this approach aligns with the NICE Decision Support Unit[199] recommendations to prioritise EQ-5D data collected directly from patients (Section 10.1.6).

For late-stage disease (CKD 4/ESKD), using HRQoL data from the ILLUMINATE-C trial to derive utilities would have been inappropriate due to 1) the small sample size, exacerbated by the fact that EQ-5D self-reporting is unreliable in young patients and is not feasible in the very young (<2 years); 2) lack of face validity of available evidence, which would introduce unnecessary uncertainty into the CEA, as indicated by the NICE Decision Support Unit[199] recommendations; and 3) the challenges associated with controlling for confounding factors, such as the extent and severity of systemic oxalosis complications. Therefore, EQ-5D data collected during the health-state vignette study were used as a source of utility values for patients in late-stage disease with uncontrolled oxalate (plasma oxalate >50 µmol/L) on high-intensity dialysis, reflecting the current health situation for patients with PH1 (ECM arm in the model). The use of health-state vignettes in the absence of robust clinical data aligns with the NICE Decision Support Unit[199] recommendations (Section 10.1.6).

It should be noted that the health-state vignette study did not capture HRQoL in populations with CKD 4/ESKD with 1) uncontrolled oxalate and normal-intensity dialysis (lumasiran arm in the model), 2) controlled oxalate (plasma oxalate ≤50 µmol/L threshold) and high-intensity dialysis (ECM arm), and 3) controlled oxalate and normal-intensity dialysis (lumasiran arm), since none of these scenarios reflect current health situations for patients with PH1. To obtain utilities for these populations in the CEA, utilities obtained from ILLUMINATE-A for CKD 1–3b populations were used as a starting point from which to apply utility decrements due to systemic oxalosis complications and dialysis. This approach prioritises EQ-5D data collected directly from patients in accordance with NICE Decision Support Unit[199] recommendations, and then applies utility decrements as appropriate.

Five non-PH1 CKD publications identified during a targeted literature search (Jersky et al. 2016[200]; Neri et al. 2012[201]; Okubo et al. 2013[202]; Tajima et al. 2010[203]; van Haalen et al. 2020[204]) were used to isolate the utility decrement of CKD 4/ESKD relative to CKD 1–3b without considering PH1-specific factors, such as systemic oxalosis complications and high-intensity dialysis. These relative differences were multiplied by the utilities for CKD 1–3b from ILLUMINATE-A to generate utility values for the late-stage health states, to which utility decrements due to systemic oxalosis complications and dialysis were applied.

Sullivan et al. (2011)[205] and Torrance et al. (2014)[206] were used to model the disutility of each specific systemic oxalosis condition (weighted by prevalence) and applied to all CKD 4/ESKD health states. Lee et al. (2005)[207] was used to determine the burden of normal-intensity and high-intensity dialysis, which was applied to the CKD 4/ESKD health states that could not be represented by the vignette study.

The health-state vignette study was used to obtain utilities for patients following transplantation, since EQ-5D data were available for the post combined liver–kidney transplantation (cLKT) health states (Table C17). Ratcliffe et al. (2005)[208] was used to estimate the burden of transplantation, which was applied as a one-off disutility at the moment of transplantation (acute period post-transplant). Perl et al. (2012)[209] was used to estimate the burden of graft failure, which was applied to the cLKT health states as applicable based on the incidence of graft failure.

The methodology for deriving utility values for each health state in the CEA is described in full in Section 10.1.9.

10.1.8 How adverse events have an impact on HRQoL

Although it is expected that several AEs may have a negative impact on patients' HRQoL, the studies returned by the search and meeting the inclusion criteria provided no data specifically on the relationship between

AEs and HRQoL in patients with PH1. The impact of AEs on HRQoL was therefore modelled using the catalogues of EQ-5D scores for the UK published by Sullivan et al. (2011) (Table C18).

Table C18. Utility decrements due to adverse events

Adverse event	Utility decrement	Source
Headache	−0.027	Sullivan et al. (2011)[205]; 084 Headache, Including Migraine
Injection-site erythema	−0.001	Assumed equal to rhinitis
Injection-site pain	−0.027	Assumed equal to headache
Injection-site reaction	−0.027	Assumed equal to headache
Rhinitis	−0.001	Sullivan et al. (2011)[205]; ICD-9 477 Allergic Rhinitis
Upper respiratory infection	−0.037	Sullivan et al. (2011)[205]; ICD-9 519 Other Respiratory System Diseases

10.1.9 HRQoL data used in the cost-effectiveness analysis

General approach for deriving utility values for health states in the economic model

Since no disease-specific classification system exists for categorising disease severity in PH1,[4,34] clinical practice guidelines for this disease largely stratify management on the basis of CKD stage.[20] The economic model encompasses nine distinct health states defined by CKD stage, plasma oxalate levels (based on a threshold of 50 µmol/L; Section 7.2.2), and/or transplant status, plus death (Section 12.1.3).

The utility by health state, adjusted over time by gender- and age-specific utility of the general population, is used as a base from which to subtract the utility decrements of events/conditions not already considered within the base estimation of HRQoL of PH1 patients at a given disease state. The utility decrements pertain to renal stone events, manifestations of systemic oxalosis in late-stage health states (CKD 4 or ESKD) with controlled oxalate levels (plasma oxalate ≤50 µmol/L), manifestations of systemic oxalosis not captured in the description of the health-state vignettes for late-stage health states with uncontrolled oxalate levels (plasma oxalate >50 µmol/L), dialysis for late-stage health states where the utility is not able to be estimated based on health-state vignettes, transplantation (acute period post-transplant), graft failure, and drug-related AEs. For the purpose of adjusting base utilities by age and gender, the utility in the general population, by age and gender, is estimated using the equation reported in the study by Ara and Brazier (2011):[210]

EQ-5D = 0.9508566 + 0.0212126*male − 0.0002587*age − 0.0000332*age^2

Utility values in CKD 1–3b

Utility values for the adult and paediatric CKD 1–3b health states were sourced from pooled patient-level EQ-5D-5L and EQ-5D-Y data from the ILLUMINATE-A study (Section 10.1.7). [redacted] (Table C16). EQ-5D-5L data were mapped to EQ-5D-3L to derive utility values, using UK tariffs. EQ-5D-3L tariffs were used for EQ-5D-Y (Section 10.1.4).

In addition, per-event utility decrements due to AEs (Section 10.1.8) and renal stone events were applied to CKD 1–3b health states. [redacted] The utility decrement due to renal stone events derived from Modersitzki et al. (2019)[198] was applied to the base utility values for the adult and paediatric CKD 1–3b health states to model the impact of renal stone events on HRQoL (*Calculation of health-state utility decrement due to renal stone events*).

Utility values in CKD 4/ESKD uncontrolled oxalate health states on high-intensity dialysis

Utility values for the adult and paediatric CKD 4/ESKD uncontrolled oxalate (plasma oxalate >50 µmol/L threshold) health states on high-intensity dialysis were derived from the adult and paediatric health-state vignettes for CKD 4/ESKD (Section 10.1.7).

The adult CKD 4 health-state vignette did not capture manifestations of systemic oxalosis, due to the variable presentation of these complications in CKD 4. The experts who developed the health-state vignettes were unable to determine one particular, or even a set, of systemic oxalosis complications that were representative of the adult CKD 4 health state. Therefore, adult utility decrements due to all systemic oxalosis complications (i.e., bone, cardiac, cutaneous and vascular, neurologic, and ophthalmologic) were derived from Sullivan et al. (2011)[205] and Torrance et al. (2014),[206] combined using a multiplicative approach to calculate disutility for patients with multiple manifestations of systemic oxalosis based on the prevalence of these conditions, and applied to the adult CKD 4 health state (*Calculation of health-state utility decrements due to manifestations of systemic oxalosis*).

The adult ESKD health-state vignette captured bone and cutaneous and vascular manifestations of systemic oxalosis, because the experts who developed the health-state vignettes agreed that these complications were sufficiently representative of the adult ESKD health state. Since cardiac, neurologic, and ophthalmologic manifestations of systemic oxalosis may also occur in adults with ESKD, adult utility decrements due to these complications were calculated using the multiplicative approach described above and applied to the adult ESKD health state.

The paediatric CKD 4/ESKD health-state vignettes captured bone, cutaneous and vascular, and ophthalmologic manifestations of systemic oxalosis for the reasons described above. Since cardiac and neurologic complications may also occur in children with CKD 4/ESKD, paediatric utility decrements due to these complications, were calculated using the multiplicative approach described above and applied to the paediatric CKD 4/ESKD health-state vignettes.

Per-event utility decrements due to AEs and renal stone events were applied to the CKD 4/ESKD uncontrolled oxalate health states on high-intensity dialysis (Section 10.1.8 and Section 10.1.9 *Calculation of health-state utility decrements due to renal stone events*).

Utility values in CKD 4/ESKD uncontrolled oxalate health states on normal-intensity dialysis

The adult and paediatric CKD 4/ESKD health-state vignettes reflect the impact of high-intensity dialysis used in PH1 and were inappropriate for estimating utility values in patients on normal-intensity dialysis. Therefore, base CKD 4 and ESKD health state utilities not including the impact of high-intensity dialysis or systemic oxalosis complications were calculated from the utility decrement of CKD 4/ESKD relative to CKD 1–3b non-PH1 populations obtained from the literature,[200-204] and applied to the utility values for adult and paediatric CKD 1–3b health states obtained from ILLUMINATE-A (C*alculation of utility decrements due to CKD 4/ESKD free of systemic oxalosis complications and dialysis*). These base CKD 4 and ESKD health state utility values were used as a starting point from which to apply utility decrements due to normal-intensity dialysis and systemic oxalosis complications.

Adult and paediatric utility decrements due to normal-intensity dialysis were derived from Lee et al. (2005) as described in *Calculation of utility decrements due to dialysis*.

Adult and paediatric utility decrements due to all systemic oxalosis complications observed in the uncontrolled oxalate cohort were derived from Sullivan et al. (2011)[205] and Torrance et al. (2014)[206] as previously described (*Calculation of health-state utility decrements due to manifestations of systemic oxalosis*).

Per-event utility decrements due to AEs and renal stone events were applied to the CKD 4/ESKD uncontrolled oxalate health states on normal-intensity dialysis (Section 10.1.8 and Section 10.1.9 *Calculation of health-state utility decrements due to renal stone events*).

Utility values in CKD 4/ESKD controlled oxalate health states on normal-intensity or high-intensity dialysis

The adult and paediatric CKD 4/ESKD health-state vignettes reflect the health state of patients with PH1 in the absence of effective oxalate-lowering therapy (i.e., uncontrolled oxalate) and were inappropriate for estimating utility values in patients with controlled oxalate. Therefore, the relative differences between utility values in CKD 4/ESKD and CKD 1–3b non-PH1 populations obtained from the literature[200-204] were applied to the utility values for adult and paediatric CKD 1–3b health states obtained from ILLUMINATE-A, to derive base CKD 4/ESKD utility values in the absence of uncontrolled plasma oxalate levels and systemic oxalosis complications. These based utilities were used as a starting point from which to apply utility decrements due to normal-intensity or high-intensity dialysis (as applicable) and systemic oxalosis complications in patients with controlled oxalate levels.

Lee et al. (2005)[207] was used to estimate adult and paediatric utility decrements due to normal-intensity and high-intensity dialysis (*Calculation of health-state utility decrements due to dialysis*).

Adult and paediatric utility decrements due to all systemic oxalosis complications were derived from Sullivan et al. (2011)[205] and Torrance et al. (2014),[206] considered at the prevalence assumed for controlled oxalate health states, and combined using the multiplicative approach (C*alculation of health-state utility decrements due to manifestations of systemic oxalosis*).

Per-event utility decrements due to AEs and renal stone events were applied to the CKD 4/ESKD controlled oxalate health states on normal-intensity or high-intensity dialysis (Section 10.1.8 and Section 10.1.9 *Calculation of health-state utility decrements due to renal stone events*).

Utility values in post-cLKT health states

Utility values for the adult and paediatric post-cLKT health states were obtained from the adult and paediatric health-state vignettes representing cLKT, given the absence of appropriate clinical trial data and the availability of relevant EQ-5D data from the health-state vignette study (Section 10.1.7).

In addition, a one-off disutility was applied at the moment of transplantation. The disutility from transplantation was estimated over 3 months from transplant using Ratcliffe et al. (2005)[208] and their longitudinal analysis of post-transplant EQ-5D data from 400 patients (non-PH1) listed for liver transplantation at six centres in the UK. Health-state utilities were 0.635 at 3 months after transplant compared with 0.730 at 24 months post-transplant. In the CE model, the estimated utility decrement immediately following transplantation was calculated based on the mean difference between utilities observed by Ratcliffe et al. at 3 months post-transplantation versus 24 months post-transplantation. The resulting utility decrement of −0.095 lasting 91.32 days (i.e., 3 months) was applied at the time of transplantation.

The disutility from graft failure was estimated using Perl et al. (2012)[209] and their analysis of SF-36 data from a large, international cohort of renally impaired patients with or without a history of kidney graft failure. Mean scores were significantly lower across several SF-36 domains for patients with prior kidney transplant failure compared with transplant-naïve patients. The between-group differences in SF-36 scores were mapped onto the EQ-5D index to derive disutility estimates for these events by summing 1) the constant from the mapping equation as reported by Rowen et al. 2009[211]; 2) linear domain coefficients from the mapping equation reported in Rowen et al. 2009 multiplied by corresponding domain scores from Perl et al; and 3) the product of each pair of corresponding matrix elements in the SF-36 domain score matrix derived from Perl et al. and the matrix of coefficients reported by Rowen et al. 2009. This resulted in a −0.055 utility decrement lasting 91.32 days for graft failure, which was applied to the transplantation health states as applicable based on the incidence of graft failure in these health states.

Calculation of utility decrements due to renal stone events

The cost-effectiveness (CE) model incorporates both the HRQoL impact (i.e., disutility) and treatment-specific costs of managing renal stone events occurring in any adult/paediatric CKD health state. Health-state utility decrements due to acute renal stone events were estimated from SF-36 domain profiles in

Modersitzki et al. (2019),[198] which was retrieved in the SLR search (Section 10.1.6). The authors analysed SF-36 results according to time from last renal stone event in 56 patients with PH1 surveyed at multiple time points, for a total of 184 separate SF-36 administrations across the study population. SF-36 scores were mapped onto the EQ-5D index to derive disutility estimates due to acute renal stone events by summing 1) the constant from the mapping equation as reported by Rowen et al. 2009[211]; 2) linear domain coefficients from the mapping equation reported in Rowen et al. 2009 multiplied by corresponding domain scores from Modersitzki et al; and 3) the product of each pair of corresponding matrix elements in the SF-36 domain score matrix derived from Modertsitzki et al. and the matrix of coefficients reported by Rowen et al. 2009. This resulted in a mean health-state utility of ~0.65 when assessed within 365 days of the renal stone event, and ~0.71 when assessed >365 days after the renal stone event (Figure C25).

Based on Modersitzki et al., an acute (6-month) utility decrement of −0.064 was applied to the baseline CKD stage–specific health-state utility for the occurrence of any renal stone event for a duration of 182.64 days. Since Modersitzki et al. estimated that disutility from renal stone event persisted over 1 year from the onset of the event, this 6-month duration of disutility is a conservative assumption.

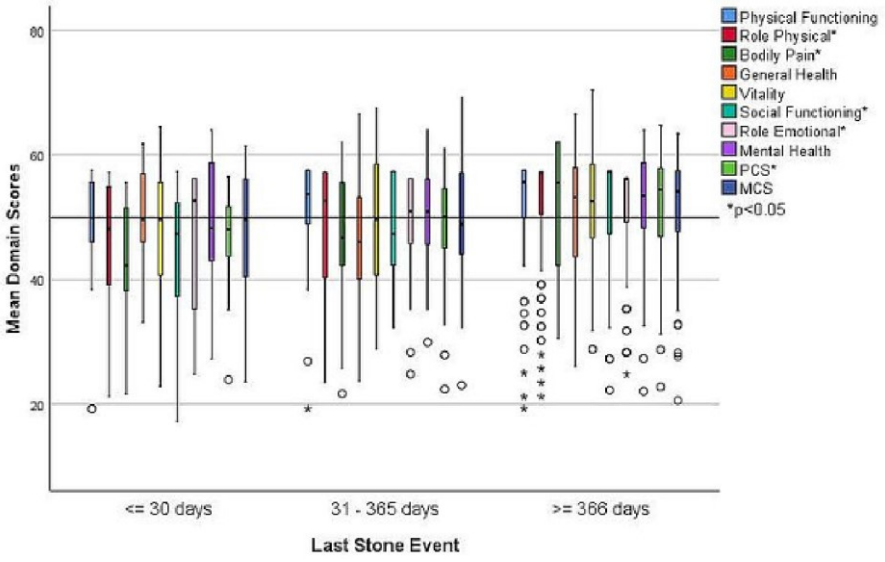

Figure C25. Acute disutility associated with renal stone events
Dark horizontal line depicts mean domain score of 50.
Source: Modersitzki et al. (2019)[198]

Calculation of utility decrements due to CKD 4/ESKD free of systemic oxalosis complications and dialysis

Five non-PH1 CKD publications identified during a targeted literature search (Jersky et al. 2016[200]; Neri et al. 2012[201]; Okubo et al. 2013[202]; Tajima et al. 2010[203]; van Haalen et al. 2020[204]) were used to isolate the utility decrement of CKD 4/ESKD relative to CKD 1–3b without considering PH1-specific factors, such as systemic oxalosis complications and high-intensity dialysis. Mean relative differences (0.898 for CKD 4 and 0.793 for ESKD) were multiplied by the utilities for CKD 1–3b as established by ILLUMINATE-A ([redacted] for adults and [redacted] for children) to generate utility values for the late-stage health states. The estimated utilities were 0.794 (CKD 4) and 0.702 (ESKD) for adults and 0.763 (CKD 4) and 0.674 (ESKD) for children, and were applied to the CKD 4/ESKD health states that could not be represented by the vignette study utilities. It is unclear whether the relative difference in utility estimated using this approach includes the impact of dialysis, since some of the non-PH1 CKD publications identified in the literature search reported utilities in CKD 4/ESKD free of dialysis. Therefore, the estimated utilities stated above were used as a starting point from which to apply utility decrements due to systemic oxalosis complications and dialysis.

Calculation of utility decrements due to dialysis

For patient populations not covered by the vignette study, health-state utility decrements due to high-intensity and normal-intensity dialysis were estimated using data from Lee et al (2005),[207] who analysed EQ-5D results

from 422 patients captured in the renal unit database of a UK (Welsh) hospital. Lee et al. compared health-state utility index values for renal transplant recipients with those of patients on or awaiting initiation of dialysis (Table C19).

Normal-intensity dialysis recipients were assumed to be on a regimen of three haemodialysis or seven peritoneal dialysis sessions per week, as more frequent regimens are atypical outside PH1. Mean utility decrements of −0.130 and −0.040 per cycle were observed for patients receiving normal-intensity haemodialysis and normal-intensity peritoneal dialysis, respectively, compared with predialysis patients.[207]

High-intensity dialysis recipients with PH1 are assumed to be on a regimen of six haemodialysis and seven peritoneal dialysis sessions per week. High-intensity dialysis utility decrements were estimated from the mean utility decrements for normal-intensity dialysis from Lee et al. and the difference in frequency between high-intensity and normal-intensity dialysis schedules. A mean utility decrement of −0.260 per cycle was estimated for high-intensity haemodialysis (i.e., −0.130 × 2), while a mean utility decrement of −0.040 per cycle was used for high-intensity peritoneal dialysis. A mean utility decrement of −0.282 per cycle was estimated for the cohort receiving high-intensity haemodialysis in combination with peritoneal dialysis (Table C19).

The total disutility of dialysis was obtained by multiplying the frequency of haemodialysis and/or peritoneal dialysis (as appropriate) by the respective disutility. The estimated utility decrements were –0.118 (normal intensity) and –0.263 (high-intensity) for adults and –0.130 (normal intensity) and –0.260 (high-intensity) for children.

In the base-case analysis, the disutility of high-intensity analysis is applied to CKD 4/ESKD health states with controlled oxalate (ECM arm). However, the disutility of high-intensity dialysis is not applied to the CKD 4/ESKD health states with uncontrolled oxalate levels (ECM arm), since the vignettes used to inform utility values for these health states captured the burden of high-intensity dialysis.

Table C19. Health-state utility for a subset of the model cohort receiving dialysis

	Mean	SD	Dialysis disutility
Predialysis	0.570	0.330	0
Normal-intensity dialysis*			
Peritoneal dialysis	0.530	0.340	−0.040
Haemodialysis	0.440	0.320	−0.130
Haemodialysis + peritoneal dialysis	0.409	NA	NA
High-intensity dialysis†			
Peritoneal dialysis	0.530	NA	−0.040
Haemodialysis	0.310	NA	−0.260
Haemodialysis + peritoneal dialysis	0.288	NA	−0.282

*Haemodialysis 3× week or peritoneal dialysis 7× week.
†Haemodialysis 6× week plus peritoneal dialysis 7× week. Mean values and utility decrements for high-intensity dialysis were estimated from Lee et al. (2005) and the difference in dialysis frequency between high-intensity and normal-intensity regimens.
NA=not applicable; SD=standard deviation
Source: Lee et al. (2005)[207]

Calculation of utility decrements due to manifestations of systemic oxalosis

Sullivan et al. (2011)[205] and Torrance et al. (2014)[206] provide a UK catalogue of disutility scores by condition based on EQ-5D that were used to estimate the impact of systemic oxalosis on HRQoL. Disutility scores reported by Sullivan et al. and Torrance et al. were used to model the disutility of each specific condition related to systemic oxalosis as distinct from HRQoL impairment attributable to PH1-related renal decline. Disutility scores were combined using a multiplicative approach to calculate disutility for patients with multiple manifestations of systemic oxalosis based on the prevalence of these conditions (Table C20).

The utility decrements for systemic oxalosis presented in Table C20 only apply to the CKD 4 and ESKD health states where systemic oxalosis is expected to occur. Consequently, manifestations of systemic oxalosis have not been included in the health-state utility estimates for the earlier CKD stages (1–3b).

Moreover, for the cohort in CKD 4 or ESKD with uncontrolled oxalate (i.e., the cohort for whom vignette-based utilities are used), disutilities were applied only for those manifestations of systemic oxalosis not captured by the health-state vignettes, as follows:

- Adult CKD 4 health state with uncontrolled oxalate: utility decrements of all manifestations of systemic oxalosis were considered as none were captured in the health-state vignette
- Paediatric CKD 4 health state with uncontrolled oxalate: utility decrements of cardiac and neurologic systemic oxalosis were considered as these were not captured in the health-state vignette
- Adult ESKD health state with uncontrolled oxalate: utility decrements of cardiac, neurologic, and ophthalmologic systemic oxalosis were considered as these were not captured in the health-state vignette
- Paediatric ESKD health state with uncontrolled oxalate: utility decrements of cardiac and neurologic systemic oxalosis were considered as these were not captured in the health-state vignette

For adult and paediatric CKD 4/ESKD health states with controlled oxalate (in which health-state utility values were not estimable from the vignette study), utility decrements of all manifestations of systemic oxalosis were considered at prevalence assumed for the controlled oxalate health states and combined using the multiplicative approach described above.

Calculation of utility decrements for caregivers

In addition to patients' utility decrements associated with acute and chronic consequences of PH1, the model considers caregiver disutility by health states. No published studies were identified reporting caregiver disutility in PH1. However, disutility values for parental caregivers of children aged 6–17 years with PH1 were obtained from an observational study on caregiver health status comparing the burden on caregivers responsible for children with abnormal kidney function versus those responsible for children with normal kidney function.[54]

EQ-5D-5L data from this observational study were converted to EQ-5D-3L value sets using UK tariffs from van Hout (2012).[197] Disutility was multiplied by the average number of caregivers per patient from pooled observations in ILLUMINATE-A and ILLUMINATE-B trials (patients with at least one caregiver). A disutility decrement of [redacted] was applied to the CKD 4 and ESKD health states. [redacted][54]; therefore, [redacted]

HRQoL values in the CEA

Table C20 provides a summary of the HRQoL values used in the CEA.

Table C20. Summary of HRQoL values for CEA

State	Utility value	SE	Reference in submission	Assumption
Health-state utility estimates				
CKD 1–2, children	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33]	[redacted] data were pooled for all patients <18 years
CKD 3a, children	[redacted]	[redacted]		
CKD 3b, children	[redacted]	[redacted]		
CKD 4-Ox_U and high-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: Vignette study[44] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206]	Starting from the vignette-based utility estimate, this utility value also considers disutilities related to cardiac and neurological systemic oxalosis complications from the literature (prevalence weighted, multiplicative approach), as these were not captured in the health-state vignettes

State	Utility value	SE	Reference in submission	Assumption
CKD 4-Ox_U and normal-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] CKD 4 vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between CKD 4 and CKD1-3b in non-PH1 CKD literature Disutilities related to all systemic oxalosis complications were considered (prevalence weighted, multiplicative approach), along with normal-intensity dialysis
CKD 4-Ox_C and high-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] CKD 4 vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] High-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between CKD 4 and CKD1-3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for high-intensity dialysis was considered
CKD 4-Ox_C and normal-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] CKD 4 vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between CKD 4 and CKD1-3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for normal-intensity dialysis was considered
ESKD-Ox_U and high-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: Vignette study[44] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206]	Starting from vignette-based utility estimate, this utility value also considers disutilities related to cardiac and neurological systemic oxalosis complications from the literature (prevalence weighted, multiplicative approach), as these were not captured in the health-state vignettes

State	Utility value	SE	Reference in submission	Assumption
ESKD-Ox$_U$ and normal-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] ESKD vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between ESKD and CKD1-3b in non-PH1 CKD literature Disutilities related to all systemic oxalosis complications was considered (prevalence weighted, multiplicative approach), along with normal-intensity dialysis
ESKD-Ox$_C$ and high-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] ESKD vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] High-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between ESKD and CKD1-3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for high-intensity dialysis was considered
ESKD-Ox$_C$ and normal-intensity dialysis, children*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] ESKD vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between ESKD and CKD1-3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for normal-intensity dialysis was considered
Post-cLKT, children	[redacted]	[redacted]	EQ-5D: Vignette study[44]	
CKD 1–2, adults	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33]	[redacted] pooled between all patients ≥18 years
CKD 3a, adults	[redacted]	[redacted]		
CKD 3b, adults	[redacted]	[redacted]		
CKD 4-Ox$_U$ and high-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: Vignette study[44] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206]	Starting from the vignette-based utility estimate, this utility value also considers disutilities related to all systemic oxalosis complications from the literature (prevalence weighted, multiplicative approach), as these were not assessed in the health-state vignettes

State	Utility value	SE	Reference in submission	Assumption
CKD 4-Ox_U and normal-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] CKD 4 vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis : [207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between CKD 4 and CKD1–3b in non-PH1 CKD literature Disutilities related to all systemic oxalosis complications were considered (prevalence weighted, multiplicative approach), along with normal-intensity dialysis
CKD 4-Ox_C and high-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] CKD 4 vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] High-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between CKD 4 and CKD1–3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for high-intensity dialysis was considered
CKD 4-Ox_C and normal-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] CKD 4 vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between CKD 4 and CKD1-3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for normal-intensity dialysis was considered
ESKD-Ox_U and high-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: Vignette study[44] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206]	Starting from the vignette-based utility estimate, this utility value also considers disutilities related to cardiac, ophthalmologic, and neurologic systemic oxalosis complications from the literature (prevalence weighted, multiplicative approach), as these were not captured in the health-state vignette

State	Utility value	SE	Reference in submission	Assumption
ESKD-Ox$_U$ and normal-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] ESKD vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between ESKD and CKD1-3b in non-PH1 CKD literature Disutilities related to all systemic oxalosis complications were considered (prevalence weighted, multiplicative approach), along with normal-intensity dialysis
ESKD-Ox$_C$ and high-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] ESKD vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] High-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between ESKD and CKD1-3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for high-intensity dialysis was considered
ESKD-Ox$_C$ and normal-intensity dialysis, adults*	[redacted]	[redacted]	EQ-5D: ILLUMINATE A[33] ESKD vs. CKD 1–3b: Jersky et al. (2016)[200]; Neri et al. (2012)[201]; Okubo et al. (2013)[202]; Tajima et al. (2010)[203]; van Haalen et al. (2020)[204] Systemic oxalosis: Sullivan et al. (2011)[205]; Torrance et al. (2014)[206] Normal-intensity dialysis: Lee et al. (2005)[207]	ILLUMINATE-A CKD1–3b utility values adjusted for relative difference between ESKD and CKD1-3b in non-PH1 CKD literature Disutility (multiplicative approach) related to all systemic oxalosis complications was considered at the prevalence assumed for controlled oxalate health states Disutility for normal-intensity dialysis was considered
Post-cLKT, adults	[redacted]	[redacted]	EQ-5D: Vignette study[44]	
Disutility estimates				
Renal stone events				
Disutility per event	−0.064	0.006	Modersitzki et al. (2019)[198]	Disutility in Modersitzki 2019 was observed to persist over 1 year from renal stone event. Thus 6 months duration of disutility is a conservative assumption
Event duration (days)	182.64	18.26		
Dialysis				
High-intensity HD disutility	−0.260	0.026	Lee et al. (2005)[207]	Estimated based on Lee et al. and the difference in high-intensity vs. normal-intensity dialysis frequency
High-intensity HD + PD disutility	−0.282	0.028	Lee et al. (2005)[207]	

State	Utility value	SE	Reference in submission	Assumption
Normal-intensity HD disutility	−0.130	0.013	Lee et al. (2005)[207]	
Normal-intensity PD disutility	−0.040	0.004	Lee et al. (2005)[207]	
Manifestations of systemic oxalosis				
Bone disorders	−0.102	0.010	Sullivan et al. (2011)[205]	Disutility equal to that associated with "203 Osteoarthritis"
Cardiac disorders	−0.103	0.010	Sullivan et al. (2011)[205]	Disutility equal to that associated with "108 Congestive Heart Failure, Nonhypertension"
Cutaneous and vascular disorders	−0.071	0.007	Sullivan et al. (2011)[205]	Disutility equal to that associated with ICD-9 707 Chronic Ulcer of Skin
Ophthalmologic disorders	−0.041	0.004	Sullivan et al. (2011)[205]	Disutility equal to that associated with ICD-9 368 Visual Disturbances
Neurologic disorders	−0.234	0.023	Torrance et al. (2014)[206]	The difference in utilities between patients with and without neuropathy was used to determine the disutility due to neuropathy
Total disutility due to systemic oxalosis†				
CKD 4-Ox_U, children*	−0.056	NA	Sullivan et al. (2011)[205] Torrance et al. (2014)[206]	Disutilities of cardiac and neurologic systemic oxalosis complications weighted by prevalence were considered as these were not captured by the health-state vignettes
CKD 4-Ox_U, adults*	−0.100	NA	Sullivan et al. (2011)[205] Torrance et al. (2014)[206]	Disutilities of all systemic oxalosis complications weighted by prevalence were considered as none were captured by the health-state vignettes
ESKD-Ox_U, children*	−0.131	NA	Sullivan et al. (2011)[205] Torrance et al. (2014)[206]	Disutilities of cardiac and neurologic systemic oxalosis complications weighted by prevalence were considered as these were not captured by the health-state vignettes
ESKD-Ox_U, adults*	−0.145	NA	Sullivan et al. (2011)[205] Torrance et al. (2014)[206]	Disutilities of cardiac, neurologic, and ophthalmologic systemic oxalosis complications weighted by prevalence were considered as these were not captured by the health-state vignettes
CKD 4-Ox_C	−0.081	NA	Sullivan et al. (2011)[205] Torrance et al. (2014)[206]	Disutilities of all systemic oxalosis complications weighted by prevalence were considered
ESKD-Ox_C	−0.190	NA	Sullivan et al. (2011)[205] Torrance et al. (2014)[206]	Disutilities of all systemic oxalosis complications weighted by prevalence were considered
Transplant				
Acute post-transplantation disutility	−0.095	0.010	Ratcliffe et al. (2005)[208]	Applied as a one-off disutility at the moment of transplantation
Transplant duration (days)	91.32	9.13	Ratcliffe et al. (2005)[208]	Disutility in Ratcliffe et al. 2005 over 3 months from transplant

State	Utility value	SE	Reference in submission	Assumption
Graft failure disutility	−0.055	0.005	Perl et al. (2012)[209]	SF-36 scores for patients with history of graft failure vs. those without were mapped onto the EQ-5D index to derive disutility estimates for graft failure events using the method reported by Rowen et al. (2009).[211]
Graft failure duration (days)	91.31	9.13	Perl et al. (2012)[209]	Disutility in Perl et al. was estimated over 3 months from transplant failure
AE disutility				
Headache	−0.027	0.007	Sullivan et al. (2011)[205]; 084 Headache, Including Migraine	
Injection-site erythema	−0.001	0.001	Sullivan et al. (2011)[205]; ICD-9 477 Allergic Rhinitis	Assumed equal to rhinitis
Injection-site pain	−0.027	0.007	Sullivan et al. (2011)[205]; 084 Headache, Including Migraine	Assumed equal to headache
Injection-site reaction	−0.027	0.007	Sullivan et al. (2011)[205]; 084 Headache, Including Migraine	Assumed equal to headache
Rhinitis	−0.001	0.001	Sullivan et al. (2011)[205]; ICD-9 477 Allergic Rhinitis	
Upper respiratory infection	−0.037	0.012	Sullivan et al. (2011)[205]; ICD-9 519 Other Respiratory System Diseases	
AE duration (days)	14.00	1.400	Assumption	
Caregiver disutility				
CKD 1–2	[redacted]	[redacted]	[redacted][54]	[redacted]
CKD 3a	[redacted]	[redacted]		
CKD 3b	[redacted]	[redacted]		
CKD 4	[redacted]	[redacted]		EQ-5D-5L was converted to EQ-5D-3L value sets using UK tariffs from van Hout (2012).[197] Disutility (for parental caregivers of children with PH1) was multiplied by the average number of caregivers per patient from pooled observations in ILLUMINATE-A and ILLUMINATE-B (patients with at least 1 caregiver)
ESKD	[redacted]	[redacted]		

*A threshold of 50 µmol/L was used to distinguish controlled vs. uncontrolled oxalate.
†Estimated based on prevalence of systemic oxalosis disorders by health state and the systemic oxalosis disutility values noted above (with the multiplicative approach to combine disutility values of multiple conditions in order to calculate disutility for patients with multiple manifestations of systemic oxalosis).
AE=adverse event; CKD=chronic kidney disease; cLKT=combined liver–kidney transplant; EQ-5D-3L=EQ-5D, Three-Level Questionnaire; EQ-5D-5L=EQ-5D, Five-Level Questionnaire; ESKD=end-stage kidney disease; HD=haemodialysis; HRQoL=health-related quality of life; NA=not applicable; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; PD=peritoneal dialysis; PH1=primary hyperoxaluria type 1; SE=standard error

10.1.10 Assessment of the applicability of values or estimates of any values by clinical experts

In 2020, Alnylam Pharmaceuticals commissioned a third-party consultancy to conduct a study estimating HCRU associated with the management of PH1. Based on a review of current methods of eliciting expert opinion for parameter estimation in economic analyses and healthcare decision making, the study

methodology was informed by a structured expert elicitation (SEE) framework developed by the Centre for Health Economics (CHE) at the University of York.[212]

Per the York SEE framework, an elicitation protocol was developed that included a questionnaire intended to elicit resource use estimates from participating experts. The experts were requested to complete the questionnaire, after which semi-structured one-on-one interviews were scheduled to allow the experts to clarify and elaborate upon their responses to the questionnaire. Interviewers were trained and provided with relevant background information in accordance with the York SEE guidelines. Following these interviews, experts were sent a copy of their responses as recorded from their questionnaires and interview feedback, and were asked to confirm or amend as appropriate.

Expert recruitment for this study was led by the third-party consultancy with support provided as needed by Alnylam Pharmaceuticals. The predefined objective of recruitment was to yield a sample of UK clinicians who had recent experience in managing PH1 and would collectively offer perspective on the entire clinical management pathway for the full range of patients with PH1 in terms of age and disease severity. Based on these criteria, five experts were contacted, of whom three agreed to participate: a general adult nephrologist, a paediatric nephrologist, and a transplant surgeon with recent experience in the management of PH1.

Responses from the three UK experts were aggregated to obtain mean values where feasible for use in the economic model for lumasiran.

10.1.11 Definition of what a patient experiences in the health states in terms of HRQoL

The HRQoL of a patient is assumed to vary depending on the health state and the burden of treatment and disease complications associated with each health state. Refer to Sections 10.1.1, 10.1.2, and 10.1.9.

10.1.12 Health effects identified in the literature or clinical trials that were excluded from the analysis

No relevant health effects identified in the literature or clinical trials were excluded from analysis.

10.1.13 Baseline HRQoL assumed in the analysis

Baseline HRQoL in the CEA was informed by the pivotal, phase 3 ILLUMINATE-A trial, the health-state vignettes, and by applying utility decrements obtained from the literature on non-PH1 populations with CKD/ESKD to the utilities derived from ILLUMINATE-A for health states not captured by the vignettes (Section 10.1.9).

eGFR, which can be mapped to CKD stage, was regularly monitored throughout the ILLUMINATE-A trial. EQ-5D data were also collected at scheduled 6-month intervals. Therefore, health-state utilities could be calculated by CKD stage specifically for patients who were followed in ILLUMINATE-A. Analysis of the ILLUMINATE-A data revealed that health-state utilities were [redacted] across CKD stages 1–3b. This was [redacted] in early stages of CKD. The average adult [redacted] and paediatric [redacted] health-state utilities across CKD stages 1–3b were applied at baseline across each of these model states.

In the absence of robust clinical data, the health-state vignettes were used to derive utility values for late-stage health states (CKD 4/ESKD) involving uncontrolled oxalate and high-intensity dialysis. Factoring in systemic oxalosis complications and the additional burden of high-intensity dialysis generated utilities of [redacted] (CKD 4) and [redacted] (ESKD) for adults and [redacted] (CKD 4) and [redacted] (ESKD) for children. For health states where the vignettes were inappropriate for estimating utility values (i.e., late-stage patients with uncontrolled oxalate and normal-intensity dialysis, late-stage patients with controlled oxalate levels regardless of dialysis), ILLUMINATE-A CKD1–3b utility values were adjusted to account for the relative difference in utilities between CKD 4/ESKD and CKD 1–3b from the non-PH1 CKD literature. From there, the burden of PH1-specific factors (i.e., systemic oxalosis, dialysis) was applied.

For patients with PH1 who have progressed to later-stage kidney disease (CKD 4/ESKD), combined liver–kidney transplantation is the only option known to resolve the underlying metabolic defect and restore renal

function. The post-cLKT utilities, which were obtained from the health-state vignettes, are substantially higher than those modelled for patients in late-disease health states, despite the risks associated with transplantation (i.e., complications, immediate post-transplant utility decrement, possibility of graft failure). In fact, the utility value for paediatric patients post cLKT ([redacted]) suggests that this group of patients is able to achieve HRQoL similar that observed in CKD 1–3b ([redacted]). Although adult patients do not recover HRQoL to the same degree as paediatric patients (post-cLKT, [redacted]), they are able to achieve a similar HRQoL to that observed in adults in CKD 4 who are on normal-intensity dialysis (controlled oxalate, 0.713; uncontrolled oxalate, 0.694; Table C20).

10.1.14 Clarification of whether HRQoL is assumed to be constant over time

HRQoL is not assumed to be constant over time, given that PH1 has a variable rate of progression and is characterised by progressive kidney disease leading to kidney failure, and multiorgan damage from systemic oxalosis (Sections 10.1.1 and 10.1.2).[4,56]

10.1.15 Amended values from the baseline HRQoL inputs

No values have been amended.

10.1.16 Treatment continuation rules

The Summary of Product Characteristics suggests that use of lumasiran could be considered during pregnancy and breast-feeding, taking into account the benefit/risk balance of lumasiran.[73] Given the very small PH1 population in the UK, these scenarios are only expected to affect a very small number of patients and have therefore not been included in the CEA.

Section D – Value for Money and cost to the NHS and personal social services

11 Existing economic studies

11.1 Identification of studies

11.1.1 Strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data

The SLR search described in Section 9.1 was designed to identify relevant economic evidence concerning PH1 in the published literature and in unpublished sources (also refer to Appendix 1: Search strategy for clinical evidence).

11.1.2 Inclusion and exclusion criteria used to select studies from the published and unpublished literature

In addition to clinical evidence, the SLR search was designed to identify relevant economic and HRQoL evidence, including studies reporting healthcare resource use and associated costs, and cost-effectiveness data. The selection criteria for economic studies are outlined in Section 9.2.

11.1.3 Numbers of published studies included and excluded at each stage in an appropriate format

Figure C1 shows the PRISMA diagram for the SLR in PH1 and indicates the number of articles that were identified as containing economic evidence. Only two studies (Perera et al. 2011 and Perera et al. 2009),[174,175] both evaluating transplantation to treat PH1, reported HCRU data relevant to the UK. No cost data were identified in either of these publications. No UK-specific pharmacoeconomic models or cost-effectiveness analyses were identified by the SLR.

11.2 Description of identified studies

11.2.1 Brief review of each study, stating the methods, results and relevance to the scope

No pharmacoeconomic models or cost-effectiveness analyses were identified; therefore, no studies were considered relevant to the submission. As per the NICE guidance, productivity losses and caregiver time costs are not included in the NHS/Prescribed Specialised Services (PSS) perspective for the economic model. Studies that reported HRQoL/utility data and their relevance to the scope and applicability to the economic model have been previously described in Sections 10.1.6 and in Appendix 1: Search strategy for clinical evidence.

11.2.2 Complete quality assessment for each health economic study identified

As no economic evaluations (i.e., cost-effectiveness or cost-utility studies) were identified by the SLR, the Drummond checklist was not used for quality assessment.

12 Economic analysis

- A de novo Markov model was developed that incorporated nine different health states defined by CKD stage, oxalate levels, and transplant status.
- The model used data from the pivotal RCT, ILLUMINATE-A, and the single-arm, interventional, open-label, phase 3 studies, ILLUMINATE-B and ILLUMINATE-C. Model inputs and assumptions were validated by clinical experts.

- Lumasiran plus established clinical management (ECM) compared with ECM yields an undiscounted incremental cost-effectiveness ratio (ICER) of £[redacted]/quality-adjusted life-year (QALY) and a discounted ICER of £[redacted]/QALY, which includes a proposed confidential patient access scheme discount ([redacted]). These results are relatively robust to a range of sensitivity and scenario analyses.
- Applying a highly specialised technology QALY weighting of [redacted], which is deemed appropriate for technologies with incremental QALYs gained [redacted], yields a discounted ICER of £[redacted]/QALY.
- The CEA results for lumasiran should be considered in the context of the high unmet need for this patient population, as no safe and effective disease-modifying therapy was previously available to treat PH1 in the UK.

12.1 Description of the de novo cost-effectiveness analysis

12.1.1 Patient groups included in the cost-effectiveness analysis

The CEA considers patients of any age with PH1, per the final NICE scope (Table A1). For patients in the early stage of disease (CKD 1–3b), the distribution of ages in the CE model is consistent with the patient population in the pivotal RCT, ILLUMINATE-A and the single-arm phase 3 study, ILLUMINATE-B.[8,79] For patients in the advanced stages of disease (CKD 4 and ESKD), the distribution of age is consistent with the patient population in the single-arm, phase 3 study, ILLUMINATE-C.[11] Demographic data inputs to the CEA were obtained from the baseline characteristics of participants in these trials.[33,79]

12.1.2 Technology and comparator

The CEA considers lumasiran plus ECM versus ECM without lumasiran, as summarised in Section 8.2 and in accordance with the NICE scope (Table A1). ECM is consistent with the control arm of the ILLUMINATE-A trial.[8] In the CEA and in line with the NICE scope, ECM may include an oxalate-controlled diet, hyperhydration, pyridoxine, and oral citrate supplements to inhibit calcium oxalate crystallisation.[8,20,34] Haemodialysis and peritoneal dialysis may also be required to reduce calcium oxalate supersaturation in the plasma and minimise systemic oxalosis in individuals in more advanced stages of renal impairment. In such stages of impairment, combined or sequential liver–kidney transplantation may ultimately be warranted to replace the oxalate-overproducing liver and restore renal function.[20,34,62] Although isolated liver transplantation is a potentially useful procedure to correct the underlying metabolic defect in patients with PH1, it cannot restore lost renal function to the patient.[34] The procedure is not considered an ECM procedure for PH1 in the CEA, as it is not guideline recommended, except for in highly selected cases.[20] This is most likely due to the lack of literature reporting this practice and the fact that whether or not isolated liver transplantation is performed depends primarily on the personal position of the individual physician and not on the characteristics of the patient. Together, these attributes are highly indicative that isolated liver transplantation is not an ECM approach.

12.1.3 Model structure

No economic models for lumasiran or for other technologies used in UK clinical practice in the indicated population had been published at the time of model development. Therefore, a de novo CE model was developed that conforms with NICE requirements as expressed in the Guide to the Methods of Technology Appraisal.[156]

This standard Markov model was developed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) to assess costs and effects, life-years (LYs) and QALYs of lumasiran and ECM in a simulated cohort of patients with PH1. The cohort transitioned through nine health states defined by CKD stage, plasma oxalate levels, and/or transplant status, plus death. Figure D1 shows the design of the de novo Markov model for the CEA for lumasiran (for the full CE model, refer to Appendix 6: Cost-effectiveness model). The threshold

of 50 µmol/L plasma oxalate was used to signify the transition between late-stage health states with uncontrolled versus controlled oxalate levels, based on the use of this threshold in the literature to define a treatment target in PH1 and determine potential candidates for transplantation (Section 7.2.2). The model was designed to account for potential differences in natural history input values, rates of disease progression, and clinical management between patients with infantile onset of PH1, paediatric patients who develop PH1 after infancy, and adult patients. This economic analysis reports the weighted average of these two populations.

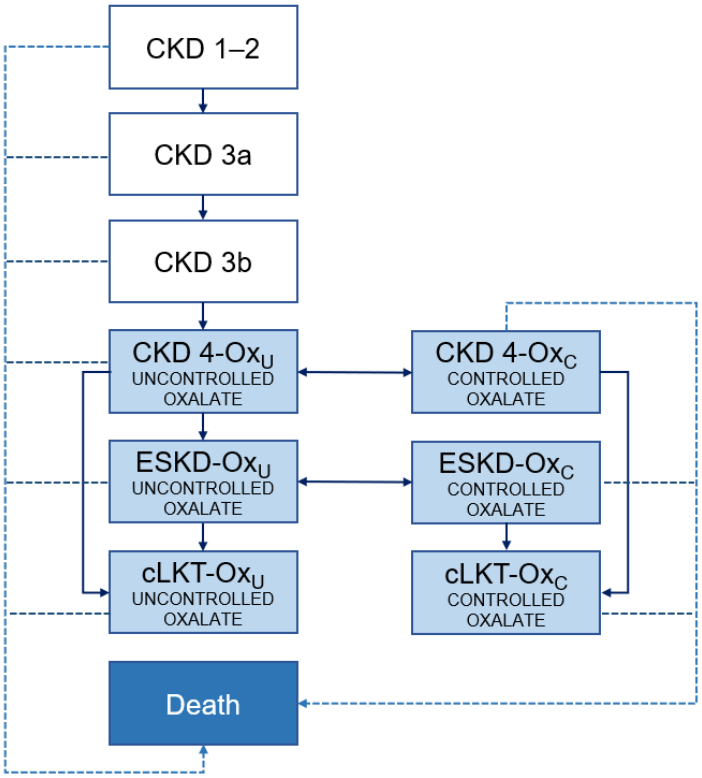

Figure D1. PH1 Markov model structure
A threshold of 50 µmol/L was used to distinguish controlled vs. uncontrolled oxalate based on the treatment target in PH1 identified from the literature (Section 7.2.2).
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ESKD=end-stage kidney disease; Ox_C=controlled oxalate levels; Ox_U=uncontrolled oxalate levels; PH1=primary hyperoxaluria type 1

No disease-specific classification system exists for categorising disease severity in PH1.[4,34] Instead, clinical practice guidelines for this disease largely stratify management on the basis of CKD stage.[20] This is clinically appropriate because renal decline is the central manifestation of clinical progression in PH1, and CKD stage maps directly to renal function (eGFR) and thus is a key indicator of disease progression and a determinant of the need for transplantation.[4,34] Moreover, HRQoL and/or disease-related complications may vary across CKD stages.[195] Definitions of CKD stages based on defined thresholds of eGFR have been formalised by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (Table D1).[194] As noted, these categories are associated with differences in HRQoL and/or disease-related complications in PH1, and they also correlate with healthcare costs.[213] As such, these categories are relevant health states to include in health-economic models.

Table D1. KDIGO Clinical Practice Guideline definitions of CKD stages

CKD stage	eGFR (mL/min/1.73m^2)	Description of eGFR category
1	≥90	Normal or high
2	60–89	Mildly decreased
3a	45–59	Mildly to moderately decreased
3b	30–44	Moderately to severely decreased
4	15–29	Severely decreased
5 (ESKD)	<15	Kidney failure

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; KDIGO=Kidney Disease: Improving Global Outcomes
Source: KDIGO 2013[194]

Furthermore, the relevance of CKD stage in PH1 has been reinforced in the KHI/OHF recommendations for appropriate endpoints for clinical trials in PH.[27] In particular, these recommendations highlight that the clinical manifestations of PH (e.g., kidney stones and oxalosis) vary by CKD stage.

In each Markov cycle, a patient who had not yet undergone transplantation could progress to the next CKD stage or remain in the same CKD stage. For the late-stage health states (CKD 4 and ESKD), transition between the uncontrolled oxalate (Ox_U) and controlled oxalate (Ox_C) states was also permitted. In the CE model, treatment with lumasiran is continued across all CKD stages; however, it is currently unknown whether clinicians in real-world practice will initiate lumasiran in patients with early-stage disease without rapid signs of progression; furthermore, it is unknown how clinical practice will vary by patient characteristics (e.g., age, age at disease onset).

For patients in the lumasiran cohort of the CE model, the transition probabilities from CKD 1 to CKD 4 were based on 12 months of observed effects of lumasiran on plasma oxalate in ILLUMINATE-A and ILLUMINATE-B. The transition probability from CKD 4/ESKD with uncontrolled oxalate to CKD 4/ESKD with controlled oxalate was based on 6 months of observed effects of lumasiran on plasma oxalate in ILLUMINATE-C. The lumasiran cohort was expected to have an increasingly higher proportion transitioning over time from late-stage health states with uncontrolled oxalate to corresponding health states with controlled oxalate.

Patients in the ECM cohort of the CE model would continue to increasingly accumulate oxalate and progress to more severe CKD stages as a result, in line with the natural disease progression of PH1 (Section 6.1.1).[26-28] The transition probabilities from CKD 1 to CKD 4 were based on the observed effects of placebo on plasma oxalate in the ILLUMINATE-A trial, and the relationship established between plasma oxalate and eGFR by Shah et al. (2020[28]; Section 12.2.1) Patients in the ECM cohort progressing beyond CKD 3b or entering the model with late-stage disease were assumed to have uncontrolled oxalate levels. It was assumed that patients on ECM could not transition from uncontrolled health states to controlled health states.

Transition to a less severe CKD stage was not permitted in either cohort, based on evidence from other renal conditions that suggests that once renal function is lost, it cannot be recovered.

For patients in either cohort in CKD 4 with uncontrolled oxalate, time to ESKD was modelled on the ESKD-free survival curves reported by the Harambat et al. (2010)[32] study retrieved during a systematic review of the literature (Appendix 1: Search strategy for clinical evidence). Harambat et al. was identified as the most relevant source for estimating the time to ESKD, given the size of the cohort and the duration of patient follow-up. The ESKD-free survival curves were reported by age and were complete, that is, all patients reached ESKD by age 80 years. Despite the retrospective design of the Harambat et al. study and the substantial number of patients lost to follow-up, this publication presents a robust description of the natural history of the rare disease, PH1, over a long timeframe. Since the distribution of the Harambat et al. study population leaned more towards CKD 3 than CKD 4, the ESKD-free survival curves reported by Harambat et al. were used to model the transition of patients from CKD 4-Ox_U to ESKD-Ox_U. The cohort in the CKD 4-Ox_U health state transitions to ESKD-Ox_U in a manner determined by the age-specific probability of ESKD described by the ESKD-free survival curves in all PH1 patients reported by Harambat et al. As a result, for such patients,

the model replicates the observed data from this sample of PH1 patients being managed in routine clinical practice. The application of Harambat et al. in CKD 4-Ox_U is conservative, since the study included patients in earlier stages of CKD (i.e., CKD 3).

Patients in the CKD 4-Ox_C health state were assumed to be stable and not experience disease progression (i.e., these patients could not transition to ESKD-Ox_C). Since oxalate is central to PH1 pathophysiology,[4] patients with oxalate levels being held below the threshold for control (50 µmol/L) have disease stabilisation and do not transition to the corresponding ESKD health state. Lumasiran selectively and durably silences the mRNA for the enzyme glycolate oxidase in the liver to achieve this level of control.[7]

The model allowed patients reaching CKD 4-Ox_U, CKD 4-Ox_C, ESKD-Ox_U, or ESKD-Ox_C to undergo combined/sequential liver–kidney transplantation (cLKT), in line with European clinical practice guidelines for PH1.[20] The per-cycle probability of transplantation was determined from the literature and transplantation activity in the UK.[52,214,215] Upon transplantation, these patients would remain in the post-transplantation health state (cLKT) or move to the absorbing health state (i.e., Death).

The cohort receiving transplant from CKD 4-Ox_U or ESKD-Ox_U transitions to cLKT-Ox_U and has worse post-transplant prognosis than the cohort receiving transplant from CKD 4-Ox_C or ESKD-Ox_C and transitioning to cLKT-Ox_C. This assumption is based on the effect of clinical status on post-transplant mortality from graft failure and other causes as observed over long-term follow-up in the Jamieson et al. (2005)[135] study of PH1 patients. Jamieson et al. found that the clinical status of a patient with PH1 immediately prior to transplantation has a significant impact on their post-transplantation outcomes (Section 7.2.2). The cLKT health state in the CE model accounts for the higher mortality and risk of graft failure in the first 5 years post-transplant for patients with poorer clinical status pretransplantation. Patients who were previously in late-stage health states with uncontrolled oxalate levels (i.e., unstable disease), and therefore had greater systemic oxalosis, were modelled as having poorer outcomes following transplantation. Those in late-stage states with controlled oxalate levels (i.e., stable disease) immediately prior to transplantation were assumed to have fewer systemic oxalosis–related complications and better outcomes following transplantation. After validation with clinical experts, the average of the two Kaplan–Meier (KM) curves from the Jamieson et al. (2005) study that referred to patients in *Very Good* and *Good* pre-operative condition was used to estimate post-transplantation mortality among patients with controlled oxalate levels. The average of the two KM curves referring to patients in *Fair* and *Poor* pre-operative condition was used to model patients with uncontrolled oxalate levels.

The cohorts in the CE model could transition to death from any live health state, with probabilities based on national statistics for the age-specific mortality rate in the population,[216] and adjusted by CKD stage–specific mortality multipliers. The same mortality rates were used for each of the late-stage health states (CKD 4 or ESKD) regardless of oxalate levels. These multipliers were derived from an analysis by Go et al. (2004) of longitudinal data for more than 1.1 million patients,[217] which have also been used in a published microsimulation model of the progression and treatment of CKD.[218]

The model structure and the definition of the health states were validated by UK clinical experts.

12.1.4 Justification of the CE model structure in line with the clinical pathway of care

Basing the model on progression through CKD stages is relevant in the context of a disease that is characterised by oxalate-related renal decline inevitably leading to ESKD.[17,18,30,31] PH1 clinical practice guidelines largely stratify management based on CKD stage.[20] This is clinically appropriate because CKD stage maps directly to eGFR and thus is a key indicator of disease progression and determinant of the need for transplantation.[4,34] Differences in CKD stage can also account for differences in HRQoL and disease-related complications.[195] PH1 disease characteristics have a progressive impact on patient HRQoL; advanced renal impairment can have a profound negative impact on patients and their caregivers,[42,43] while systemic oxalosis in the later stages of renal impairment[42,43] and transplantation also impact HRQoL and place patients at significant risk for life-threatening complications (Section 7.1).[26,51,53,219]

12.1.5 List and justification for all assumptions in the model

Table D2 summarises the major assumptions in the CE model for lumasiran. The CE model assumptions were validated by clinical experts as described in Section 12.2.5.

Table D2. Lumasiran CE model assumptions

Assumptions	Justification	References
Patients entering the model with late-stage disease (i.e., CKD 4 or ESKD) will have uncontrolled oxalate levels.	Patients with low eGFR have high plasma oxalate, according to publications on the natural history of PH1.[27,104] Based on an assessment of ILLUMINATE-C baseline data, PH1 patients with late-stage CKD are assumed to have severe, unstable disease with oxalate levels higher than threshold (50 µmol/L).[11] Oxalate levels lower than threshold would only be expected in PH1 patients with late-stage CKD who are on a successful oxalate-lowering therapeutic intervention.	Section 7.2.2 Section 12.2.1
Patients in the CKD 4-Oxc health state cannot transition to ESKD-Oxc.	Since oxalate is central to PH1 pathophysiology,[4] patients with oxalate levels being held below the threshold for control (50 µmol/L) have disease stabilisation and do not transition to the corresponding ESKD health state. Lumasiran selectively and durably silences the mRNA for the enzyme glycolate oxidase in the liver to achieve this level of control.[7]	Section 12.2.1
ECM-treated patients in CKD 4 or ESKD cannot transition from uncontrolled to controlled oxalate health states.	Natural history data show that current supportive management procedures, including dialysis, are generally not sufficient to consistently lower oxalate levels and stabilise PH1 in patients with advanced disease.[34]	Section 12.2.1
Over time, an increasingly higher proportion of patients in the lumasiran cohort are expected to transition from late-stage health states with uncontrolled to controlled oxalate levels.	In early-stage health states, the initial reduction in oxalate, typically to normal or near-normal, is expected to be maintained over the long term, based on 12-month data from ILLUMINATE-A and ILLUMINATE-B, and the phase 2 OLE showing no loss of therapeutic effect over the duration of follow-up (median follow-up 15 months; range, 11–22).[8,63,66,67,79] In late-stage health states, a longer phase of decline in oxalate is expected, based on the meaningful reductions in oxalate observed to 6 months ILLUMINATE-C[11] and the fact that plasma oxalate reductions resulting from inhibition of hepatic oxalate production may be counterbalanced by resorption of oxalate tissue stores into plasma until these stores are more completely drawn down (which requires a prolonged duration of effective oxalate-lowering therapy).[7,34]	Section 7.2.2 Section 9.6.1 Section 12.2.1
Transition probabilities for lumasiran apply to all cycles for as long as patients are on treatment.	The trend observed over 12 months in ILLUMINATE-A is expected to be maintained over time. This is based on 1) data from extension studies showing no loss of therapeutic effect over the duration of follow-up in patients treated with lumasiran;[66] 2) the mechanism of action of lumasiran, which selectively and durably silences the mRNA for the enzyme glycolate oxidase in the liver;[7] 3) lack of evidence from preclinical or clinical studies to suggest the potential for tachyphylaxis (rapidly diminishing response to successive doses) with lumasiran; and 4) lack of recognised mechanisms by which the biological pathways responsible for PH1 could adapt so that patients develop tolerance to chronic administration of hepatic GO enzyme RNAi silencing therapeutics. No increase in eGFR (i.e., recovery of lost eGFR) was permitted in the base case, which was a conservative assumption given the inverse relationship between oxalate and eGFR.[28]	Section 12.2.2
ECM transition probabilities are applied following lumasiran discontinuation in patients in CKD 1–3b health states.	Lumasiran treatment discontinuation in CKD 1–3b patients is modelled on time-on-treatment data obtained from ILLUMINATE-A and ILLUMINATE-B at 12 months and extrapolated beyond the trial period using log-normal parametric distribution. The cohort discontinuing lumasiran is then modelled using ECM transition probabilities following lumasiran discontinuation.	Section 12.2.1

Assumptions	Justification	References
Transition to less severe CKD stages is not permitted.	This assumption is based on consensus that once renal function is lost, it cannot be recovered. Evidence to the contrary is limited.	Section 12.2.1
Mortality RRs by health state for PH1 are based on a model of non-PH1-related CKD.	It is appropriate to use these multipliers, even though they were not developed within a PH1 population, because the aim of this aspect of the CE model is to quantify the mortality impact of renal dysfunction independently of the presence of PH1, to obtain the increased risk of death related to each CKD stage. This is a conservative assumption that does not account for increased risk of mortality due to systemic oxalosis or infantile onset of PH1.	Section 12.2.1

CE=cost effectiveness; CEA=cost-effectiveness analysis; CI=confidence interval; CKD=chronic kidney disease; ECM=established clinical management; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; HRQoL=health-related quality of life; mRNA=messenger ribonucleic acid; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; PH1=primary hyperoxaluria type 1; RR=relative risk

12.1.6 Definition of what the model's health states are intended to capture

Acute and chronic consequences of PH1

Within each of the alive health states, the model estimates the impact of both acute and chronic PH1 consequences, considering the following:

- The risk of renal stone events by treatment that may occur at every cycle in any of the health states, over the entire time horizon of the model. Utility decrements and costs associated with managing renal stone events were considered in the model (Section 10.1.9)
- The impact of CKD itself (i.e., separate from PH1-related complications) on HRQoL, as this is the key driver of HRQoL impairment as the disease progresses
- The per-cycle prevalence and associated costs of high-intensity and normal-intensity dialysis for patients in CKD 4/ESKD (Section 10.1.9)
- The per-cycle prevalence of systemic oxalosis complications for patients with CKD 4/ESKD, and associated disutilities and costs
- The per-cycle probability of liver–kidney transplantation for patients with CKD 4/ESKD), and its associated costs, disutilities, and mortality, together with the per-cycle probability, costs, and disutilities associated with graft failure and retransplantation in post-transplant health states

The ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C trials served as key sources of data on the clinical effectiveness of lumasiran for this CEA. The clinical endpoints in these trials were designed to align with the essential goals of PH1 treatment described in Sections 7.2.2 and 8.4. In earlier stages of disease, the goal is to halt and thus avoid the consequences of disease progression. In later stages of disease, the goal is to reduce the need for dialysis, stabilise the disease, prevent the incidence of new complications of systemic oxalosis, or promote reversal of systemic oxalosis among affected individuals. These improvements are expected to enable more patients to reach and achieve better post-transplantation outcomes.

The key endpoints of ILLUMINATE-A, change in urinary and plasma levels of oxalate,[33,179] are meaningful short-term measures since these directly reflect the extent of oxalate overproduction by the liver, which drives the symptomatology and complications of PH1.[4,28,56,220] Oxalate levels are also practical measures over the relatively short time scale typical of RCTs,[27] providing sensitive readouts for treatments like lumasiran that target PH1 by reducing hepatic oxalate output. Oxalate levels provide a snapshot of disease activity at a given point in time. Their incorporation in the CEA allows fine-scale mapping of clinical data from the ILLUMINATE trials to key health-economic parameters in the model.

Elevated oxalate levels directly and causally drive kidney damage and renal stone formation, as highlighted by the KHI/OHF recommendations.[27] Since the kidneys are the primary site of organ pathology caused by

oxalate,[4,34] eGFR is the main measure used in clinical practice to monitor the degree of morbidity caused by exposure to oxalate, as well as to define disease progression and guide disease management decisions.[20] Progressive renal decline with eventual renal failure is the core long-term consequence of PH1 and of paramount importance to patients,[27,45] while also driving the intensity of HCRU and associated costs (e.g., by requiring dialysis and potentially a combined liver–kidney transplant in the late stages of renal decline[20]). Accordingly, renal function is the main measure used in the CEA to model the effectiveness of lumasiran.

Association between oxalate and kidney function in PH1

eGFR is collected and analysed as a secondary endpoint in all ILLUMINATE studies (except in dialysis patients) strictly to understand the effects of lumasiran on this measure over longer periods. eGFR was not included in the statistical testing hierarchy for the 6-month double-blind study period of ILLUMINATE-A, as there was no expectation that lumasiran would show a statistically significant effect versus ECM during this period, as explained in Section 9.9.2. As such, hepatic oxalate production is considered a more appropriate short-term indication of disease activity and the key driver of chronic renal decline in PH1.

Publications reporting on associations between oxalate and eGFR in PH1 were identified through the SLR described in Section 9.1 and two targeted literature reviews. The SLR, which was performed to identify clinical, economic, and HCRU data in PH1, retrieved three studies of interest: Garrelfs et al. (2021),[8] Michael et al. (2020),[67] and Milliner et al. (2021).[104] The first targeted literature review was performed to gather data on the rate of CKD progression/GFR decline over time in PH, the relationship between CKD progression/GFR decline and urinary or plasma oxalate levels, the impact of pyridoxine, and other prognostic factors for progression. The following databases/abstract booklets were searched: PubMed, Case Reports, Embase/Web of Science, the ASN (2016–2019), ESPN (2017–2018), IPNA (2016 and 2019), ISN (2019–2020), and the ISPOR Presentations Database. A total of 127 publications from 1,632 search results were included in the first targeted literature review. After removing duplicates, 50 publications were determined to be highly relevant to the research questions, of which three (Morgan et al. 1987[221]; Watts et al. 1983[222]; Hoppe et al. 1998[223]) were determined to be of particular relevance to CKD progression/eGFR decline and oxalate levels.

The second targeted literature review was performed to gather data on the differential progression to ESKD by age at clinical onset, the relationship of oxalate (and any other relevant variable measured in the ILLUMINATE studies) with eGFR, and the natural history of acute kidney injury in PH1. The following databases were searched: PubMed, the ISPOR Presentations Database, and Google Scholar. Fifty-three out of 595 search results were included in the second targeted literature review. After removing duplicates, 16 publications were determined to be highly relevant to the research questions, of which five (Milliner et al. 2020[27]; Perinpam et al. 2017[224]; Shah et al. 2020[28]; Selistre et al. 2018[225]; Hoppe et al. 2017[226]) were determined to be of particular relevance to the relationship between oxalate and eGFR in PH1.

Studies were evaluated based on the:

- Relevance of the patient population and comparability of baseline characteristics to the ILLUMINATE-A and ILLUMINATE-B populations
- Suitability of the study design, data sources, and sample sizes. Post hoc analyses of clinical trials, observational studies, and studies with larger samples were prioritised
- Appropriateness of the patient population in which the association between oxalate and eGFR was reported. Studies with a higher proportion of patients with PH1 were prioritised
- Availability and robustness of reported eGFR and oxalate measurements
- Type of association between oxalate and eGFR reported (e.g., linear vs. nonlinear; cross-sectional vs. longitudinal). Longitudinal studies reporting regression equations and association figures were prioritised as they better reflect the complex association between oxalate and eGFR[29]

Two out of the nine non-lumasiran studies reported on urinary oxalate. Watts et al. (1983)[222] reported patient-level urinary oxalate values at baseline, but no association with eGFR was available. Perinpam et al. (2017)[224]

reported a regression equation between urinary oxalate, plasma oxalate, and eGFR, but in a mixed patient population (PH and non-PH patients).[222,224] We focused on the association between plasma oxalate and eGFR due to lack of urinary oxalate data in the nine non-lumasiran studies retrieved. Of the studies retrieved, Shah et al. (2020), Milliner et al. (2020), Milliner et al. (2021), and Perinpam et al. (2017) were considered relatively high-quality studies, based on the evaluation criteria listed above. These studies were further analysed to characterise the association between plasma oxalate and eGFR.

Of the studies listed in Table D3, Shah et al (2020)[28] was the only longitudinal follow-up of individual patients that established a temporal link between eGFR and plasma oxalate. The longitudinal design and availability of patient-level data makes Shah et al. the preferred choice to model the relationship between eGFR and plasma oxalate. Shah et al. report this association as a slope; eGFR is reduced by 1.27 mL/min/1.73 m^2 for every 1 µmol increase in plasma oxalate. Use of this relationship from Shah et al. is justified since eGFR data from the ILLUMINATE trials are unlikely to be representative of a true clinical effect. This is evident from the noisy eGFR data (i.e., wide CIs around point estimates; Section 9.6), the small sample sizes, and the [redacted] (Section 9.9.2).

Table D3. Key study characteristics and reported associations between plasma oxalate and eGFR

	ILLUMINATE-A[8] ILLUMINATE-B[67]	Shah et al. 2020[28]	Perinpam et al. 2017[224]	Milliner et al. 2020[27]	Milliner et al. 2021[104]
Study characteristics					
Data source	Pooled clinical trials of lumasiran	The patient sample likely overlaps with the patient sample analysed in Milliner et al. 2020 as both use data from the RKSC PH registry	Electronic medical records from Mayo Clinic	The patient sample likely overlaps with the patient sample analysed in Shah et al. 2020 as both use data from the RKSC PH registry	Three clinical trials of an *Oxalobacter formigenes* preparation for treatment of PH1
Study design	ILLUMINATE-A: Phase 3 randomised, double-blind, placebo-controlled clinical trial ILLUMINATE-B: Phase 3 open-label, single-arm clinical trial of lumasiran	Retrospective observational study	Retrospective observational study	Retrospective observational study	Post hoc trial analysis
Sample size	Lumasiran arm 44 (26 from ILLUMINATE-A and 18 from ILLUMINATE-B)	227, of which 59 were assessed for correlation between POx and eGFR	39	128	OC3-DB-01: 42 OC3-DB-02: 36 OC5-DB-01: 28
Patient characteristics					
PH1, %	100%	Not reported specifically for the subset of patients assessed for correlation. 72% among all included patients	Assessed but not reported	75%	OC3-DB-01: 83.3% OC3-DB-02: 86.1% OC5-DB-01: 92.9%

	ILLUMINATE-A[8] ILLUMINATE-B[67]	Shah et al. 2020[28]	Perinpam et al. 2017[224]	Milliner et al. 2020[27]	Milliner et al. 2021[104]
Age at baseline	ILLUMINATE-A: Paediatrics and adults ILLUMINATE-B: Infants and children <6 years old	Not reported specifically for the subset of patients assessed for correlation. Likely a mix of paediatrics and adults	Paediatrics and adults	Paediatrics and adults	Paediatrics and adults
CKD stage	ILLUMINATE-A: CKD 1: 9 (34.6%) CKD 2: 13 (50.0%) CKD 3a: 2 (7.7%) CKD 3b: 2 (7.7%) ILLUMINATE-B: CKD 1–3a: 100% (eGFR >45 mL/min/1.73 m^2 in patients ≥12 months; non-elevated serum creatinine if <12 months)	Among all included patients (not the subset assessed for correlation) CKD 1: 118 (32%) CKD 2: 135 (36%) CKD 3a: 72 (19%) CKD 3b: 45 (12%)	Not reported	Not reported	80.5% - 85.7% had CKD 1–2 (Inclusion criteria permitted recruitment of patients with CKD 1–3): OC3-DB-01: 85.7% OC3-DB-02: 80.5% OC5-DB-01: 85.7%
Outcomes					
eGFR estimation	• MDRD formula (age ≥18 years) • Schwartz equation (age <18 years)	• CKD-EPI equation (age ≥18 years) • Schwartz equation (age <18 years)	• CKD-EPI equation (age ≥18 years) • Schwartz equation (age <18 years)	• CKD-EPI equation (age ≥18 years) • Schwartz equation (age <18 years)	• MDRD formula (age ≥18 years) • Schwartz equation (age <18 years)
eGFR range	ILLUMINATE-A: Range from Fig. 15 of the clinical study report, mL/min/1.73 m^2: Baseline: 30–130 During study: 30–180 ILLUMINATE-B: Range, (from 16/18 patients age ≥1 years) mL/min/1.73 m^2: Baseline: 64.67–174.06	Not reported	From the figure, the range of the points, mL/min/1.73 m^2: 15–200	From the figure, the range of the points, mL/min/1.73 m^2: 7.5–150	From the figure, the range of the points, mL/min/1.73 m^2: OC3-DB-01: 40–155 OC3-DB-02: 25–137 OC5-DB-01: 25–155 Pooled OC3-DB-02 and OC5-DB-01: 25–155
Plasma oxalate range	ILLUMINATE-A and ILLUMINATE-B pooled: POx at baseline, µmol/L: Mean (SE): 14.1 (1.1) 95% CI: 12.0, 16.3 ILLUMINATE-A: Range: 7.0–43.5 ILLUMINATE-B: Range: NR*	Not reported	From the figure, the range of the points, µmol/L: 1–50	From the figure, the range of the points, µmol/L: 0–77.5	From the figure, the range of the points, µmol/L: OC3-DB-01: 3–25 OC3-DB-02: 5–35 OC5-DB-01: 4–44 Pooled OC3-DB-02 and OC5-DB-01: 3–44

	ILLUMINATE-A[8] ILLUMINATE-B[67]	Shah et al. 2020[28]	Perinpam et al. 2017[224]	Milliner et al. 2020[27]	Milliner et al. 2021[104]
Formula	Not applicable	Not reported eGFR slope: eGFR reduced by 1.27 mL/min/1.73 m2 per 1 mol/L increase in POx; (p < 0.001)	Ln(POx)=5.2531−0.8734*Ln(eGFR)−0.7814*(Group=EH)−1.3604*(Group=USD)−1.3295*(Group=Non Stone Former) Can be used in the form of: Ln(POx)=5.2531−0.8734*Ln(eGFR)	Not reported, but curve is available	OC3-DB-01: POx=13.63−0.072*eGFR OC3-DB-02: POx=23.79−0.14*eGFR OC5-DB-01: POx=29.45−0.169*eGFR Pooled OC3-DB-02 and OC5-DB-01: POx=25.39−0.142*eGFR
Model used	Not applicable	Generalised estimating equations (GEE) adjusting for time were used to evaluate the association between plasma oxalate and eGFR throughout follow-up	The relationships between plasma oxalate and eGFR were compared for the four study groups (i.e., PH, enteric hyperoxaluria, urinary stone disease, and nonstone–forming patients) with a scatterplot (both on the natural log scale to account for skewness), and with a linear GEE model	Third degree polynomial regression	- Linear regressions - For the pooled data, a nonparametric smooth curve (local polynomial regression) was also generated
Data extraction from figures	Not applicable	Not applicable	Not feasible	Figure 2	Figures 1–2

*The range of baseline plasma oxalate values in ILLUMINATE-B (6.6–30.6 µmol/L) has since been published by Sas et al. (2021)[9] and included here for transparency.

CI=confidence interval; CKD=chronic kidney disease; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; EH=enteric hyperoxaluria; GEE=generalised estimating equation; MDRD=Modification of Diet in Renal Disease; NR=not reported; PH=primary hyperoxaluria; PH1=primary hyperoxaluria type 1; POx=plasma oxalate; RKSC=Rare Kidney Stone Consortium; SE=standard error; USD=urinary stone disease

12.1.7 Key features of the model not previously reported

Table D4 summarises the additional key features of the model.

Table D4. Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime horizon	The lifetime horizon is the appropriate time scale for the CEA, given that PH1 is a genetic disease that commonly presents in infancy or childhood and requires long-term specialist management across a patient's lifetime. The model simulation runs until the cohort reaches 100 years of age.	NICE Guide to the Methods of Technology Appraisal (2013)[156]
Discount rates	Both costs and outcomes (LYs and QALYs) were discounted at 3.5% annually.	The chosen discount rate for costs and outcomes is in line with the NICE Guide to the Methods of Technology Appraisal.	NICE Guide to the Methods of Technology Appraisal (2013)[156]
Perspective (NHS/PSS)	Third party payer perspective (NHS and PSS) in England.	In the base-case setting the perspective of the UK NHS/PSS is considered, including only direct medical costs.	NICE Guide to the Methods of Technology Appraisal (2013)[156]

Factor	Chosen values	Justification	Reference
Cycle length	The simulation is conducted in cycles of 6 months.	The cycle duration was selected to match the duration of the primary analysis periods of the ILLUMINATE trials, the key sources of data for the model.[8,79,181] Shorter cycle lengths would not permit the measurement of meaningful changes in oxalate. Longer cycle lengths would fail to capture real-time progression in CKD.	ILLUMINATE-A[33]

CEA=cost-effectiveness analysis; CKD=chronic kidney disease; LY=life-years; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PH1=primary hyperoxaluria type 1; PSS=Personal Social Services; QALY=quality-adjusted life-years, UK=United Kingdom

12.2 Clinical parameters and variables

12.2.1 Clinical evidence used in the cost-effectiveness analysis

Data sources

Data on PH1-related clinical variables needed to populate the model were identified in the SLR described in this submission (Section 9.1 to 9.3). Where required, values for clinical variables were also obtained from the ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C studies. In addition, four targeted literature searches were conducted between May 2020 and April 2021 to identify studies reporting on prognostic indicators of CKD progression in PH1, the relationship between oxalate and CKD progression, the rate of progression to ESKD in PH1, the relationship between oxalate and transplant outcomes, and transplantation rates.

Health states

As described in Section 12.1.3, the health states for the model were based on CKD stage, oxalate levels (for late-stage disease only), and transplantation status.

In the CE model, the cohort starts the simulation in one of the three early disease stages (i.e., CKD 1–2, 3a, or 3b) or in one of two late-stage health states (i.e., CKD 4-Ox_U or ESKD-Ox_U) with uncontrolled oxalate, defined as plasma oxalate greater than 50 µmol/L (Table D6). The initial distribution of CKD stages was informed by the pooled distribution of patients from Singh et al. (2021).[25] Based on their initial measurement, approximately two-thirds of patients with PH1 have early disease (CDK 1–3b) and one-third have late-stage disease (CKD 4 or ESKD). The distribution of the cohort at baseline is described in more detail below.

CKD stages 1 and 2 were combined to form the first health state. Setting aside laboratory values, it is difficult to distinguish CKD 1 from CKD 2 in PH1, since these stages are expected to have identical use of resources, HRQoL, and care provided. Patients have relatively well-preserved renal function and treatment strategies are similar. Cochat et al. (2012)[20] provides guidance for early-stage PH1 patients and then more specifically for individual later stages of renal impairment. In doing so, Cochat et al. does not distinguish between CKD 1 and CKD 2. The rarity of the disease as well as the small number of patients participating in the ILLUMINATE-A and ILLUMINATE-B trials support this approach, as unnecessarily dividing health states would increase the uncertainty relating to the estimated transition probabilities.

Baseline characteristics

Table D5 shows the characteristics of the simulated patient cohort at model entry, based on the baseline characteristics of the population in the ILLUMINATE trials, and the literature.

Table D5. Baseline model cohort characteristics

Characteristic	Model input	Source
Initial age (years)		
Paediatric population	[redacted]	ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C at baseline,[33,64,79] children <18 years
Adult population	[redacted]	ILLUMINATE-A and ILLUMINATE-C at baseline,[33,64] adults ≥18 years
Mean weight (kg)		
Paediatric population	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline,[33,64,79] children <18 years
Adult population	[redacted]	ILLUMINATE-A and ILLUMINATE-C at baseline,[33,64] adults ≥18 years
Percentage of males	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline[33,64,79]
Percentage of paediatric patients	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline[33,64,79]

CKD=chronic kidney disease; ESKD=end-stage kidney disease

Health state distribution of cohort at baseline

The proportion of the cohort entering the model in each state was informed by the pooled distribution of patients on entry to the Singh et al. (2021) study (Table D6).[25] Patients reported by Singh et al. to be in CKD 3 (without distinction between CKD 3a and CKD 3b) were assumed to be equally distributed between stages 3a and 3b. Patients entering the model in the late-stage health states were assumed to have uncontrolled oxalate levels, i.e., higher than the threshold of 50 µmol/L (Section 12.1.3).

Table D6. Cohort distribution by model health state

Health state	Proportion
CKD 1–2	38.2%
CKD 3a	12.1%
CKD 3b	12.1%
CKD 4-Ox_U	9.7%
ESKD-Ox_U	27.9%
Total	**100%**

Patients entering the model at CKD 4 or ESKD were assumed to have oxalate levels higher than the threshold of ≥50 µmol/L.
CKD=chronic kidney disease; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate
Source: Singh et al. (2021)[25]

Treatment effectiveness

Treatment effectiveness was based on changes in plasma oxalate linking to eGFR in both the lumasiran and ECM cohorts, but in the ECM cohort, this was based on the available 6-month data from the placebo-arm of the ILLUMINATE-A trial. Note that 12-month data are unavailable for the ECM arm since patients in the placebo-controlled ILLUMINATE-A trial crossed over to lumasiran in the extension phase after Month 6.

In the ECM cohort, treatment effectiveness was based on absolute change in plasma oxalate over 6 months in the ILLUMINATE-A trial (placebo arm, 2.23 µmol/L change) and the temporal link between eGFR and plasma oxalate determined by Shah et al. (2020).[28] According to Shah et al., there is a mean absolute eGFR decrease of 1.27 mL/min/1.73 m^2 per 1 µmol/L increase in plasma oxalate. Together, these values were used to estimate the transition rate per cycle across pre-ESKD health states (from CKD 1–2 to CKD 3a, from CKD 3a to CKD 3b, and from CKD 3b to CKD 4) in the ECM cohort. This analysis excluded [redacted].

The plasma oxalate–based eGFR decline was applied to each health state within the range from CKD1 through 3b to model pre-ESKD CKD progression, based on the assumption that each health state was assumed to start at the mean eGFR observed among patients included in ILLUMINATE-A (placebo and lumasiran arms pooled) who were in that health state at baseline and progress to later states via modelled eGFR decline (Table D7).

Table D7. eGFR by pre-ESKD CKD health states and eGFR distance to next CKD stage

Pre-CKD health state	eGFR (mL/min/1.73 m^2)			Decrement to next health state
	Lower bound	Upper bound	Mean	
CKD 1–2	60.0	120.0	89.95*	37.68
CKD 3a	45.0	59.0	52.27*	15.25
CKD 3b	30.0	44.0	37.02*	15.02
CKD 4	15.0	29.0	22.00†	—

*Mean eGFR was obtained from pooled lumasiran and placebo data from the ILLUMINATE-A trial.
†Arithmetic mean of the lower and upper bound.
CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease
Source: Alnylam Data on File (ILLUMINATE-A [ALN-GO1-003] CSR)[33]

Then, the mean time required to transition from one pre-ESKD health state to the next more severe health state was calculated for the ECM cohort. This was based on the eGFR distance from the starting state to the next more severe state (Table D7) and the estimated annual change in eGFR (based on the observed change in plasma oxalate and the relationship between plasma oxalate and eGFR as previously described). Using these figures, the annual probability of transitioning to the next more severe health state was estimated as the inverse of the mean number of years required to transition. As a final step, annual probability was converted to the 6-month per-cycle probability.

The lumasiran treatment effect on plasma oxalate was modelled on percent rather than absolute change, since absolute reduction in patients is expected to be higher at first and decrease as lower plasma oxalate levels are reached. Additionally, an absolute reduction in plasma oxalate may lack face validity since negative values of plasma oxalate are reached within a few cycles if the same absolute reduction in plasma oxalate is applied to each cycle. Therefore, in the lumasiran cohort, treatment effectiveness in the pre-ESKD health states was based on percent change in plasma oxalate observed [redacted] The mean change in plasma oxalate [redacted].

These changes in plasma oxalate across pre-ESKD health states in patients treated with lumasiran are expected to correspond to no reduction in eGFR (a conservative assumption), according to the relationship between plasma oxalate and eGFR as reported by Shah et al., i.e., a decrease of 1.27 mL/min/1.73 m^2 per 1 µmol/L increase in plasma oxalate. [redacted] (Section 9.6), [redacted].

The mean change [redacted] was used to estimate the treatment effectiveness and the transition rate per cycle [redacted]. Note that this mean change [redacted] (Table C12) [redacted].

Transition probabilities in pre-ESKD health states—lumasiran arm

Modelling progression across pre-ESKD health states in the lumasiran arm followed the methodology described above. The per-cycle rate of oxalate change was informed by [redacted] It is expected that the trend observed over 12 months would be maintained over time, based on 1) data from extension studies showing no loss of therapeutic effect over the duration of follow-up in patients treated with lumasiran;[63,66,68] 2) the mechanism of action of lumasiran, which selectively and durably silences the mRNA for the enzyme glycolate oxidase (GO) in the liver[7]; 3) lack of evidence from preclinical or clinical studies to suggest the potential for tachyphylaxis (rapidly diminishing response to successive doses) with lumasiran; and 4) lack of recognised mechanisms by which the biological pathways responsible for PH1 could adapt so that patients develop tolerance to chronic administration of hepatic GO enzyme RNAi silencing therapeutics. No increase in eGFR (i.e., recovery of lost eGFR) was permitted in the base case, which was a conservative assumption given the inverse relationship between oxalate and eGFR.[28]

Table D8 reports the transition matrices corresponding to the per-cycle probabilities of progression across the pre-ESKD health states in the lumasiran arm. The cycle probabilities were estimated by applying the method described in the *Treatment effectiveness* section and applying a probability of zero to transitions to lower (i.e., less severe) pre-ESKD health states. Progression to more severe health states (i.e., CKD 4/ESKD) only applied to the proportion of the CKD 1–3b cohort having discontinued lumasiran treatment, at which point ECM transitions are applied.

Table D8. Transition matrix within the pre-ESKD health states, lumasiran arm

From ↓ \ To→	CKD 1–2	CKD 3a	CKD 3b	CKD 4-OxC
Any cycle				
CKD 1–2	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]

CKD=chronic kidney disease; ESKD=end-stage kidney disease; Ox_C=controlled oxalate

Transition probabilities in pre-ESKD health states—ECM arm

Modelling progression across pre-ESKD health states in the ECM arm reflects an understanding that ongoing accumulation of oxalate produced by the liver results in progressive decline in renal function.[4,30,31]

In the CE model, the per-cycle rate of oxalate accumulation was informed by data from the placebo arm in the ILLUMINATE-A study. In this study an increase in plasma oxalate concentration by 2.23 units was observed in the 6 months of placebo treatment. This corresponded to a per-cycle decrease in eGFR of 2.83 units based on the relationship between oxalate and eGFR quantified by Shah et al (2021).[28]

Table D9 reports the transition matrices corresponding to the per-cycle probabilities of progression across the pre-ESKD health states (CKD 1–2, CKD 3a, CKD 3b, and CKD 4 with uncontrolled oxalate) in the ECM arm for all extrapolation periods. The cycle probabilities were estimated by applying the method described in the *Treatment effectiveness* section above and applying a probability of zero to transitions to lower (i.e., less severe) pre-ESKD health states.

Table D9. Transition matrix within the pre-ESKD health states, ECM arm

From↓ \ To→	CKD 1–2	CKD 3a	CKD 3b	CKD 4-Ox_U
Any cycle				
CKD 1–2	0.925	0.075	0.000	0.000
CKD 3a	0.000	0.814	0.186	0.000
CKD 3b	0.000	0.000	0.811	0.189

CKD=chronic kidney disease; ESKD=end-stage kidney disease; Ox_U=uncontrolled oxalate

Transition probabilities from CKD 4 to ESKD—lumasiran arm

[redacted]. The lumasiran treatment effect is assumed to continue, based on data from extension studies showing no loss of therapeutic effect over the duration of follow-up in patients treated with lumasiran.[63,66] No progression from CKD 4 to ESKD was modelled for the lumasiran cohort based on the observed reduction in plasma oxalate. This change in plasma oxalate is expected to correspond to no reduction in eGFR (i.e., improvement in CKD stage), which is a conservative assumption.

Transition probabilities between CKD 4/ESKD health states differentiated by oxalate levels—lumasiran arm

Only the lumasiran cohort is expected to transition from late-stage health states with oxalate levels above 50 µmol/L (CKD 4-Ox_U or ESKD-Ox_U) to health states with oxalate levels below 50 µmol/L (CKD 4-Ox_C or ESKD-Ox_C), as a result of the lumasiran treatment effect. The ECM cohort is assumed to have no probability of transitioning to health states with oxalate levels below 50 µmol/L.

[redacted] (Alnylam, Data on File). This was assumed to represent the mean plasma oxalate level in the CKD 4-OxU and ESKD-OxU health states.

The per-cycle probability of transitioning from CKD 4-Ox_U or ESKD-Ox_U health states to the corresponding health states with controlled oxalate levels was estimated for patients receiving lumasiran. The distance to health states with controlled oxalate levels was calculated (Table D10). This distance was assumed to be identical across both late-CKD stages (i.e., CKD 4 and ESKD).

Table D10. Plasma oxalate in CKD 4 and ESKD health states and plasma oxalate distance to next CKD stage

	Mean plasma oxalate (µmol/L)	Plasma oxalate distance to health state with oxalate lower than threshold (µmol/L)*
CKD 4-Ox_U or ESKD-Ox_U	[redacted]	[redacted]
CKD 4-Ox_C or ESKD-Ox_C	[redacted]	[redacted]

*Threshold was defined as 50 µmol/L.
CKD=chronic kidney disease; ESKD=end-stage kidney disease; NA=not applicable; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

The percent reduction in plasma oxalate for each cycle was calculated based on the per-cycle reduction in plasma oxalate [redacted] (Table D11). Since at every next cycle the average starting plasma oxalate level is lower than in the preceding cycle, the resulting absolute reduction in plasma oxalate obtained by applying the percentage plasma oxalate reduction, will also be lower from one cycle to the next.

Table D11. Reduction in plasma oxalate for each cycle in CKD 4 and ESKD health states

	Reduction in plasma oxalate
Percent reduction in plasma oxalate, %	
Per-cycle	[redacted]
Absolute reduction in plasma oxalate, µmol/L	
Cycle 1	[redacted]
Cycle 2	[redacted]
Cycle 3	[redacted]
Cycle 4	[redacted]

The plasma oxalate distance from the health state with uncontrolled oxalate to the corresponding health state with controlled oxalate was used, together with the estimated average percent reduction from baseline in plasma oxalate per cycle, to calculate the mean number of years required to transition from the former to the latter state. Based on this analysis, there was a [redacted] probability per cycle of transitioning from health states with uncontrolled oxalate to health states with controlled oxalate during the first cycle of treatment and a probability of 1 at the second cycle (i.e., the cohort would take 2 cycles to reduce plasma oxalate levels to below the threshold) (Table D12).

Table D12. Transition probability from uncontrolled oxalate to controlled oxalate CKD 4/ESKD health states

	Years needed to reach the threshold (return period)	Annual exceedance probability (1/return period)	Probability per 6-month cycle
Cycle 1	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]

The maximum probability is capped at 1.00.

CKD=chronic kidney disease; ESKD=end-stage kidney disease

Note that transition between CKD 4-Ox_C and ESKD-Ox_C is not permitted for the reasons stated in *Transition probabilities from CKD 4 to ESKD—lumasiran arm*.

Transition probabilities from CKD 4 to ESKD—ECM arm

The transition from CKD 4-Ox_U to ESKD-Ox_U in the ECM cohort was modelled using ESKD-free KM survival curves published by Harambat et al.[32] Harambat et al. estimated time to ESKD by patient age in a large European PH1 cohort (n=155 for analysis). The analysis revealed an increasing hazard of ESKD as patients age, indicating that over time, a greater proportion of pre-ESKD patients will progress to ESKD.

The published ESKD-free KM survival curves were digitised and patient-level data were reconstructed via the Guyot method (based on the published number at risk; Figure D2). Based on Akaike information criterion (AIC) estimators, the Gompertz model resulted in the best-fitting distributions for the KM survival curve (Table D13). Although the survival curve shown in Figure D2 was complete, this parametric curve was used to smooth the ESKD-free survival curve.

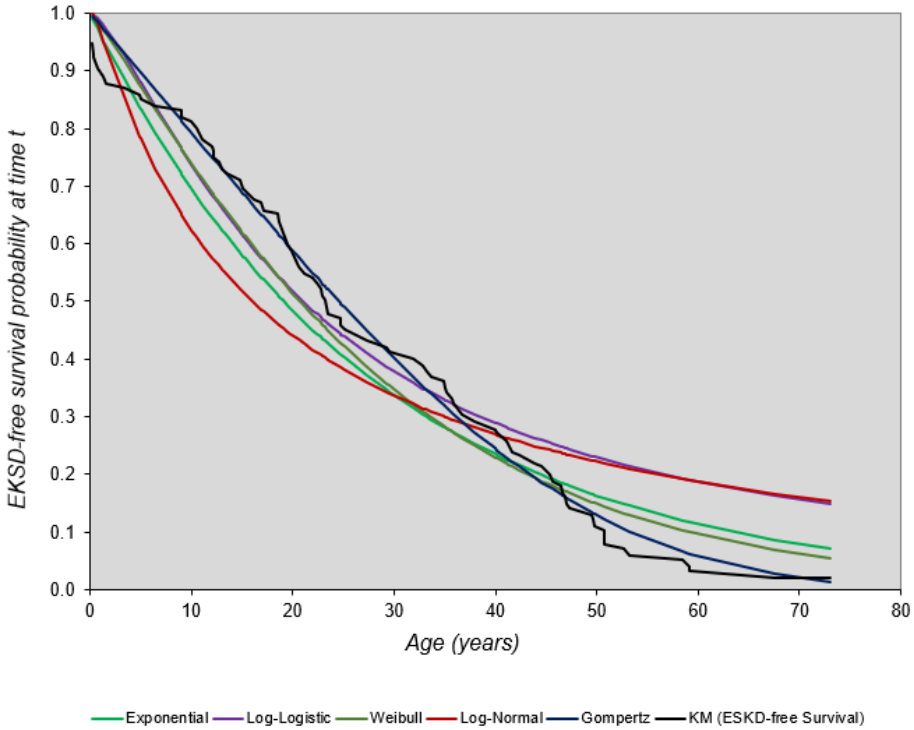

Figure D2. ESKD-free survival curve and parametric extrapolations
ESKD=end-stage kidney disease; KM=Kaplan–Meier

Source: Harambat et al. (2010)[32]

Table D13. AIC fit statistics of ESKD-free survival curve

	All PH1 patients (n=155)
Exponential	1314.20
Weibull	1312.59
Log-logistic	1365.74
Log-normal	1391.92
Gompertz	**1290.51**

AIC=Akaike information criterion; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria type 1

The ESKD-free survival curve was used to calculate the per-cycle probability of transitioning from the CKD 4-Ox_U health state to the ESKD-Ox_U health state. This is a conservative approach given that the Harambat population included a mix of patients including some in lower CKD stages than CKD 4 (i.e., patients who were, on average, further from progression to ESKD when compared with a pure CKD4-Ox_U cohort).

The resulting proportions of the model cohort free from ESKD in the lumasiran and ECM arms are presented in Figure D3 for the adult and paediatric populations. Since a proportion of the overall cohort enters the model in ESKD, the proportion free of ESKD at the start is less than 1. Note that the lumasiran cohort free from ESKD included the proportion of the cohort who discontinued treatment and to whom the probability of transition to ESKD was applied as for the ECM cohort.

A. Paediatric population

B. Adult population

Figure D3. Proportion of cohort who have not reached ESKD over the time horizon of the CE model
The proportion of the paediatric (A) and adult (B) cohorts who have not reached ESKD, based on 27.9% of the overall cohort entering the model in ESKD (Table D6).
CE=cost effectiveness; ECM=established clinical management; ESKD=end-stage kidney disease

Transition probabilities from CKD 4 or ESKD to transplantation

PH1 guidelines state that combined/sequential liver–kidney transplantation is an option for patients in CKD 4 or ESKD, but are unclear regarding eligibility and timing.[20] In the CE model, transition to the cLKT health state was permitted only from CKD 4 and ESKD in the lumasiran and ECM arms.

The transition probabilities for late-stage CKD cohorts with controlled oxalate are expected to be similar to the transplantation rates observed across non-PH1 CKD patients, since patients with controlled oxalate are likely to be considered better candidates for transplantation than patients with uncontrolled oxalate (Section 7.2.2). Rates of liver and kidney transplantation occurring within 3 years of the patient being listed on NHS transplant lists (children, 89% and 81%; adults, 82% and 66%) were derived from transplant activity in the UK[214,215] and combined by multiplication to estimate 3--year rates of combined liver–kidney transplantation (children, 72%; adults, 54%). These transplantation rates were transformed into a 6-month cycle probability and applied to CKD 4 and ESKD health states with controlled oxalate (Table D14). It was assumed that 100%

of patients in these health states would be placed on the waiting list for transplantation and therefore the transplantation rate is only dependent on organ availability.

For late-stage CKD cohorts with uncontrolled oxalate, transplantation rates were estimated using data from the Compagnon et al. (2014)[52] study (Table D14). Compagnon et al. reported on 33 combined transplants performed in patients with PH1 in France over 31 years (from 1979 to 2010). If we consider data on file suggesting an average prevalence of [redacted] PH1 patients in France over the period covered by the study by Compagnon et al., the estimated annual probability per patient is [redacted] (= [redacted] transplants / ([redacted] × [redacted]) person-years). The annual probability was transformed into a cycle probability (6 months) and applied to the CKD 4 and ESKD health states with uncontrolled oxalate for paediatric and adult cohorts, since there was no distinction in the Compagnon study between paediatric and adult patients or CKD 4 and ESKD.

Table D14. Per-cycle probability of combined liver–kidney transplantation

Transition from	Per-cycle probability	Source
Paediatric cohort		
CKD 4-Ox_C	0.19204	NHS Blood and Transplant (2021)[214,215]; assuming that 100% of patients are placed on the transplant list
CKD 4-Ox_U	0.00213	Compagnon et al. (2014)[219]
ESKD-Ox_C	0.19204	NHS Blood and Transplant (2021)[214,215]; assuming that 100% of patients are placed on the transplant list
ESKD-Ox_U	0.00213	Compagnon et al. (2014)[219]
Adult cohort		
CKD 4-Ox_C	0.12205	NHS Blood and Transplant (2021)[214,215]; assuming that 100% of patients are placed on the transplant list
CKD 4-Ox_U	0.00213	Compagnon et al. (2014)[219]
ESKD-Ox_C	0.12205	NHS Blood and Transplant (2021)[214,215]; assuming that 100% of patients are placed on the transplant list
ESKD-Ox_U	0.00213	Compagnon et al. (2014)[219]

Annual probability reported in Compagnon et al. was transformed into cycle probability.
CKD=chronic kidney disease; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

Lumasiran treatment was assumed to continue until transplantation for the lumasiran cohort in CKD 4 or ESKD based on the rationale described in Sections 7.2.2 and 8.2.5, and summarised here:

- The positive impact of lumasiran treatment on stabilisation of disease, reduction of dialysis, and minimisation of systemic oxalosis–related complications in patients with advanced disease prior to transplantation.
- The rationale that effective oxalate lowering with lumasiran is a critical pretransplantation step, irrespective of organ availability, to position patients for better outcomes, fewer complications, and longer survival following combined liver–kidney transplantation once suitable donor organs are available.[191]

Reflecting the anticipated role of lumasiran in improving patients' suitability for transplantation and post-transplant prognosis, the model incorporates a higher probability of transplantation to the lumasiran arm due to the oxalate-lowering effect of lumasiran. Effective oxalate lowering in turn lowers the likelihood of transplant-related events, including graft failure and retransplantation, while improving overall survival.

Probability of retransplantation

Modelling of retransplantation was based on data published by Compagnon et al. (2014),[52] who reported four instances of kidney retransplantation over a maximum follow-up of 239 months. Data on retransplantation and follow-up duration were used to calculate the probability of retransplantation per 6-month cycle for the cLKT-Ox_U health state, as shown in Table D15. For the cLKT-Ox_C health state, the per-cycle probability of

retransplantation was assumed to equal the per-cycle probability observed in the cLKT-Ox_U health state, multiplied by the difference in the probability of graft failure between controlled and uncontrolled PH1 patients within the first 10 years of transplantation (0.2155) following reconstruction of patient-level data from the Jamieson et al. (2005)[135] publication.

Table D15. Per-cycle probability of retransplantation

Health state	Per-cycle probability	Source
cLKT-Ox_U	0.0032	Compagnon et al. (2014)[219]
cLKT-Ox_C	0.0007	Assumed to equal the per-cycle probability of retransplantation in the Ox_U cohort (from Compagnon et al. 2014[219]) multiplied by the probability of graft failure in controlled vs. uncontrolled PH1 patients within the first 10 years of transplantation (from Jamieson et al. 2005[135])

Compagnon et al. reported that four of 33 transplantations required retransplantation at a maximum follow-up of 239 months. cLKT=combined liver–kidney transplantation; Ox_C=controlled oxalate levels; Ox_U=uncontrolled oxalate levels; PH1=primary hyperoxaluria type 1

Renal stone events

Renal stones in patients with PH1 usually consist of more than 95% calcium oxalate monohydrate, and elevated oxalate levels cause recurrent renal stone events.[4] For the CKD 1–3b health states, the annualised rate of renal stone events was obtained from pooled baseline data in the ILLUMINATE-A and ILLUMINATE-B trials. The frequency of renal stone events occurring in the ECM cohort was sourced from the placebo arm of ILLUMINATE-A (6 months). The frequency of renal stone events occurring in the lumasiran arm was obtained from pooled ILLUMINATE-A and ILLUMINATE-B data at 6 months (representing Cycle 1) and at 12 months (representing Cycle 2+). [redacted] As expected [redacted] (Table D16).

For the CKD 4 and ESKD health states, the annualised rate of renal stone events for the ECM cohort was obtained from baseline data in the ILLUMINATE-C study. The annualised rate of renal stone events for the lumasiran cohort was obtained from ILLUMINATE-C 6 month data (i.e., after 6 months of lumasiran treatment). Annualised renal stone event rates were divided by two to obtain the rate of renal stone events per cycle (Table D16).

Table D16. Renal stone event rate by treatment and health state

	Mean	Standard error	Source
Annualised rate in CKD 1–3b			
Baseline	[redacted]	[redacted]	ILLUMINATE-A and ILLUMINATE-B, pooled baseline
Renal stone event HR vs. baseline rate in CKD 1–3b, by treatment			
ECM, any cycle	1.222	0.122	ILLUMINATE-A, 6 months
Lumasiran, Cycle 1	[redacted]	[redacted]	ILLUMINATE-A and ILLUMINATE-B, pooled 6 months
Lumasiran, Cycle 2+	[redacted]	[redacted]	ILLUMINATE-A and ILLUMINATE-B, pooled 12 months
Annualised rate in CKD 4/ESKD			
ECM, any cycle	[redacted]	[redacted]	ILLUMINATE-C, pretreatment historical rate
Lumasiran, any cycle	[redacted]	[redacted]	ILLUMINATE-C, 6 months

CKD=chronic kidney disease; ECM=established clinical management; HR=hazard ratio
Source: Alnylam Data on File (ILLUMINATE-A [ALN-GO1-003] CSR[33]; ILLUMINATE-B [ALN-GO1-004] CSR[79]; ILLUMINATE-C [ALN-GO1-005] CSR[64])

Systemic oxalosis

Few studies exist that investigate the epidemiology and impact of systemic oxalosis in patients with PH1. The prevalence of complications associated with systemic oxalosis in patients with late-stage CKD and uncontrolled oxalate was therefore obtained from a survey of UK clinical experts who treat PH1.

The probability of experiencing systemic oxalosis complications is assumed to be zero in CKD 1–3b health states, since systemic oxalosis is associated with incomplete renal clearance of oxalate, which is typically observed after CKD 3b in PH1. Furthermore, as systemic oxalosis arises from the accumulation of oxalate in plasma (and the subsequent deposition of oxalate crystals in organs beyond the kidneys), a [redacted] in systemic oxalosis complications is, as per clinical opinion, expected among patients in CKD 4 or ESKD with oxalate levels below the 50 µmol/L threshold. Therefore, the prevalence of systemic oxalosis complications in patients with late-stage CKD with controlled oxalate levels was estimated by applying a 20% relative reduction to the values observed in late-stage CKD with uncontrolled oxalate levels (Table D17).

Table D17. Prevalence of systemic oxalosis complications in CKD 4 and ESKD health states

	Prevalence per cycle			
Systemic oxalosis complication	**CKD 4-Ox_U**	**ESKD-Ox_U**	**CKD 4-Ox_C**	**ESKD-Ox_C**
Bone	30%	80%	[redacted]	[redacted]
Cardiac	15%	40%	[redacted]	[redacted]
Cutaneous and vascular	15%	35%	[redacted]	[redacted]
Ophthalmic	18%	40%	[redacted]	[redacted]
Neurologic	18%	40%	[redacted]	[redacted]

CKD=chronic kidney disease; ESKD=end-stage kidney disease; Ox_C=controlled oxalate levels; Ox_U=uncontrolled oxalate levels
Sources: Third-party survey of UK clinical experts; Interviews with clinical experts

Dialysis

Table D18 shows the distribution of types of dialysis among patients receiving high-intensity and normal-intensity dialysis, respectively, obtained from a survey of UK clinical experts who treat PH1 (Section 10.1.10).

Table D18. Dialysis distribution

Population	Dialysis	Probability
High-intensity dialysis		
Paediatric	Haemodialysis, 7×week	[redacted]
	Haemodialysis, 6×week plus peritoneal dialysis 7×week	[redacted]
Adult	Haemodialysis, 7×week	[redacted]
	Haemodialysis, 6×week plus peritoneal dialysis 7×week	[redacted]
Normal-intensity dialysis		
Paediatric	Haemodialysis, 3×week	[redacted]
	Peritoneal dialysis 7×week	[redacted]
Adult	Haemodialysis, 3×week	[redacted]
	Peritoneal dialysis 7×week	[redacted]

Source: Third-party survey of UK clinical experts

In the ECM cohort, 100% of the CKD 4 and 100% of the ESKD health states receive high-intensity dialysis as an add-on to ECM, based on PH1 clinical guidelines.[20] In the lumasiran cohort, 0% of the CKD 4 health state receives normal-intensity dialysis, since the kidney is functioning in CKD 4 and plasma oxalate is controlled by lumasiran. However, it is assumed that all patients with ESKD will require renal replacement therapy (but not higher-intensity dialysis to control oxalate, given the use of lumasiran for this purpose). Therefore, the proportion of the lumasiran cohort in ESKD with normal-intensity dialysis was set to 100%.

Lumasiran treatment discontinuation

Treatment discontinuation represents unplanned interruption of lumasiran due to any reason and could occur within any of the early CKD health states (i.e., CKD 1–3b). A time-on-treatment (ToT) curve derived from

ILLUMINATE-A and ILLUMINATE-B patient-level data was used to simulate the proportion of the CKD 1–3b cohorts discontinuing treatment with lumasiran at each cycle of the model. Following treatment discontinuation, the cohort was assumed to experience the clinical effect observed in the ECM arm, specifically with respect to transition probabilities across all pre-ESKD health states, transition probabilities from pre-ESKD to ESKD, probabilities of transition to transplantation, the prevalence of systemic oxalosis complications, the renal stone event rate, and dialysis schedules.

Data on treatment discontinuation due to any reason in patients receiving lumasiran were obtained from the ILLUMINATE-A and ILLUMINATE-B trials at the 12-month cut-off. Beyond the trial period, ToT was extrapolated by fitting parametric models to observed time-to-event data. AIC and Bayesian information criterion (BIC) estimators were used to evaluate the relative fit of the parametric models considered, namely exponential, Weibull, Gompertz, log-normal, and log-logistic (Table D19). The log-normal function was selected to inform the fraction of patients still on treatment at each time point in the simulation based on the goodness of fit. Figure D4 shows how the parametric curves compare for the extrapolation of the ToT for lumasiran. A piecewise approach was followed, where the KM points were used for the duration of directly observed follow-up available and thereafter the best-fitting parametric curve was used to define the probability of discontinuation.

Table D19. Fit statistics of parametric models to lumasiran time-on-treatment data

	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

AIC=Akaike information criterion; BIC=Bayesian information criterion

[redacted]

Figure D4. Extrapolation of the ToT for lumasiran
KM=Kaplan–Meier; OS=overall survival; ToT=time on treatment

No benefit of lumasiran treatment was assumed beyond treatment discontinuation; therefore, the effect of treatment was not applied for the proportion of the cohort who discontinued treatment.

A discontinuation rate of zero was applied to CKD 4 and ESKD cohorts, since no discontinuations were observed in ILLUMINATE-C within the first 6 months.

General population mortality

General population mortality was defined as age- and gender-specific all-cause mortality and has been included in the model based on country-specific mortality tables for England.[216] The general mortality rate used in the model corresponded to the age of the cohort at each given cycle and was adjusted based on the proportion of males in the analysis.

CKD-related mortality

The CEA simulates CKD-related mortality in the model cohort by applying a higher risk of mortality with increasingly severe PH1 health states, applied over the time horizon of the model. The relative risk of death in each model state versus the general population mortality was obtained from the retrospective database analysis by Go et al. of longitudinal eGFR data,[217] which has also been used in a published microsimulation model of CKD developed by the US Centers for Disease Control and Prevention (CDC) CKD Initiative.[218] The CDC model was validated by comparing its predictions with survey and epidemiologic data. Notably, it is appropriate to use relative risk–based multipliers from Go et al. (applied to general population mortality estimates) in this CE model even though they were not obtained within a PH1 population, because the aim of this aspect of the CE model was to quantify the mortality impact of renal dysfunction independently of the presence of PH1, to obtain the increased risk of death related to each CKD stage.

Table D20 presents the health-state–specific mortality multipliers used in the current analysis. The reference group (eGFR ≥60 mL/min/1.73m^2, or CKD 1–2) was assumed to have normal background mortality. The mortality multipliers in Table D22 are likely to be conservative estimates given the challenges of modelling further mortality risk due to systemic oxalosis complications in the later stages of CKD in PH1.

Table D20. Mortality multiplier of PH1 health states

Health state	Mortality relative risk vs. general population
CKD 1–2	1.0
CKD 3a	1.2
CKD 3b	1.8
CKD 4	3.2
ESKD	5.9

Hazard ratio estimates were applied as CKD stage–specific multipliers of background (general population) mortality risk.
CKD=chronic kidney disease (stage); ESKD=end-stage kidney disease; PH1=primary hyperoxaluria type 1

Source: Go et al. 2004[217]

Transplant-related mortality (time to death from first transplant)

Data published by Jamieson et al. (2005)[135] were used to model overall survival following combined/sequential liver–kidney transplantation. KM curves available in the Jamieson et al. publication were digitised, and patient-level data were reconstructed via the Guyot method (based on the published number at risk).

After validation with clinical experts, the average of the two KM curves referring to patients in *Very Good* and *Good* pre-operative condition was used to estimate the overall survival of patients in the post-cLKT health state with controlled oxalate. The average of the two KM curves referring to patients in *Fair* and *Poor* pre-operative condition was used to estimate the overall survival of patients in the post-cLKT health state with uncontrolled oxalate (Section 12.2.5).

Since the fitting of the extrapolation curves for some KM curves reported by Jamieson et al. was very poor, a piecewise approach was used whereby the average KM curve was used for the duration of observed follow-up available, after which the best-fitting extrapolation curve was used. If at the end of observed period survival was lower than that estimated with the best-fitting extrapolation curve, the last observed survival was applied until the time point at which it was matched by the estimate from the best-fitting extrapolation curve, after which values from the extrapolation curve were used (Table D21).

Table D21. Long-term risk of post-transplantation mortality

Time period	Estimation of post-transplantation mortality risk
Up to Year 4 (short term)	Time point-specific probability of mortality was estimated from the parameterisation of overall survival curves for the cohort of interest (*Very Good* / *Good* condition or *Fair* / *Poor* condition) receiving combined/sequential liver–kidney transplantation (Jamieson et al. 2005[135])
Years 5–29 (medium term)	Fixed probability of mortality, calculated as the average over Years 5–29 following the methodology described (estimation from Jamieson et al.[135]), to avoid using more than 10 tunnel states
Year 30+ (long term)	Assumed to equal the age-specific mortality rate of the general population

12.2.2 Extrapolation of costs and clinical outcomes: assumptions and justification

Data on treatment discontinuation due to any reason in CKD 1–3b patients receiving lumasiran were obtained from the ILLUMINATE-A and ILLUMINATE-B trials at the 12-month cut-off. Beyond the trial period, ToT was extrapolated by fitting parametric models to observed time-to-event data for discontinuation as described in Section 12.2.1.

The trend observed over 12 months in ILLUMINATE-A and ILLUMINATE-B with respect to treatment efficacy is expected to be maintained over time. This is based on data from the phase 2 OLE showing no loss of therapeutic effect over the duration of follow-up in patients treated with lumasiran (median follow-up 15 months; range, 11–22).[66] It is also based on the mechanism of action of lumasiran, which selectively and durably silences the mRNA for the enzyme GO in the liver, the low rate of ADA observed in ILLUMINATE-A, and the lack of observed impact of this low-titre ADA on PK or the magnitude or duration of oxalate reduction (Section 9.6.1).[7,33]

No data for ECM are available from ILLUMINATE-A beyond 6 months because at this point patients originally assigned to placebo treatment transitioned to lumasiran. However, there is a large body of evidence on the natural history of PH1 showing that most patients on ECM progress through CKD stages, ultimately reaching ESKD.[4,30,31]

12.2.3 Linking of intermediate outcome measures to final outcomes

Excess oxalate is the driver of PH1 morbidity and mortality—its accumulation leads to severe kidney damage and damage in organs beyond the kidneys.[4,5,31] As expected based on the central causal role of oxalate in PH1, longitudinal patient follow-up data from the RKSC PH registry have shown that urinary oxalate excretion, plasma oxalate levels, and incident nephrocalcinosis (the appearance of oxalate deposits on renal ultrasound) are all positively associated with the risk of ESKD in patients with PH. In addition, therapeutic interventions that decrease or stop oxalate production have been shown to prevent disease progression, with published reports documenting stable or improved eGFR (relative to pretransplant levels) over follow-up durations of up to 20 years in patients undergoing pre-emptive liver transplantation for PH1. In summary, then, biological data indicate the role of oxalate as the central actor in the causal pathway responsible for renal impairment in PH1, natural history data extend this finding by demonstrating that various indicators of oxalate production are positively correlated with ESKD in PH1, and finally, data from the transplant literature highlight how therapeutic oxalate lowering can arrest the progression of renal decline in PH1.

In phase 3 clinical trials, lumasiran demonstrated the ability to significantly reduce oxalate levels. Among patients with preserved renal function, lumasiran has demonstrated the ability to reduce oxalate to normal or near-normal levels in the majority of treated patients, regardless of age.[8,33,63,67,68,79] Among patients with advanced renal disease, lumasiran treatment leads to meaningful reductions in plasma oxalate in all patients, regardless of age and whether or not the patient is receiving dialysis.[11,64] [redacted] (Section 12.1.6). Therefore, the relationship between plasma oxalate and eGFR quantified by Shah et al. (2020) has been used to model eGFR changes in the ECM cohort over time, as plasma oxalate is a leading indicator of eGFR loss, and treatment effects have been shown on

this measure in trials of lumasiran.[28] Lumasiran-induced reductions in plasma oxalate across pre-ESKD health states are expected to correspond to no reduction in eGFR, a conservative assumption (12.2.1).

12.2.4 Inclusion of adverse events in the cost-effectiveness analysis

The incidences of AEs associated with lumasiran and ECM in the model were based on 6-month data from ILLUMINATE-A. The analysis included treatment-related AEs reported by at least 10% of patients in either group, with adjustments to incidence made to account for the 6-month cycle length (Table D22).

Table D22. Cycle probabilities of treatment-related AEs

	Lumasiran (cycle incidence)	ECM/placebo (cycle incidence)
Headache	0.115	0.231
Injection-site erythema	0.115	0.000
Injection-site pain	0.346	0.000
Injection-site reaction	0.385	0.000
Rhinitis	0.077	0.154
Upper respiratory infection	0.077	0.154

AE=adverse event; ECM=established clinical management
Source: Alnylam Data on File (ILLUMINATE-A [ALN-GO1-003] CSR)[33]

12.2.5 Validation of the clinical model parameter and inputs used in the analysis

In 2021, Alnylam Pharmaceuticals solicited expert opinion to validate key model inputs and assumptions from a clinical perspective. The criteria for selecting experts were designed to capture feedback from clinicians:

- Who are members of the PH1 RDCN,
- Whose experience, in totality, spanned the full spectrum of ages over which patients may be impacted by PH1, from infancy to adulthood, and
- Who had been investigators in the ILLUMINATE study programme, to obtain their insights into how lumasiran would be utilised in clinical practice based on their hands-on experience using the drug in these trials

Two UK-based clinical experts meeting all of these criteria were approached to participate in web-based interviews. Both clinical experts agreed to these interviews.

One interview was conducted with the first clinical expert, a consultant paediatric nephrologist. Two interviews were conducted with the second clinical expert, a consultant nephrologist. Both clinicians are investigators on ongoing studies sponsored by Alnylam, as noted, and have served as congress speakers and advisors on behalf of Alnylam.

The information provided by Alnylam and verbalised during interviews as background for discussion consisted of an overview of the modelling assumptions in this submission, along with data from Jamieson et al. (2005),[135] Singh et al. (2021),[25] and the transplant rates from the NICE appraisal of Tolvaptan for treating autosomal dominant polycystic kidney disease [TA358].[227]

Clinical advisers' feedback on key model inputs and assumptions as discussed in these interviews are summarised in Table D23.

Table D23. Clinical validation of the CE model assumptions and methodology

Parameters/inputs	Details
Plasma oxalate threshold indicative of disease control	The clinical experts validated the use of a plasma oxalate threshold of 50 µmol/L as being indicative of meaningful disease control, resulting in improved health status, improved suitability for transplantation, and more favourable prognosis post-transplant for patients achieving plasma oxalate levels below this threshold relative to patients with higher plasma oxalate levels.
Correspondence of plasma oxalate control to clinical states defined by Jamieson et al. (2005)[135]	The clinical experts noted that patients with plasma oxalate levels below the threshold of 50 µmol/L can be expected to correspond to those categorised as having *Very Good* or *Good* overall clinical status in the analysis conducted by Jamieson et al. to assess the relationship between pretransplantation clinical status and post-transplant survival in patients undergoing combined liver–kidney transplantation for PH1, while patients with plasma oxalate levels above this threshold can be expected to correspond to those categorised as having *Fair* or *Poor* clinical status in the same analysis.
Transplant eligibility for patients with controlled plasma oxalate levels	The clinical experts confirmed that all patients with plasma oxalate levels below the threshold indicative of disease control would, by virtue of their improved post-transplant outlook, be considered eligible for transplantation if they were sufficiently fit, such that their rate of advancement to combined liver–kidney transplantation would be limited only by the availability of suitable donor organs (and not by PH1-specific concerns relating to patients' oxalate burden and its impact on post-transplant outcomes). Accordingly, the clinicians validated the assumption that transplant rates for patients with controlled plasma oxalate levels would match the rates observed in the general population of patients requiring transplantation for reasons unrelated to PH1. The clinical experts suggested using transplantation rates from annual transplantation reports published by the NHS.
Relationship between plasma oxalate control and prevalence of systemic oxalosis complications	The clinical experts agreed that the prevalence of systemic oxalosis complications is lower for patients with controlled plasma oxalate levels than for those with uncontrolled plasma oxalate levels. The assumption that complications of systemic oxalosis would be [redacted] less prevalent in patients in the former group vs. those in the latter group aligned with clinical opinion.
Dialysis practices specific to PH1	The consultant paediatric nephrologist estimated that among paediatric patients with PH1 who are receiving intensive dialysis for management of systemic oxalosis and/or ESKD, 100% would be expected to receive daytime haemodialysis and that smaller percentages would also receive night-time peritoneal dialysis 7 days per week (~60%) or night-time haemodialysis 6 days per week (20%).
CKD stage distribution of patients with PH1 in the UK	The clinical experts confirmed that at the level of the overall population, the distribution of CKD stages reported by Singh et al. (2021)[25] for patients with PH1 in the RKSC PH registry is consistent with the distribution observed in the prevalent PH1 population in the UK. Nonetheless, the consultant paediatric nephrologist clarified that in the specific subpopulation of patients with infantile onset of PH1 in the UK, this distribution is skewed more heavily toward later CKD stages (0% in CKD1–3b, 10% in CKD4, and 90% in ESKD).

CKD=chronic kidney disease; ESKD=end-stage kidney disease; NHS=National Health Service; PH=primary hyperoxaluria; PH1, primary hyperoxaluria type 1; RKSC=Rare Kidney Stone Consortium

12.2.6 Summary of all variables included in the cost-effectiveness analysis

The patient characteristics and clinical variables used in the CE model are summarised in Table D24. The HRQoL inputs to the CE model are summarised in Section 10.1.9.

Table D24. Summary of variables included in the CE model

Variable	Value	OWSA		PSA distribution	Source
		Lower value	Upper value		
Initial age, years					
Infants	0.50	0.40	0.60	Gamma	Midpoint of infant age range; infants are considered from birth to 1 year of age
Paediatric population	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A, -B, and -C at baseline,[33,64,79] children <18 years
Adult population	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A and -C at baseline,[33,64] adults ≥18 years
Mean weight, kg					
Paediatric population	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A, -B, and -C at baseline,[33,64,79] children <18 years
Adult population	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A and -C at baseline,[33,64] adults ≥18 years
Proportion of males	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A, -B, and -C at baseline[33,64,79]
Proportion of paediatric patients	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A, -B, and -C at baseline[33,64,79]
Initial cohort distribution					
CKD 1–2	38.2%	30.7%	45.7%	Dirichlet	Singh et al. (2021)[25;25] CKD 3 patients were assumed to be equally distributed between CKD 3a and CKD 3b
CKD 3a	12.1%	9.7%	14.5%	Dirichlet	
CKD 3b	12.1%	9.7%	14.5%	Dirichlet	
CKD 4-Ox_U	9.7%	7.8%	11.6%	Dirichlet	
ESKD-Ox_U	27.9%	22.4%	33.3%	Dirichlet	
Natural disease progression with ECM					
Absolute change in plasma oxalate, CKD1–3b, any cycle	2.23	1.79	2.67	Normal	ILLUMINATE-A, baseline to Month 6,[33] ECM arm
Absolute eGFR change per unit increase in plasma oxalate, CKD1–3b	–1.27	–1.52	–1.02	Normal	Shah et al. (2020)[28]
Lumasiran effect on natural disease progression					
Percentage change in plasma oxalate, CKD 1–3b, per cycle	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A and -B 12-month data,[33,79] lumasiran arm
Percentage change in plasma oxalate, CKD 4 / ESKD, per cycle	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-C 6-month data[64]
Annualised rate of renal stone events, early-stage disease					
CKD 1–3b, baseline	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A and -B at baseline[33,79]
Renal stone event HR vs. baseline, CKD1–3b					
ECM, any cycle	1.22	0.98	1.46	Normal	ILLUMINATE-A[33]
Lumasiran, Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A and -B[33,79]
Lumasiran, Cycle 2+	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-A and -B[33,79]
Annualised rate of renal stone events, late-stage disease					
ECM, any cycle	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-C[64]
Lumasiran, any cycle	[redacted]	[redacted]	[redacted]	[redacted]	ILLUMINATE-C[64]
Mortality relative risk					
CKD 1–2	1.00	1.00	1.20	Normal	Go et al. (2004)[217]
CKD 3a	1.20	1.00	1.44	Normal	
CKD 3b	1.80	1.45	2.15	Normal	
CKD 4	3.20	2.57	3.83	Normal	
ESKD	5.90	4.74	7.06	Normal	

Variable	Value	OWSA		PSA distribution	Source
		Lower value	Upper value		
Per-cycle probability of cLKT, paediatric population					
From CKD 4-Ox_C	0.19204	0.15440	0.22968	Beta	NHS Blood and Transplant (2021)[214,215]
From CKD 4-Ox_U	0.00213	0.00171	0.00255	Beta	Compagnon et al. (2014)[219]
From ESKD-Ox_C	0.19204	0.15440	0.22968	Beta	NHS Blood and Transplant (2021)[214,215]
From ESKD-Ox_U	0.00213	0.00171	0.00255	Beta	Compagnon et al. (2014)[219]
Per-cycle probability of cLKT, adult population					
From CKD 4-Ox_C	0.12205	0.09813	0.14597	Beta	NHS Blood and Transplant (2021)[214,215]
From CKD 4-Ox_U	0.00213	0.00171	0.00255	Beta	Compagnon et al. (2014)[219]
From ESKD-Ox_C	0.12205	0.09813	0.14597	Beta	NHS Blood and Transplant (2021)[214,215]
From ESKD-Ox_U	0.00213	0.00171	0.00255	Beta	Compagnon et al. (2014)[219]
Per-cycle probability of retransplantation					
Post LKT-Ox_U	0.0032	0.003	0.004	Beta	Compagnon et al. (2014)[219]
Post LKT-Ox_C	0.0007	0.001	0.001	Beta	Assumed to equal the probability of retransplantation per cycle in the Ox_U cohort (from Compagnon et al. 2014[219]) multiplied by the probability of graft failure in Ox_C vs. Ox_U patients within the first 10 years of transplant (from Jamieson et al. 2005[135])
Survival post-cLKT, by condition prior to cLKT					
Very Good	NA	NA	NA	Observed values	Jamieson et al. (2005)[135]
Good				Log-Normal parametric function	
Mean	5.93418	NA	6.52725	Cholesky for PSA	
SD	0.87903	NA	1.35478	Cholesky for PSA	
Fair				Weibull parametric function	
Shape	0.32113	NA	0.46150	Cholesky for PSA	
Scale	891.63063	NA	890.94981	Cholesky for PSA	
Poor				Log-Normal parametric function	
Mean	4.33154	NA	4.09863	Cholesky for PSA	
SD	4.62027	NA	4.35335	Cholesky for PSA	
Prevalence of systemic oxalosis complications in CKD 4-Ox_C					
Bone	[redacted]	NA	NA	NA	Based on the assumption that systemic oxalosis complications occur [redacted] less frequently in patients in late-stage health states with controlled vs. uncontrolled oxalate levels (from interviews with UK clinical experts)
Cardiac	[redacted]	NA	NA	NA	
Cutaneous and vascular	[redacted]	NA	NA	NA	
Ophthalmologic	[redacted]	NA	NA	NA	
Neurologic	[redacted]	NA	NA	NA	
Prevalence of systemic oxalosis complications in CKD 4-Ox_U					
Bone	0.300	0.241	0.359	Beta	Third-party survey with UK clinical experts
Cardiac	0.150	0.121	0.179	Beta	
Cutaneous and vascular	0.150	0.121	0.179	Beta	
Ophthalmologic	0.175	0.141	0.209	Beta	
Neurologic	0.175	0.141	0.209	Beta	
Prevalence of systemic oxalosis complications in ESKD-Ox_C					
Bone	[redacted]	NA	NA	NA	

Variable	Value	OWSA Lower value	OWSA Upper value	PSA distribution	Source
Cardiac	[redacted]	NA	NA	NA	Based on the assumption that systemic oxalosis complications occur [redacted] less frequently in patients in late-stage health states with controlled vs. uncontrolled oxalate levels (from interviews with UK clinical experts)
Cutaneous and vascular	[redacted]	NA	NA	NA	
Ophthalmologic	[redacted]	NA	NA	NA	
Neurologic	[redacted]	NA	NA	NA	
Prevalence of systemic oxalosis complications in ESKD-Ox_U					
Bone	0.800	0.643	0.957	Beta	Third-party survey with UK clinical experts
Cardiac	0.400	0.322	0.478	Beta	
Cutaneous and vascular	0.350	0.281	0.419	Beta	
Ophthalmologic	0.400	0.322	0.478	Beta	
Neurologic	0.400	0.322	0.478	Beta	
Reduction in prevalence of systemic oxalosis complications for controlled oxalate					
CKD 4-Ox_C/ESKD-Ox_C vs. Ox_U	[redacted]	[redacted]	[redacted]	Beta	Interviews with UK clinical experts
Proportion on dialysis					
High-intensity dialysis add-on to ECM					
CKD 4	1.00	0.80	1.00	Beta	PH1 clinical guidelines[20]
ESKD	1.00	0.80	0.00	Beta	
Proportion of patients receiving normal-intensity dialysis as add-on to lumasiran					
CKD 4	0.00	0.00	0.00	Beta	Assumed that the kidney is functioning and plasma oxalate is controlled by lumasiran
ESKD	1.00	0.80	1.00	Beta	Assumed that all patients with ESKD require renal replacement therapy
Per-cycle probability of AEs, ECM					
Headache	0.231	0.186	0.276	Beta	ILLUMINATE-A 6-month data,[33] ECM arm
Injection-site erythema	0.000	0.000	0.000	Beta	
Injection-site pain	0.000	0.000	0.000	Beta	
Injection-site reaction	0.000	0.000	0.000	Beta	
Rhinitis	0.154	0.124	0.184	Beta	
Upper respiratory infection	0.154	0.124	0.184	Beta	
Per-cycle probability of AEs, lumasiran					
Headache	0.115	0.093	0.138	Beta	ILLUMINATE-A 6-month data,[33] lumasiran arm
Injection-site erythema	0.115	0.093	0.138	Beta	
Injection-site pain	0.346	0.278	0.414	Beta	
Injection-site reaction	0.385	0.309	0.460	Beta	
Rhinitis	0.077	0.062	0.092	Beta	
Upper respiratory infection	0.077	0.062	0.092	Beta	

AE=adverse event; CE=cost effectiveness; CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; HR=hazard ratio; NA=not applicable; OWSA=one-way sensitivity analysis; PSA=probabilistic sensitivity analysis; Ox_U=uncontrolled oxalate levels

12.3 Resource identification, measurement and valuation

12.3.1 NHS reference costs

NHS reference costs and Personal Social Services Research Unit (PSSRU) costs for the clinical management of this condition are listed in Appendix 5: Supplemental data.

12.3.2 Resource identification, measurement and valuation studies

The SLR summarised in Table C1 and Appendix 1: Search strategy for clinical evidence was designed with broad search terms to capture any relevant resource data for the NHS in England.

12.3.3 Assessment of the applicability of the resources used in the model

The process used to assess the applicability of resources used in the model has been described in Section 12.2.5.

12.3.4 Technology and comparators' costs

The list price for lumasiran is £61,068.98 per 94.5-mg vial.[228]

12.3.5 Justification if the list price is not used in the de novo CE model

The price for lumasiran used in the CE model is £[redacted] per 94.5-mg vial, which includes a proposed confidential patient access scheme discount ([redacted]).

12.3.6 Annual costs associated with lumasiran and ECM applied in the CE model

Lumasiran

The loading and maintenance doses of lumasiran are based on body weight measurements (Section 2.3). Table D25 shows the lumasiran dose per administration and number of administrations per quarter.

Table D25. Lumasiran dose and number of administrations

Weight	<10 kg	≥10 to <20 kg	≥20 kg
Dose (mg/kg) per administration			
Loading dose	6	6	3
Maintenance dose	3	6	3
Administrations per quarter, n			
Loading dose	3	3	3
Maintenance dose	3	1	1

The average number of administrations per quarter across the model cohort is [redacted] for the loading dose and [redacted] for the maintenance dose. This equates to an average number of vials per quarter of [redacted] for the loading dose and [redacted] for the maintenance dose for the paediatric population, and [redacted] and [redacted] for the adult population, respectively, based on cohort weight at model entry. Therefore, the average number of administrations per cycle in the model is [redacted] for Cycle 1 and [redacted] for subsequent cycles, regardless of the population. The average number of vials per cycle in the model is [redacted] for Cycle 1 and [redacted] for subsequent cycles for the paediatric population, and [redacted] for Cycle 1 and [redacted] for subsequent cycles for the adult population. It should be noted that if the proportion of paediatric patients were to increase over time as incident patients enter the treated population, average vial consumption would be expected to decrease, thus reducing average treatment costs in the lumasiran arm. No vial sharing is included, meaning that any opened vial may not be reused and therefore the entire cost is accounted for even if the dose administered in less than the entire vial. [redacted] The average cost of lumasiran for a paediatric patient is £[redacted] for the first 6-month cycle and £[redacted] for subsequent 6-month cycles. The average cost of lumasiran for an adult patient is £[redacted] for the first 6-month cycle and £[redacted] for subsequent cycles (Table D26).

Table D26. Lumasiran drug and administration costs per cycle

Lumasiran cycle	Vials per cycle	Admin. per cycle	RDI	Drug cost per admin (£)	Drug cost per cycle (£)	Drug + admin. Costs per cycle (£)*
Paediatric						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult						
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Calculated based on the number of administrations per cycle, cost per administration (£43.44),[229] and drug cost per cycle. Admin.=administration; RDI=relative dose intensity

The cost of pharmacologic therapy with lumasiran includes both the drug and the administration cost. Lumasiran is administered subcutaneously, at a cost of £43.44 per administration.[229] Based on the number of administrations listed in Table D26, the resulting administration cost for lumasiran is £169.86 in the first cycle and £84.93 in subsequent cycles for paediatric patients, and £509.57 in the first cycle and £254.79 in subsequent cycles for adult patients.

The total cost of lumasiran, including both drug acquisition and administration costs, is £[redacted] in the first cycle and £[redacted] for subsequent cycles for a paediatric patient. The total cost is £[redacted] in the first cycle and £[redacted] for subsequent cycles for an adult patient (Table D26). For patients who interrupt treatment, a £0 pharmacological treatment cost is applied.

Pyridoxine

Pyridoxine is included in the model as a component of ECM. The listing price for pyridoxine is £21.93 per pack of 28, 50-mg tablets.[230] The per-cycle cost of treatment with pyridoxine was calculated based on the dose per kg, average weights of the paediatric and adult populations, and the proportion of the lumasiran and ECM cohorts in the ILLUMINATE-A trial on pyridoxine. The average per-cycle cost of pyridoxine treatment is £1.96 for children and £5.48 for adults in the lumasiran arm, and £2.71 for children and £7.59 for adults in the ECM arm. The cost of administration is assumed to be £0.

12.3.7 Dialysis costs

High-intensity and normal-intensity dialysis costs were calculated from the sum of the product of average unit cost and proportion of resource use for each currency description within each age category (Appendix Table 6). This was multiplied by the number of days per month patients underwent dialysis to give monthly costs for a paediatric patient and adult patient (Table D27).

Table D27. Monthly cost of high-intensity dialysis

Patient	Haemodialysis 7 × week*				Haemodialysis 6 × week + peritoneal dialysis 7 × week†					
	HD				HD			PD		
	Days per week	Days per month	Cost per month (£)		Days per week	Days per month	Cost per month (£)	Days per week	Days per month	Cost per month (£)
Paediatric	7	30.44	13,938.77		6	26.09	11,947.52	7	30.44	3,089.08
Adult	7	30.44	5,170.97		6	26.09	4,432.26	7	30.44	2,425.60

HD=haemodialysis; PD=peritoneal dialysis
Source: *Diaz et al (2004)[231]; †Plumb et al. (2013)[150]

Table D28. Monthly cost of normal-intensity dialysis

Patient	Haemodialysis 3 × week				Peritoneal dialysis 7 × week		
	Days per week	Days per month	Cost per month (£)		Days per week	Days per month	Cost per month (£)
Paediatric	3	13.04	6,493.44		7	30.44	3,089.08
Adult	3	13.04	2,131.24		7	30.44	2,425.60

Source: NICE Technology Appraisal Guidance T481[232]

The monthly costs of dialysis shown in Table D27 and Table D28 were weighted based on the proportion of patients receiving each service and were then multiplied by six to calculate the per-cycle cost of high-intensity and normal-intensity dialysis. The per-cycle costs used in the CE model are shown in Table D29.

Table D29. Dialysis costs in the CE model

Per-cycle costs (£)	Base case	OWSA range		PSA distribution
		Lower value	Upper value	
High-intensity dialysis				
Paediatric patient	83,632.63	67,240.63	100,024.62	Gamma
Adult patient	32,371.95	26,027.04	38,716.85	Gamma
Normal-intensity dialysis				
Paediatric patient	38,960.67	31,324.38	46,596.96	Gamma
Adult patient	13,022.37	10,469.98	15,574.75	Gamma

CE=cost effectiveness; OWSA=one-way sensitivity analysis; PSA=probabilistic sensitivity analysis
Source: National Schedule of NHS Costs 2019/20[229]

The average cost for high-intensity dialysis per cycle in the UK for adults and children equals £32,371.95 and £83,632.63, respectively, according to NHS reference costs. The average cost for normal-intensity dialysis per cycle in the UK for adults and children equals £13,022.37 and £38,960.67, respectively.

12.3.8 Renal stone event costs

The one-off cost associated with managing renal stone events was calculated from the sum of the product of unit cost and proportion of resource use for each currency description (Appendix Table 7). Renal stone event costs are presented in Table D30

Table D30. Renal stone event costs in the CE model

Per-cycle costs (£)	Base case	OWSA range		PSA distribution
		Lower value	Upper value	
Renal stone event	806.64	648.54	964.75	Gamma

CE=cost effectiveness; OWSA=one-way sensitivity analysis; PSA=probabilistic sensitivity analysis;
Source: National Schedule of NHS Costs 2019/20[229]

12.3.9 Systemic oxalosis complications costs

Per-cycle costs for the management of each systemic oxalosis complication were obtained from the literature and inflated to 2021 costs using the Consumer Prices Index (CPI) for the UK. Costs reported in other currencies were converted into British pound sterling (GBP). The per-cycle costs associated with systemic oxalosis complications are shown in Table D31. These costs, pro-rated by the prevalence of each systemic oxalosis manifestation, were applied to the cohort in late-stage health states (CKD 4 or ESKD) as shown in Table D17.

Table D31. Systemic oxalosis complications costs in the CE model

Per-cycle systemic oxalosis complication costs (£)	Base case*	OWSA range		PSA distribution	Reference
		Lower value	Upper value		
Bone	1,313.17	1,055.79	1,570.55	Gamma	Borgström et al. (2020)[233]; assumed equal to the annual cost of distal forearm fractures in the year following the fracture. EUR converted into GBP using the PPP at the year of costing
Cardiac	1,948.67	1,566.73	2,330.60	Gamma	Danese et al. (2016)[234]; assumed equal to the per-cycle cost after an event of heart failure (Months 7–36 after the event)
Cutaneous and vascular	3,937.46	3,165.72	4,709.21	Gamma	Patel et al. (2020)[235]; assumed equal to the annual NHS & PSS cost in subsequent years to the first year from stroke occurrence
Ophthalmologic	625.77	503.12	748.42	Gamma	Galvin et al. (2020)[236]; assumed equal to the health-system cost of inherited retinal diseases in the UK (i.e., £25 million divided by 20,815 cases)
Neurologic	1,513.24	1,216.64	1,809.83	Gamma	Liedgens et al. (2016)[237]; assumed equal to the per-cycle cost of neuropathic pain

*Annual costs were inflated to 2021 prices and divided by two to obtain per-cycle costs (Appendix Table 8).
CE=cost effectiveness; EUR=Euro; GBP=British pound sterling; NHS=National Health Service; OWSA=one-way sensitivity analysis; PPP=purchasing power parities; PSA=probabilistic sensitivity analysis; PSS=Personal Social Services

12.3.10 Transplantation-related costs

The costs associated with transplantation were calculated from the sum of the product of average unit cost and proportion of resource use for each currency description within each age category (Appendix Table 9). Table D32 shows the costs for liver, kidney, combined liver–kidney transplantation, pre- and post-transplantation costs, and transplant failure. The costs for liver and kidney transplantations were summed to calculate the cost of combined liver–kidney transplantation, which varied by age. The one-off cost for combined liver–kidney transplantation was £56,566.33 for paediatric patients and £35,028.41 for adults.

Table D32. Transplantation costs

	Transplantation-related costs (£)					
Patients	**Liver**	**Kidney**	**Pretransplantation**	**cLKT**	**Post-cLKT**	**Retransplantation**
Paediatric	35,430.78	20,580.15	555.4	56,566.33	280.56	28,560.86
Adult	20,826.52	13,699.77	502.12	35,028.41	280.56	17,765.26

cLKT=combined liver–kidney transplantation
Source: National Schedule of NHS Costs 2019/20[229]

Table D33 shows the one-off cost for combined liver–kidney transplantation together with per-cycle monitoring/treatments costs and other transplantation-related costs used in the CE model.

Table D33. Transplantation-related costs in the CE model

Costs (£)	Base case	OWSA range		PSA distribution	Reference
		Lower value	Upper value		
One-off liver–kidney transplantation					
Paediatric population	56,566.33	45,479.33	67,653.33	Gamma	National Schedule of NHS Costs 2019/20[229]; liver transplant plus kidney transplant
Adult population	35,028.41	28,162.84	41,893.97	Gamma	National Schedule of NHS Costs 2019/20[229]; liver transplant plus kidney transplant
Per-cycle post-transplant monitoring	280.56	225.57	335.55	Gamma	National Schedule of NHS Costs 2019/20[229]
Per-cycle post-transplant immunosuppression	102.70	82.57	122.83	Gamma	Assumed immunosuppressive treatment with prednisone. Jones-Hughes et al. (2016)[238] for dosing scheme (16.3 mg per day); MIMS[239] for drug price (prednisone 10 mg × 28 tablets, £9.66)
One-off graft failure post-transplantation (kidney)	3,724.04	2,994.13	4,453.95	Gamma	National Schedule of NHS Costs 2019/20[229]
One-off retransplantation (kidney)					
Paediatric population	28,560.86	22,962.93	34,158.79	Gamma	National Schedule of NHS Costs 2019/20[229]
Adult population	17,765.26	14,283.27	21,247.25	Gamma	National Schedule of NHS Costs 2019/20[229]

BNF=British National Formulary; CE=cost effectiveness; OWSA=one-way sensitivity analysis; PSA=probabilistic sensitivity analysis

12.3.11 Health-state costs

Annual resource use of laboratory tests, procedures, and visits was obtained from a survey completed by UK clinical experts. This was converted into per-cycle (6-month) monitoring costs for each health state (Appendix Table 10 and Appendix Table 11).

Table D34 shows the unit costs of laboratory tests, procedures, and visits used in the CE model that were derived from NHS reference costs listed in Appendix Table 12 to Appendix Table 17.

Table D34. Unit costs of laboratory tests, procedures, and visits

	Base case	OWSA range		PSA distribution	Assumption
		Lower value	Upper value		
24-h urine oxalate	1.20	0.96	1.43	Gamma	
Full blood count	1.20	0.96	1.43	Gamma	
Spot urine oxalate:creatinine ratio	1.20	0.96	1.43	Gamma	
Plasma oxalate	1.20	0.96	1.43	Gamma	
Serum creatinine	1.20	0.96	1.43	Gamma	
Electrolytes	1.20	0.96	1.43	Gamma	
Urea	1.20	0.96	1.43	Gamma	
Bone chemistry, calcium phosphate	1.20	0.96	1.43	Gamma	
Bone chemistry, parathyroid hormone level	1.20	0.96	1.43	Gamma	
Iron status	1.20	0.96	1.43	Gamma	
Bicarbonate (acid status)	1.20	0.96	1.43	Gamma	
Antibody screening tests from laboratory	1.20	0.96	1.43	Gamma	

		OWSA range			
	Base case	Lower value	Upper value	PSA distribution	Assumption
Plasma creatinine	1.20	0.96	1.43	Gamma	
Renal ultrasound	65.56	52.71	78.40	Gamma	
Bone x-ray	68.97	55.45	82.49	Gamma	
Electrocardiogram	480.59	386.40	574.79	Gamma	
Echocardiogram	109.39	87.95	130.82	Gamma	
Fundoscopic eye examination for adult patients	107.72	86.60	128.83	Gamma	
Fundoscopic eye examination for paediatric patients	103.40	83.13	123.67	Gamma	Assumed equal to an ophthalmology visit
Skin/muscle biopsy	231.51	186.14	276.89	Gamma	
CT scan	124.72	100.28	149.17	Gamma	
Specialist consultation for adult patients: nephrologist	89.98	72.34	107.61	Gamma	
Specialist consultation for paediatric patients: nephrologist	169.88	136.58	203.18	Gamma	
Specialist consultation: nutritionist	322.19	259.04	385.34	Gamma	
Specialist nurse	17.41	13.99	20.82	Gamma	GP surgery–based nurse unit cost per hour (Curtis and Burns 2020[240])
Urologist (for stones) for adult patients	89.98	72.34	107.61	Gamma	
Urologist (for stones) for paediatric patients	169.88	136.58	203.18	Gamma	Assumed equal to a nephrology consultation
Social worker for adult patients	23.12	18.59	27.65	Gamma	Social worker unit cost per hour (Curtis and Burns 2020[240])
Social worker for paediatric patients	23.76	19.11	28.42	Gamma	Social worker unit cost per hour (Curtis and Burns 2020[240])
Psychologist	200.97	161.58	240.36	Gamma	

Unit costs are shown in British pound sterling.
CT=computed tomography; GP=general practitioner; OWSA=one-way sensitivity analysis; PSA=probabilistic sensitivity analysis
Source: Curtis and Burns (2020)[240]; National Schedule of NHS Costs 2019/20[229]

Table D35 shows disease monitoring costs for each health state, by paediatric and adult patient, which were calculated from the per-cycle frequency of monitoring and the costs associated with each laboratory exam, procedure, and visit listed in Table D34.

Table D35. CKD monitoring costs in the CE model

Health state	Base case	OWSA range		PSA distribution
		Lower value	Upper value	
Paediatric patient				
CKD 1–2	215.24	173.05	257.43	Gamma
CKD 3a	217.83	175.13	260.52	Gamma
CKD 3b	220.41	177.21	263.62	Gamma
CKD 4	1,525.57	1,226.56	1,824.58	Gamma
ESKD	4,299.29	3,456.63	5,141.95	Gamma
Adult patient				
CKD 1–2	139.33	112.03	166.64	Gamma
CKD 3a	141.92	114.10	169.74	Gamma
CKD 3b	144.51	116.18	172.83	Gamma
CKD 4	444.83	357.65	532.02	Gamma
ESKD	747.08	600.65	893.50	Gamma

Unit costs are shown in British pound sterling.
CE=cost effectiveness; CKD=chronic kidney disease; ESKD=end-stage kidney disease; OWSA=one-way sensitivity analysis; PSA=probabilistic sensitivity analysis
Source: National Schedule of NHS Costs 2019/20[229]

12.3.12 Adverse event costs

The costs of managing AEs associated with lumasiran and ECM (Section 12.2.4) were derived from NHS reference costs listed in Appendix Table 18. Table D36 shows the costs included in the CE model.

Table D36. List of AEs and summary of costs included in the CE model

AE	Base case	OWSA		PSA distribution
		Lower value	Upper value	
Headache	403.42	324.35	482.49	Gamma
Injection-site erythema	266.93	214.61	319.25	Gamma
Injection-site pain	266.93	214.61	319.25	Gamma
Injection-site reaction	266.93	214.61	319.25	Gamma
Rhinitis	266.93	214.61	319.25	Gamma
Upper respiratory infection	324.94	261.25	388.63	Gamma

Unit costs are shown in British pound sterling.
AE=adverse event; CE=cost effectiveness; OWSA=one-way sensitivity analysis; PSA=probabilistic sensitivity analysis
Source: Curtis and Burns (2020)[229]

12.3.13 Miscellaneous costs

An end-of-life cost of £4,200.00 was included in the model as a one-off cost in the last 6 months of life. This is equivalent to the cost of a 5-day inpatient stay, specialist palliative care (£398 per day), and five outpatient medical specialist visits (£202 per visit), and was applied to the proportion of new deaths at each cycle of the model.[240]

12.3.14 Other opportunities for resource savings or redirection of resources that it has not been possible to quantify

No further opportunities were identified.

12.4 Approach to sensitivity analysis

12.4.1 Investigation of the uncertainty around structural assumptions

Deterministic (one-way) and probabilistic sensitivity analyses were conducted on the model base-case parameters. Scenario analyses were conducted to further test the uncertainty around specific model inputs and assumptions.

12.4.2 Details of sensitivity analyses

Deterministic (one-way) sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses were performed in which key model parameters were varied one at a time around their base-case values. The 95% confidence limits were used as the high and low values when reported in the data reference. If not reported, the 95% CI was approximated by setting high and low values at the base-case value ±1.96 × standard error. When the standard error was not reported, ±10% of the base-case value was used as a proxy. High and low values used in the one-way sensitivity analyses are presented in Table D24.

Probabilistic sensitivity analysis

To address the uncertainty in the parameters used within the model, a probabilistic sensitivity analysis (PSA) was implemented. The PSA was performed on the comparison between lumasiran and ECM. The distribution used was beta, normal, gamma, or Dirichlet for all parameters. Mean results were calculated from the 1,000 simulations in this analysis. The PSA distributions are summarised in Table D24.

Scenario analysis: differential discounting

The current NICE Guide to the Methods of Technology Appraisal[156] states that sensitivity analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis. However, a scenario analysis using differential discounting for costs (3.5%) and health effects (1.5%) would reflect a more appropriate modelling methodology given the natural history of PH1 and the timescale over which health benefits of lumasiran are accrued.

There is considerable support in the literature for the argument that the value of health is expected to grow over time; society considers future health to be more valuable than current health, and therefore the monetary value of a future QALY is greater than the value of a QALY in the present.[241-245] Gravelle and Smith (2001) analysed cost-effectiveness from both a behavioural and social welfare point of view and found that in both cases, the value of future health is greater than the value of current health; consequently, if the focus of decision makers is to maximise social welfare, a discounting scheme must account for this difference.[241] Prominent health economists have made a compelling argument that differential discounting of health benefits versus costs is the most appropriate method for correctly applying greater weight to future health effects.[241-243,246]

In view of these considerations, a CE analysis with similar discount rates for cost and health benefits may not properly reflect that the value of future health is greater than the value of current health.[242,243] When health effects are not valued in monetary terms (as is the case when health effects are measured in QALYs), an equal discount for costs and benefits can undervalue future health benefits.[243,246] Instead, the greater weight of future versus current health effects is more appropriately accounted for by lowering the discount rate for health effects relative to costs. According to Gravelle and Smith (2001),[241] differentially discounting health benefits by 2% to 5% less than costs gives more weight to future health effects, reflecting the expectation that the value of future health is greater than the value of current health.

These considerations supporting the use of differential discounting are most clearly applicable for diseases and therapies in which costs are spent now but health benefits may not be fully realised until the future.[247] For example, cell and gene therapies (termed “advanced therapy medicinal products” [ATMPs] by the EMA) and vaccines typically require up-front payment to achieve health benefits years in the future. As noted above, discounting health gains in the same manner as costs may not reflect the relatively higher valuation of future health over current health from a societal standpoint and can therefore underestimate of the value of health technologies; this underestimation would be most pronounced for technologies with up-front costs and substantial long-term benefits. As explained in a methodological review by John et al. (2019)[247], the practice of applying the same discount rate to costs and health gains introduces a systematic bias against healthcare technologies with up-front costs and long-term health effects, and thus differential discounting with a lower

rate for health effects is a more appropriate discounting model. Accordingly, recent expert reviews of methodologies for assessing the cost-effectiveness of ATMPs by Jönsson et al. (2019)[248] and of vaccines by Jit and Mibei (2015)[249] have proposed discounting health benefits at a lower rate than costs as a way to account for this differential timing of costs and benefits, by weighting them according to when they are accrued.

Lumasiran for PH1 should be regarded in a similar context to vaccines and ATMPs, because initiating treatment incurs costs immediately, whereas important aspects of clinical benefit may not become apparent until years later in this chronic condition. In the absence of disease-modifying treatment, the natural history of PH1 is characterised by oxalate accumulation causing progressive decline in renal function and formation of renal stones, with eventual progression to ESKD, severe illness due to systemic oxalosis, and death.[4,34] In ILLUMINATE-A, normalisation or near-normalisation of urinary oxalate was achieved in 84% of patients at 6 months of double-blind treatment and sustained through Month 12 in the extension period (88%).[250] Among patients who crossed over from placebo to lumasiran in the extension period, 77% achieved normalisation or near-normalisation of urinary oxalate. Reflecting the causal role of oxalate in PH1 disease manifestations, these changes in urinary oxalate levels were accompanied by disease-modifying efficacy for lumasiran on multiple outcomes, including nephrocalcinosis and renal stone events.[179] The benefits of lumasiran continue to be seen throughout the long-term extension period of ILLUMINATE-A.[63,68] However, because gradual deposition of calcium oxalate crystals is a key driver of long-term morbidity in PH1, it may be years before differences between lumasiran-treated and untreated patients emerge for other important clinical events such as ESKD. Therefore, applying the same discount rate to costs and health outcomes would unfairly penalise lumasiran by underestimating future health gains relative to near-term costs.

Given the theoretical support for differential discounting, the chronic nature of PH1, and the long timescale over which the clinical benefit of lumasiran is expected to be realised, a lower discount rate for health benefits relative to costs is appropriate for this CE analysis.

Scenario analysis: alternative assumption for CKD distribution at model start

A scenario analysis was performed that used CKD distributions at model start separated by adult and paediatric PH1 populations from Singh et al. (2021).[25] Data on patients aged <20 years were used as a proxy for the paediatric population in the CE model, since Singh et al. reported data using this age cut-off (as opposed to the typical cut-off of age <18 years for paediatric patients). For the adult population, CKD distribution at model start was 26% for CKD 1–2, 10% for CKD 3a, 10% for CKD 3b, 12% for CKD 4, and 42% for ESKD. For the paediatric population, CKD distribution at model start was 44% for CKD 1–2, 13% for CKD 3a, 13% for CKD 3b, 8% for CKD 4, and 20% for ESKD.

Scenario analysis: alternative assumption for time to ESKD

A scenario analysis was performed that modelled time to ESKD based on the ESKD-free KM curve for PH1 patients in the US RKSC PH registry reported by Singh et al. (2021).[25]

Scenario analysis: alternative assumption for worsening of advanced renal disease–lumasiran arm

A scenario analysis was performed that permitted worsening of advanced renal disease from CKD 4-Ox_C to ESKD-Ox_C in the lumasiran cohort. The rate of ESKD observed in non-PH1 CKD patients without hyperkalaemia (3.44 per 100 patient/years) reported by Provenzano et al. (2020)[251] was converted into a per-cycle rate (0.173), and divided by the per-cycle rate (0.0511) for PH1 patients in CKD 4-Ox_U used in the CE model, to generate a hazard ratio for progression of 0.3383.

12.4.3 Summary of variables used in the sensitivity analyses

The variables used in the deterministic (one-way) sensitivity analyses are shown in Table D24. Variables used in scenario analyses are described in Section 12.4.2.

12.5 Results of economic analysis

12.5.1 Base-case analysis

The ICER results for lumasiran compared with ECM in terms of life-years gained (LYG) and QALYs from the NHS/PSS direct medical perspective are presented in Table D37. Lumasiran compared with ECM yields an undiscounted incremental cost effectiveness of £[redacted]/LYG and an incremental cost-utility of £[redacted]/QALY. The ICER is £[redacted]/LYG and £[redacted]/QALY with the inclusion of a proposed confidential patient access scheme discount ([redacted]). Applying a highly specialised technology QALY weighting of [redacted], which is deemed appropriate for technologies with incremental QALYs gained [redacted],[69] yields a discounted ICER of £[redacted]/QALY.

Table D37. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Lumasiran	[redacted]*	57.48	[redacted]	[redacted]	8.45	[redacted]	[redacted]
ECM	[redacted]	49.03	[redacted]				
Discounted (3.5% for benefits, 3.5% for costs)							
Lumasiran	[redacted]*	23.94	[redacted]	[redacted]	1.16	[redacted]	[redacted]
ECM	[redacted]	22.78	[redacted]				

*Inclusive of a proposed patient access scheme discount ([redacted]).
ECM=established clinical management; ICER=incremental cost-effectiveness ratio; LYG=life-year gained; QALY=quality-adjusted life-year

The results of this CE analysis were a weighted average of the results from the paediatric and adult cohorts. The weighting was based on the proportion of paediatric patients obtained from the pooled ILLUMINATE-A and ILLUMINATE-B trials (Table D5).

12.5.2 Comparison of outcomes from decision problem to clinically important outcomes from the clinical trials

Not applicable. The outcomes highlighted in the decision problem cannot be obtained at baseline from the clinical trials.

12.5.3 Proportion of the cohorts in each health state over time

Health-state distributions over time are shown in Figure D5 for the paediatric cohort and in Figure D6 for the adult cohort. The model predicts that at least half of patients receiving lumasiran remain in health state CKD 3b or better for most of their lifetime. In contrast, patients on ECM move through progressively worse CKD health states.

A. Lumasiran arm

B. ECM arm

Figure D5. Proportion of the paediatric patient cohort across all health states over time (Markov trace)

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

A. Lumasiran arm

B. ECM arm

Figure D6. Proportion of the adult patient cohort across all health states over time (Markov trace)
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

Table D38 and Table D39 summarise the proportion of the overall patient cohort across all health states over time for the lumasiran and ECM arms, respectively.

Table D38. Proportion of the patient cohort across all health states over time, lumasiran arm

Years	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Death
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
0	[redacted]									
0.5	[redacted]									
1	[redacted]									
1.5	[redacted]									
2	[redacted]									
2.5	[redacted]									
3	[redacted]									
3.5	[redacted]									
4	[redacted]									
4.5	[redacted]									
5	[redacted]									
6	[redacted]									
7	[redacted]									
8	[redacted]									
9	[redacted]									
10	[redacted]									
15	[redacted]									
20	[redacted]									
25	[redacted]									
30	[redacted]									
35	[redacted]									
40	[redacted]									
45	[redacted]									
50	[redacted]									
55	[redacted]									
60	[redacted]									
65	[redacted]									
70	[redacted]									
75	[redacted]									
80	[redacted]									
85	[redacted]									
90	[redacted]									
95	[redacted]									
100	[redacted]									

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

Table D39. Proportion of the patient cohort across all health states over time, ECM arm

Years	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Death
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
0	[redacted]									
0.5	[redacted]									
1	[redacted]									
1.5	[redacted]									
2	[redacted]									
2.5	[redacted]									
3	[redacted]									
3.5	[redacted]									
4	[redacted]									
4.5	[redacted]									
5	[redacted]									
6	[redacted]									
7	[redacted]									
8	[redacted]									

9	[redacted]								
10	[redacted]								
15	[redacted]								
20	[redacted]								
25	[redacted]								
30	[redacted]								
35	[redacted]								
40	[redacted]								
45	[redacted]								
50	[redacted]								
55	[redacted]								
60	[redacted]								
65	[redacted]								
70	[redacted]								
75	[redacted]								
80	[redacted]								
85	[redacted]								
90	[redacted]								
95	[redacted]								
100	[redacted]								

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

12.5.4 QALYs accrued over time

The discounted QALYs accrued over time by the different health states are summarised in Figure D7 for the paediatric cohort and in Figure D8 for the adult cohort.

A. Lumasiran arm

B. ECM arm

Figure D7. Discounted QALYs over time in the paediatric cohort

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

A. Lumasiran arm

B. ECM arm

Figure D8. Discounted QALYs over time in the adult cohort
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

The undiscounted QALYs accrued over time by the different health states are summarised in Figure D9 for the paediatric cohort and in

Figure D10 for the adult cohort.

A. Lumasiran arm

B. ECM arm

Figure D9. Undiscounted QALYs over time in the paediatric cohort
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

A. Lumasiran arm

B. ECM arm

Figure D10. Undiscounted QALYs over time in the adult cohort
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

12.5.5 LY and QALYs accrued for each health state listed for each comparator

The summary of undiscounted LYG by health state is shown in Table D40. QALYs accrued across health states are shown in Sections 12.5.6 and 12.5.7.

Table D40. Summary of undiscounted LYG by health state

Technologies	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	23.22	7.25	6.85	0.29	1.04	0.84	1.33	16.44	0.22	57.48
ECM	2.43	1.32	1.61	0.00	12.37	0.00	27.55	0.00	3.75	49.03
Difference										
Lumasiran vs. ECM	20.78	5.93	5.23	0.29	–11.33	0.84	–26.22	16.44	–3.52	8.45

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; LYG=life-years gained; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

12.5.6 Disaggregated discounted QALYs by health state

Table D41 summarises the discounted QALYs by health state. Most of the discounted QALYs [redacted]. This demonstrates the value of lumasiran in terms of being able to keep patients from progressing to more severe health states with poorer HRQoL and higher risk of death. It also demonstrates the value of lumasiran in optimising patients' suitability for and prognosis after transplantation.

Table D41. Summary of discounted QALY by health state

Technologies	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	[redacted]									
ECM	[redacted]									
Difference										
Lumasiran vs. ECM	[redacted]									

CKD=chronic kidney disease; cLKT=liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

12.5.7 Disaggregated undiscounted QALYs by health state

Table D42 shows a summary of undiscounted QALYs by health state. Most of the undiscounted QALYs [redacted], as observed with the disaggregated discounted QALYs (Section 12.5.6).

Table D42. Summary of undiscounted QALY by health state

Technologies	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	[redacted]									
ECM	[redacted]									
Difference										
Lumasiran vs. ECM	[redacted]									

CKD=chronic kidney disease; cLKT=liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

12.5.8 Costs for lumasiran and ECM by category of cost

Costs by category of cost per patient are shown in Table D43 and Table D44.

Table D43. Summary of undiscounted costs by category of cost per patient

Cost	Lumasiran costs (£)	ECM costs (£)	Increment
Drug	[redacted]*	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*Inclusive of a proposed patient access scheme discount ([redacted]).
AE=adverse event; cLKT=combined liver–kidney transplantation; ECM=established clinical management; EOL=end-of-life care

Table D44. Summary of discounted costs by category of cost per patient

Cost	Lumasiran costs (£)	ECM costs (£)	Increment
Drug	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*Inclusive of a proposed patient access scheme discount ([redacted]).
AE=adverse event; cLKT=combined liver–kidney transplantation; ECM=established clinical management; EOL=end-of-life care

12.5.9 Costs for lumasiran and ECM by health state

Undiscounted and discounted costs by health states are shown in Table D45 and Table D46, respectively.

Table D45. Summary of undiscounted costs by health state

Tech.	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference										
Lumasiran vs. ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs shown in British pound sterling.
CKD=chronic kidney disease; cLKT=liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years; Tech.=Technologies

Table D46. Summary of discounted costs by health state

Tech.	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference										
Lumasiran vs. ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs shown in British pound sterling.
CKD=chronic kidney disease; cLKT=liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years; Tech.=Technologies

12.5.10 Costs for lumasiran and ECM by AE

The summary of costs by AE is not applicable.

12.5.11 Sensitivity analysis results

Deterministic one-way sensitivity analysis of the 10 most influential model parameters

The percentage change in base-case results following lower and upper variation in the 10 most influential model parameters are presented in Table D47 and Figure D11.

Table D47. Percentage change in base-case results following lower and upper variation in the 10 most influential model parameters

Parameters	Lower value (%)	Upper value (%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Results shown are percent change in ICER when each parameter is set to its lower and upper bounds.

CKD=chronic kidney disease; ECM=established clinical management; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease

Figure D11. Tornado diagram of the percentage change in base-case results following lower and upper variation in the 10 most influential model parameters

CKD=chronic kidney disease; ECM=estimated clinical management; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; ICER=incremental cost-effectiveness ratio; POx=plasma oxalate; QALY=quality-adjusted life-years

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis (PSA) are summarised in Table D48. Figure D12 and Figure D13 show the PSA results and CE acceptability curve, respectively. The results are inclusive of the QALY weighting.

Table D48. Probabilistic sensitivity analysis results

	Costs (£)			QALY			ICER
	Lumasiran	ECM	Incremental	Lumasiran	ECM	Incremental	(£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Includes QALY weighting.

CI=confidence interval; ECM=estimated clinical management; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; QALY=quality-adjusted life-year

Figure D12. Results of the 1000 simulations in the PSA for the ICER of lumasiran vs. ECM
Includes QALY weighting.

ECM=estimated clinical management; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; QALY=quality-adjusted life-year

Figure D13. CE acceptability curve
Includes QALY weighting.

CE=cost effectiveness; QALY=quality-adjusted life-year; WTP=willingness-to-pay

Scenario analyses

Results of the scenario analyses are shown in Table D49, which are inclusive of a proposed confidential patient access scheme discount. The largest difference in ICER from the base case was seen [redacted].

Applying a highly specialised technology QALY weighting of [redacted] to the discounted ICERs in the scenario analyses yields discounted ICERs ranging from £[redacted]/QALY to £[redacted]/QALY.

Table D49. Results of the scenario analyses

#	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER vs. base case
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Differential discounting (1.5% outcomes and 3.5% costs)	[redacted]	[redacted]	[redacted]	[redacted]
2	Distribution at start from Singh et al. (2021)[25] in paediatric and adult separately	[redacted]	[redacted]	[redacted]	[redacted]
3	Model time to ESKD based on PH1 data from the US RSKC PH registry data by Singh et al. (2021)[25]	[redacted]	[redacted]	[redacted]	[redacted]
4	Worsening of advanced renal disease in the CKD4-Ox_C health state	[redacted]	[redacted]	[redacted]	[redacted]

CKD=chronic kidney disease; ESKD=end-stage kidney disease; ICER=incremental cost-effectiveness ratio; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; PH=primary hyperoxaluria; PH1=primary hyperoxaluria type 1; QALY=quality-adjusted life-year; RKSC=Rare Kidney Stone Consortium

12.5.12 Main findings of each of the sensitivity analyses

Deterministic one-way sensitivity analysis

The model results were most sensitive to the [redacted].

Probabilistic sensitivity analysis

In the PSA, [redacted] Figure D12 [redacted] (Figure D13). The [redacted] (Table D48)[redacted].

Scenario analysis

Discounted ICERs reported in the scenario analyses ranged [redacted] and were inclusive of a proposed confidential patient access scheme discount. Applying a highly specialised technology QALY weighting of [redacted] in the scenario analyses yielded discounted ICERs ranging [redacted].

12.5.13 Key drivers of the cost results in the sensitivity analyses

The key drivers of the cost results are [redacted] (Table D47 and Figure D11).

12.5.14 Miscellaneous results

All relevant results have been presented in the previous sections as part of the template.

12.6 Subgroup analysis

12.6.1 Subgroup analysis

Patients of all ages with infantile onset of PH1 and infants with infantile onset of PH1 were identified in the scope as two relevant subgroups, given the detrimental clinical manifestations of PH1 when they arise in children, and the rapid progression to ESKD and greater mortality in those with earlier clinical onset regardless of their current age (Section 5.1).

12.6.2 Characteristics of patients in the subgroup(s)

For the subgroup *Patients of all ages with infantile onset*, all patients entering the CE model are assumed to be paediatric patients, since these patients are unlikely to reach adulthood without a transplantation (Section 6.1.2). Values for the initial age and average weight of this subgroup are the same as those used for the

paediatric population in the base case (i.e., derived from ILLUMINATE data). The distribution of CKD at baseline is the same as the base case (i.e., derived from Singh et al. (2021)[25]; Table D5).

For the subgroup *Infants with infantile onset*, all patients entering the CE model were modelled as infants presenting with severe disease. The initial age of this subgroup is the midpoint of the definition used for infant age (i.e., 0.5 years).[252] The average weight of this subgroup is the same as that used for the paediatric population in the base case (i.e., derived from ILLUMINATE data; Table D5), since infants are expected to become children within one cycle of the CE model. The distribution of CKD at baseline in this subgroup is set to 10% for CKD 4 and 90% for ESKD, based on UK clinical expert opinion (Section Table D23). A hazard ratio of 6.0 for progression to ESKD is applied to infants with infantile onset of PH1 vs. patients with non-infantile onset, based on Harambat et al. (2010[32]; Section 6.1.2).

12.6.3 Inclusion of the subgroups in the CE analysis

The CE model was run separately for each of the patient subgroups described in Section 12.1.1.

12.6.4 Results of the subgroup analysis

Patients of all ages with infantile onset of PH1

Lumasiran yields a discounted ICER of £[redacted]/LYG and £[redacted]/QALY compared with ECM in patients of all ages with infantile onset (Table D50). These results, which included a proposed confidential patient access scheme discount, represent a [redacted] in the ICER versus the base case (Table D37). Applying a highly specialised technology QALY weighting of [redacted] yields a discounted ICER of £[redacted]/QALY.

Table D50. Base-case results, patients of all ages with infantile onset of PH1

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Lumasiran	[redacted]*	63.37	[redacted]	[redacted]	8.18	[redacted]	[redacted]
ECM	[redacted]	55.19	[redacted]				
Discounted (3.5% for outcomes, 3.5% for costs)							
Lumasiran	[redacted]*	24.80	[redacted]	[redacted]	0.60	[redacted]	[redacted]
ECM	[redacted]	24.20	[redacted]				

*Inclusive of a proposed patient access scheme discount ([redacted]).
ECM=established clinical management; ICER=incremental cost-effectiveness ratio; LYG=life-years gained; PH1=primary hyperoxaluria; QALY=quality-adjusted life-years

The discounted and undiscounted QALYs accrued over time by the different health states are summarised in Figure D14 and Figure D15, respectively.

A. Lumasiran arm **B. ECM arm**

Figure D14. Discounted QALYs over time in patients of all ages with infantile onset of PH1
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria type 1; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

A. Lumasiran arm **B. ECM arm**

Figure D15. Undiscounted QALYs over time in patients of all ages with infantile onset of PH1
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria type 1; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

The summaries of undiscounted LYG and QALYs by health state are shown in Table D51 and Table D52, respectively. Most of the undiscounted QALYs [redacted] (Section 12.5.7).

Table D51. Summary of undiscounted LYG by health state, patients of all ages with infantile onset of PH1

Technologies	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	25.90	8.10	7.70	0.25	0.35	0.73	2.36	17.73	0.26	63.37
ECM	2.44	1.32	1.62	0.00	3.78	0.00	41.56	0.00	4.47	55.19
Difference										
Lumasiran vs. ECM	23.46	6.78	6.07	0.25	–3.43	0.73	–39.21	17.73	–4.20	8.18

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

Table D52. Summary of undiscounted QALY by health state, patients of all ages with infantile onset of PH1

Technologies	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	[redacted]									
ECM	[redacted]									
Difference										
Lumasiran vs. ECM	[redacted]									

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

Costs by category of cost per patient are shown in Table D53 and Table D54.

Table D53. Summary of undiscounted costs by category of cost, patients of all ages with infantile

onset of PH1

Cost	Lumasiran costs (£)	ECM costs (£)	Increment
Drug	[redacted]*	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*Inclusive of a proposed patient access scheme discount ([redacted]).
AE=adverse event; cLKT=combined liver–kidney transplantation; ECM=established clinical management; EOL=end-of-life care; PH1=primary hyperoxaluria

Table D54. Summary of discounted costs by category of cost per patient of all ages with infantile onset of PH1

Cost	Lumasiran costs (£)	ECM costs (£)	Increment
Drug	[redacted]*	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*Inclusive of a proposed patient access scheme discount ([redacted]).
AE=adverse event; cLKT=combined liver–kidney transplantation; ECM=established clinical management; EOL=end-of-life care; PH1=primary hyperoxaluria

Infants with infantile onset of PH1

The analysis of infants with infantile onset of PH1 [redacted] (Table D55). This is inclusive of a proposed confidential patient access scheme discount.

Table D55. Base-case results, infants with infantile onset of PH1

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Undiscounted							
Lumasiran	[redacted]*	51.33	[redacted]	[redacted]	–7.75	[redacted]	[redacted]
ECM	[redacted]	59.08	[redacted]				
Discounted (3.5% for outcomes, 3.5% for costs)							
Lumasiran	[redacted]*	21.67	[redacted]	[redacted]	–2.74	[redacted]	[redacted]
ECM	[redacted]	24.41	[redacted]				

*Inclusive of a proposed patient access scheme discount ([redacted]).
ECM=established clinical management; ICER=incremental cost-effectiveness ratio; LYG=life-years gained; PH1=primary hyperoxaluria; QALY=quality-adjusted life-years

The discounted and undiscounted QALYs accrued over time by the different health states are summarised in Figure D16 and Figure D17, respectively.

A. Lumasiran arm **B. ECM arm**

Figure D16. Discounted QALYs over time in infants with infantile onset of PH1
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria type 1; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

A. Lumasiran arm **B. ECM arm**

Figure D17. Undiscounted QALYs over time in infants with infantile onset of PH1
CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria type 1; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

The summaries of undiscounted LYG and QALYs by health state are shown in Table D56 and Table D57. Most of the undiscounted QALYs [redacted].

Table D56. Summary of undiscounted LYG by health state, infants with infantile onset of PH1

Technologies	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	0.00	0.00	0.00	0.25	0.04	2.31	0.37	48.26	0.09	51.33
ECM	0.00	0.00	0.00	0.00	0.67	0.00	52.73	0.00	5.69	59.08
Difference										
Lumasiran vs. ECM	0.00	0.00	0.00	0.25	–0.63	2.31	–52.36	48.26	–5.59	–7.75

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; LYG=life-years gained; PH1=primary hyperoxaluria; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate

Table D57. Summary of undiscounted QALY by health state, infants with infantile onset of PH1

Technologies	CKD 1–2	CKD 3a	CKD 3b	CKD 4		ESKD		cLKT		Total
				Ox_C	Ox_U	Ox_C	Ox_U	Ox_C	Ox_U	
Lumasiran	[redacted]									
ECM	[redacted]									
Difference										
Lumasiran vs. ECM	[redacted]									

CKD=chronic kidney disease; cLKT=combined liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; PH1=primary hyperoxaluria; Ox_C=controlled oxalate; Ox_U=uncontrolled oxalate; QALY=quality-adjusted life-years

Costs by category of cost per infant with infantile onset of PH1 are shown in Table D58 and Table D59.

Table D58. Summary of undiscounted costs by category of cost per infant with infantile onset of PH1

Cost	Lumasiran costs (£)	ECM costs (£)	Increment
Drug	[redacted]*	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*Inclusive of a proposed patient access scheme discount ([redacted]).
AE=adverse event; cLKT=combined liver–kidney transplantation; ECM=established clinical management; EOL=end-of-life care; PH1=primary hyperoxaluria

Table D59. Summary of discounted costs by category of cost per infant with infantile onset of PH1

Cost	Lumasiran costs (£)	ECM costs (£)	Increment
Drug	[redacted]*	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*Inclusive of a proposed patient access scheme discount ([redacted]).
AE=adverse event; cLKT=combined liver–kidney transplantation; ECM=established clinical management; EOL=end-of-life care; PH1=primary hyperoxaluria

12.6.5 Subgroups not included in the submission

There is inadequate evidence to consider subgroup analysis for:

- Children with a family history confirmed by cord blood testing, as cord blood testing is not a part of standard clinical practice in PH1
- Children and adults presenting with kidney stones, as eventually, all patients with PH1 are expected to develop renal stone events, based on the natural history of the disease[34]

12.7 Validation

12.7.1 Methods used to validate and cross-validate the model

Design of the model and its inputs

PH1 is a rare disease and published UK-specific HCRU data were not available. The structured interviews that were used to elicit clinical and HCRU estimates from UK clinical experts and to test assumptions relating to model structure and parameters have been described in Sections 10.1.10 and 12.2.5.

Model quality check

The quality checklist used to assess the CE model of lumasiran in PH1 was based on the transparency and validation checklist in "Modeling Good Research Practices" by Caro et al. (2012)[253] and is summarised in Table D60.

Table D60. Quality checklist for lumasiran CE model

Test to be performed	Outcome
Scenario testing	
Make treatment costs equal - sense check results.	ECM cycle drug cost set equal to lumasiran drug cost, ECM add-on to lumasiran = 0 (otherwise cost is counted twice), lumasiran discontinuation due to any reason and transplant rates were set = 0. As expected, the total drug cost in lumasiran was higher than in ECM arm because of longer survival. However when dividing total undiscounted drug cost by total undiscounted LYs, the annual drug cost is equal in the two arms.
Make treatment costs for each arm very high - sense check results.	Yes, only drug costs increase.
Treatment costs: Turn off all health state costs and set AE rates to 0. Total costs should now only include treatment costs; ensure that intervention treatment costs reflect expectations given inputs.	Drug administration, monitoring by health state, renal stone event, transplant, systemic oxalosis complications, and end-of-life costs were set to 0. AE incidence was set = 0 in both arms. Total cost was equal to drug cost.
Make AE rates equal; check that associated costs are equal (assuming AE-specific costs), and that LY or QALY results change in the right direction.	Treatment AEs in ECM were set equal to rates in lumasiran arm. Only costs and QALYs (i.e., not LYs) of ECM arm were impacted since we do not consider impact of AEs on survival directly. The total QALY of ECM slightly increased as a consequence and total costs slightly decreased. The direction of change is as expected.
If a survival treatment effect exists, examine relative time in states and make sure times make sense given transition probabilities. Use judgement on LY per state, make sure nothing looks unrealistic.	Treatment impacts survival by preventing progression to late-CKD stages associated with higher mortality. Because the transplant procedure is associated with some degree of short-term mortality risk, there is a modest, transient early increase in mortality in the lumasiran arm vs. the ECM arm, as the oxalate-lowering efficacy of lumasiran makes substantially more patients who start treatment in later CKD stages suitable for transplantation. However, over the longer term, this effect is reversed due to the favourable long-term prognosis of patients with controlled oxalate who undergo transplantation relative to untransplanted patients and patients transplanted with uncontrolled oxalate. Thus the direction of impact on overall survival, taking into account the effect of lumasiran in preventing progression to late-stage CKD (in patients starting treatment in early CKD stages) and establishing pre-transplant oxalate control (in patients starting treatment in later CKD stages), is as expected.
If a treatment effect exists, set baseline event rates equal across arms, RR/HR to 1 and AE/other event	The following lumasiran data were applied in ECM engine (also in ECM post discontinuation in lumasiran engine): health-state transition probabilities, AEs, renal stone events. High-intensity dialysis was applied

Test to be performed	Outcome
rates to zero/equivalence, total LY and QALYs should be equal between arms.	in both arms in both CKD 4 and ESKD. We obtained the same QALYs and LYs in both arms.
Make both arms entirely equal (all costs, AE rates, OS, PFS). 1) Total LY and QALYs should be equal between arms. 2) Total costs should be equal between arms 3) Total costs per health state should be equal between arms.	The following lumasiran data were applied in ECM engine (also in ECM post discontinuation in lumasiran engine): health-state transition probabilities, AEs, renal stone events. High-intensity dialysis was applied in both arms in both CKD4 and ESKD. ECM cycle drug cost set equal to lumasiran cycle drug cost, ECM add-on to lumasiran = 0 (otherwise cost is counted twice), lumasiran discontinuation due to any reason set = 0 and administration cost of lumasiran applied to ECM. We obtained the same total QALYs, LYs and cost in both arms. Total costs per health state and per cost type are equal between arms.
If a survival treatment effect exists, turn off transition probability to specific health states, one at a time (assuming multiple health states). Make sure time in state = 0 for each given health state.	Since we already have a proportion of cohort at model start in most health states, this test is not applicable to all. However it was done for CKD 4 and ESKD controlled and post-cLKT health state. Results were as expected (0 total LYs in that health state).
If QoL effect exists, make all utilities and disutilities = 0. Make sure total QALYs = 0	Health-state utilities =0 (already zeroing the impact of systemic oxalosis complications and dialysis), renal stone event disutility =0, transplant acute disutilities = 0, AEs disutilities = 0. Then total QALYs in both arms =0.
If QoL effect exists, make all utilities =1 and disutilities =0. Make sure total QALYs = total LYs.	Health-state utilities =1 (already zeroing the impact of systemic oxalosis complications and dialysis), renal stone event disutility =0, transplant acute disutilities =0, AE disutilities =0, general population utility =1. Then total QALYs in each arm = total LYs in each arm
General check	
Using Formulas | Formula Auditing | Show Formulas, check to ensure consistent formulas are used, where necessary.	No issues found
Check that discount rates are being applied correctly.	Checked in both Markov engine sheets in setting part and LYs, QALYs and costs. No issues found.
Ensure all linked cells refer back to the original source (no spider webs).	No issues found.
Check that cells have appropriate formatting (currency, same number of decimals where appropriate, etc).	No issues found.
Markov/Survival analysis	
Are the discount rates for costs and outcomes correctly calculated?	Yes.
Does the time spent in the health states add up to 1?	Yes. In the lumasiran engine, the sum was done for cohort on and off treatment together.
Does the number of subjects remain constant over model cycles?	Yes = 1.
Check that time horizon/ cycles/ age are linked in correctly.	Checked in look-up and the Markov engines sheet and no issues were found.
Confirm that the first row of the Markov trace refers to the correct input.	No issues found.
Confirm that cost formulas in Markov trace refer to the right cells.	No issues found.
Confirm that QALY, LY formulas in Markov trace refer to the right cells.	No issues found.
Is the model type (Weibull, Exponential, Gompertz, etc) calculated correctly?	Checked with respect to ToT, time to ESKD, OS post-transplant, and graft survival curves and no issues were found
Check that PFS is never greater than OS (check that they never cross).	NA
Check that the choice of survival functions (e.g., for Weibull) has been justified (see log-likelihood, AIC, BIC, visual inspection, etc).	AIC and BIC align with best fitting on visual inspection
If HRs have been used, check they have been applied correctly.	Relative risk of death by health state vs. general population is applied to the probability of death of general population, which then is transformed into a rate and transformed back into a probability to avoid issues of probability of death >1. HR of renal stone events is applied correctly to

Test to be performed	Outcome
	baseline rate of renal stone events. HR of ESKD onset for infantile disease onset is applied to the overall PH1 population hazard of ESKD before being transformed into a probability per cycle (activated only for infant disease onset subgroup analysis). No issues found.
Check that the hazard of death in the model does not fall below that of the general population.	No issues found
OWSA	
Check results for OWSA - do they make sense?	Yes, variations around base-case ICER in all parameters move in expected direction.
Are there any problems with the OWSA macro?	No.
Check the graphs (example: tornado) - does the scale make sense? Are all axes labelled properly? Is there a legend for the graph? Is the base-case result clearly labelled on the graph? Is the diagram sorted?	No issues found.
Do the high and low values make sense?	All high and low values were checked and no issues were found. Confidence intervals were used when available, and if not, upper and lower values were estimated based on standard deviation.
For custom high/low values, is there data validation to ensure the range makes sense (ensure that the high range cannot be lower than the low range; bounded appropriately)	Yes, all proportions were fixed to max 1 as upper value.
PSA	
Do the results of the PSA make sense?	Yes.
Are there any problems with the PSA macro?	No.
Check the scatterplot and cost-effectiveness acceptability graphs - do these make sense based on the base-case results?	Yes, the cost-effectiveness acceptability cloud is centred around base-case results and 100% of simulations are located in North-East quadrant (positive incremental costs and effect).
Check that the average cost and outcomes calculated from PSA array are close to their point estimate values.	No issues found. Mean PSA ICER is only slightly lower than deterministic base-case results.
Check distributions (appropriateness of types of distributions - normal, beta, gamma) and low and high estimates (95% CI and SE).	No issues found
In the event of negative ICERs, was a net monetary benefit analysis included? Do the graph and results make sense?	A negative ICER is obtained only in one scenario analysis on subgroup of infants at model start. In this instance the ICER was negative because of negative incremental costs. Since this is a scenario analysis only, no net monetary benefit was included and interpretation can be done on the basis on incremental QALYs and costs separately.

AE=adverse event; AIC=Akaike information criterion; BIC=Bayesian information criterion; CE=cost-effectiveness; CKD=chronic kidney disease; CI=confidence intervals; cLKT=combined/sequential liver–kidney transplantation; ECM=established clinical management; ESKD=end-stage kidney disease; HR=hazard ratio; ICER=incremental cost-effectiveness ratio; LY=life-years; NA=not applicable; OS=overall survival; OWSA- one-way sensitivity analysis; PFS=progression-free survival; PSA=probabilistic senstivity analysis; QALY=quality-adjusted life-years; QoL=quality of life; RR=relative risk; SE=standard error; ToT=time on treatment

12.8 Interpretation of economic evidence

12.8.1 Consistency with the published economic literature

There is a scarcity of published data on the cost effectiveness of treatments for PH1 worldwide. The SLR described in Section 11 did not identify any economic literature for comparison.

12.8.2 Relevance to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope

The CEA results were based on clinical inputs from the pivotal RCT ILLUMINATE-A, and the open-label, phase 3 studies, ILLUMINATE-B and ILLUMINATE-C. Almost half the ILLUMINATE-A study population was from Europe, including seven patients from three sites in the UK. In addition, the ILLUMINATE-B trial included two patients from one UK site. The overall clinical trial population included patients with a range of disease duration, differing CKD stages and levels of control, disease complications, and experience with other therapies (i.e., pyridoxine). Given these aspects of the trial population, and given that the applied settings and input data were extensively validated by UK experts, the performed CEA is relevant to the patient population in England.

The CEA specifically highlights the benefits of lumasiran treatment in permitting patients of all ages with infantile onset of PH1 and infants with infantile onset of PH1 to move swiftly to health states in which they are suitable for, and can achieve the best outcomes following, transplantation.

12.8.3 Main strengths and weaknesses of the analysis

Strengths

- Data from the pivotal RCT ILLUMINATE-A and two open-label, phase 3 studies, ILLUMINATE-B and ILLUMINATE-C, were used to inform the model. The availability of placebo-controlled data (i.e., data from ILLUMINATE-A) is an exceptional strength in the modelling of a rare disease.
- Health states were primarily based on CKD stage, which maps directly to eGFR and thus is a key indicator of disease progression and determinant of the need for transplantation. CKD stages are validated and well accepted in the medical community as providing a clinically meaningful framework for describing patients with kidney disease, including kidney disease related to PH1.
- The relationship between plasma oxalate (an index of hepatic oxalate production) and eGFR has been quantified in the literature. The causative role of oxalate in this relationship is well recognised and underscores the relevance of using oxalate data from the ILLUMINATE trials to model changes in eGFR.
- The model structure and its inputs were either validated by or elicited from UK clinical experts with extensive experience in treating PH1.
- The model was validated and quality-assured by a recognised model quality checklist methodology.

Weaknesses

- No published data were available on the impact of PH1 on HRQoL. Utilities were derived from multiple sources; however, these included clinical trial data (ILLUMINATE-A) and health-state vignettes. The latter is a well-recognised data source in the absence of suitable EQ-5D values obtained directly from patients

12.8.4 Further analyses that could be undertaken to enhance the robustness/completeness of the results

The ongoing ILLUMINATE-A and ILLUMINATE-B extension periods will continue to provide data on endpoints, such as renal stone events and nephrocalcinosis, on which it is anticipated that lumasiran will continue to show benefit over the longer term (as already observed to Month 12 in ILLUMINATE-A[10]), as well as other outcomes on which directly observable benefits will take longer to be realised (e.g., avoidance of ESKD). Based on the known pathophysiological effects of elevated oxalate, natural history data on the association of oxalate with ESKD risk, and demonstration of stabilised renal function in patients undergoing pre-emptive liver transplantation to normalise oxalate in PH1, the oxalate-lowering effects of lumasiran are fully expected to translate to continued real-world benefit over the long term.[8,17,28,56,79,104,130,131,181]

The external validity of the model could be further enhanced by incorporating longer-term data on the clinical effectiveness and safety of lumasiran in patients with advanced PH1 (ILLUMINATE-C). It could also be

enhanced by integrating real-world data on the use of lumasiran in routine clinical practice in the UK. No such data were available at the time this analysis was conducted.

13 Cost to the NHS and Personal Social Services

13.1 Number of patients eligible for treatment in England over the next 5 years

According to the latest progress report from RaDaR, there are approximately 120 patients with any type of hyperoxaluria in the UK.[92] Based on registry data, approximately [redacted] of hyperoxaluria patients have PH1,[27,105] yielding an estimate of [redacted] PH1 patients in the UK. Expert clinician input supports an assumption that [redacted] of these patients have not already received a liver transplant or combined liver–kidney transplant. Considering that lumasiran would only be used in patients who have not already undergone these transplantation procedures, an estimated [redacted] prevalent patients with PH1 would currently be eligible for lumasiran treatment.

In addition to these prevalent patients, it is assumed that there will be approximately [redacted] new (i.e., incident) patients with PH1 eligible for lumasiran each year, based on an estimated incidence rate in Europe of 1 per 100,000 live births,[35] and national statistics reporting 613,936 live births in England and Wales in 2020.[124] This should be regarded as a worst-case scenario from the NHS perspective, because it is based on the highly conservative assumption that the increase in new patients is not offset by a reduction in patients who no longer need treatment (e.g., because they subsequently received a liver–kidney transplant).

Calculations of eligible patient numbers also incorporate survival estimates for lumasiran and ECM, in accordance with the base-case CEA presented in Section 12. The proportion of paediatric patients in the treated population is also aligned with the CEA. The total estimated number of patients eligible for treatment with lumasiran over 5 years is presented in Table D61.

Table D61. Lumasiran-eligible patients per year

	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible patients, n*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of paediatric patients, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The annual increase in the size of the eligible population is a conservative approach that assumes that the increase in new patients is not offset by a reduction in patients who no longer need treatment.

13.2 Expected uptake of lumasiran and the changes in its demand over the next 5 years

Table D62 shows the expected market uptake of lumasiran over the first 5 years after introduction, based on insights from expert clinicians and the latest company market research.

Table D62. Uptake and market share

Technology	Current practice	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population, n*	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share, %						
Lumasiran	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated population, n						
Lumasiran	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The annual increase in the size of the eligible population is a conservative approach that assumes that the increase in new patients is not offset by a reduction in patients who no longer need treatment.

ECM=established clinical management

13.3 Other significant costs associated with treatment.

The budget impact analysis considers various treatment-related costs, as summarised in Table D63, associated with the introduction of lumasiran within its licensed terms. These overall costs in the treated population are based on the per-patient costs derived from the base-case CEA reported in Section 12.5, over the 5-year time horizon, and thus incorporate the same assumptions from the CEA that determine the number of patients remaining on treatment, such as mortality, ToT, and transplant. In accordance with guidelines for budget impact analysis,[254] discounting of costs is not included, since the goal is to inform the budget holder's interest in real financial streams over the time horizon of the analysis. The 5-year projections for these cost components are shown in Table D63.

Table D63. Treatment, administration, and monitoring costs for the treated population

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
World without lumasiran					
ECM					
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with lumasiran					
Lumasiran					
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM					
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ECM=established clinical management

13.4 Estimates of resource savings associated with the use of lumasiran

Lumasiran is expected to yield savings to the NHS with respect to the management of advanced PH1 as patients are maintained in less severe disease states. Reductions in spending are anticipated for dialysis and for treatment of renal stone events and systemic oxalosis complications. Thus, the NHS will benefit from a disinvestment in resources and symptomatic treatments associated with PH1, which will partly offset the increase in costs due to treatment and cLKT that is predicted with the introduction of lumasiran. Estimates of the costs associated with these resources over the 5-year time horizon are shown in Table D64. These overall costs in the treated population are based on the undiscounted per-patient costs derived from the CEA, as for treatment-related costs above.

Table D64. Resource costs for the treated population

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5
World without lumasiran					
ECM					
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal stone events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cLKT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with lumasiran					
Lumasiran					
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal stone events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cLKT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM					
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal stone events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cLKT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; cLKT=combined liver–kidney transplantation; ECM=established clinical management; EOL=end-of-life care

13.5 Other opportunities for resource savings or redirection of resources that it has not been possible to quantify

By controlling oxalate levels and thereby alleviating the overall burden of PH1 disease, lumasiran is likely to reduce the reliance on other forms of care and support for patients with PH1, such as rehabilitation costs associated with bone fractures and joint damage. Lumasiran may also be expected to decrease the need for counselling for stress and depression by improving the disease prognosis and offering hope to patients and their caregivers.

13.6 Costs or savings associated with lumasiran that are incurred outside of the NHS and PSS

No additional costs outside of the NHS and PSS are expected with the introduction of lumasiran. Due to its demonstrated oxalate-lowering ability, lumasiran treatment is predicted to reduce costs for adult patients and for caregivers of patients of any age by reducing the overall utilisation and intensity of dialysis in the treated population, thereby decreasing travel costs and lost wages. By avoiding the most debilitating disease complications and their burdensome management, lumasiran may generally provide better life opportunities and higher lifetime income for patients with PH1.

13.7 Estimated budget impact for the NHS and PSS over the first year of uptake of lumasiran, and over the next 5 years

Introducing lumasiran for the treatment of PH1 in England is projected to add less than [redacted] to the NHS budget in the first year of uptake and is anticipated to result in a net budget impact below [redacted] in each of the first 5 years after introduction.

Table D65. Expected budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population, n*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive lumasiran, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs, £					
World without lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The annual increase in the size of the eligible population is a conservative approach that assumes that the increase in new patients is not offset by a reduction in patients who no longer need treatment.

13.8 Main limitations within the budget impact analysis

The budget impact model is consistent with the CEA for lumasiran in patients with PH1. As such, the budget impact analysis is subject to the same limitations, and many of the same underlying assumptions that are made in the CEA.

It is assumed in the budget impact assessment that the NHS faces the additional cost of 20% value-added tax (VAT) on drug costs, administration costs, and all other healthcare resources. The company does not believe that VAT is applicable to all patients across all cost categories, but as confirmation of which costs may not be subject to VAT is pending, VAT is applied uniformly. If some of the costs are not subject to VAT, the present approach will overestimate the net budget impact of lumasiran.

Finally, as they are an estimate of future uptake, market shares are inherently uncertain. However, the company's best estimate of the uptake of lumasiran, incorporating insights from expert clinicians, has been used in the budget impact analysis.

Section E – Impact of the technology beyond direct health benefits

14 Impact of the technology beyond direct health benefits

14.1 Cost savings or benefits outside of the NHS or PSS

Lumasiran is anticipated to result in significant economic benefits outside the NHS in terms of improved patient and caregiver productivity, mental health, and the ability to participate in activities of daily living. Although these wider economic benefits have not been quantified, the magnitude of the current burden of PH1 in the absence of lumasiran therapy is revealed by patient testimonials described in Section 7.1.4.

PH1 can inflict substantial strain on the patient and their family and caregivers due to intense medical requirements and associated financial hardship. Continuously maintaining hyperhydration regimens over many years can have a considerable impact on productivity, as it can be burdensome and a challenge to ensure patients drink fluids constantly throughout the day.[45] The recommended fluid intake is at least 3 L/m^2 distributed throughout 24 h. As described in Section 7.1.3, infants and younger children often require a nasogastric or gastrostomy tube to be able to comply with this intense fluid regimen.[20] Likewise, hospitalisations, emergency visits, and outpatient visits[255] for the treatment of clinical manifestations of PH1 cause interruptions to school and/or work for patients and caregivers, and these interruptions contribute to the financial burden of PH1. Daily travel to local hospitals for long dialysis sessions[96] and frequent visits to highly specialist treatment centres for PH1 are likely to prevent adult patients in advanced stages or the caregiver(s) of younger patients in such stages of PH1 from holding down jobs.[45,255]

Advanced PH1 disease may lead to a state of continuous pain, disability, decreasing independence, unemployment, depression, and sometimes suicide.[26] These inevitable consequences of untreated PH1 are likely to incur costs for mobility equipment, home equipment or adaptations, and travelling costs. Patients and caregivers may also incur indirect costs, such as paying for home repairs and maintenance projects that they were previously able to do themselves.

Lumasiran has been specifically designed to address the underlying cause of PH1 through durable reduction of oxalate to normal or near-normal levels in adult and paediatric patients.[8,63,66,67,73,74] For patients initiating lumasiran in the earlier stages of disease, the oxalate-lowering effect of lumasiran[8,63,67] is expected to halt disease progression and prevent the onset of serious complications.[6] This means that patients are expected to remain longer in the early stages of the disease where renal function is preserved. Patients are expected to have less renal impairment and experience fewer consequences of PH1 progression. For patients initiating lumasiran in the later stages of disease, the resulting reduction in oxalate is expected to reduce the need for dialysis, stabilise the disease, and prevent new manifestations of systemic oxalosis or promote reversal of systemic oxalosis among affected individuals. These improvements are expected to enable more patients reach transplantation, increase eligibility for transplantation, and achieve better outcomes post transplantation. Consequently, patients treated with lumasiran will require less treatment and fewer and shorter visits to hospital for complications of systemic oxalosis, acute events, and/or dialysis. Patients will better retain their independence, requiring less time and assistance from others, fewer mobility aids, and fewer modifications to their homes and vehicles.

14.2 Costs and saving outside of the NHS

Being a caregiver of a patient with PH1 has a substantial impact on employment. Caregiver surveys conducted [redacted]

[redacted] (Alnylam, Data on File). The reduction in work capacity of patients with PH1 and their caregivers[96] is likely to lead to increased government expenditure on unemployment benefits and statutory sick pay and decreased government revenue from income tax and National Insurance contributions.

The introduction of lumasiran is expected to reduce any expenditure currently incurred by Local Government and County Council programmes that provide support for patients with PH1 and unemployed caregivers of PH1 patients in the UK. As these cost savings are not possible to estimate at this time, they have not been considered in the CEA or budget impact analysis, resulting in conservative estimates of the cost effectiveness and budget impact for lumasiran.

14.3 Costs borne by patients that are not reimbursed by the NHS

Patients with PH1 and their caregivers face many additional costs not reimbursed by the NHS. As PH1 is a hereditary disease, each sibling of a patient with PH1 has a 25% chance of also having the disease.[79] Therefore, it is possible for more than one child in the same family to be affected by PH1, which could amplify the financial burden.[45] Some of the financial costs typically borne by patients and caregivers and families that are not reimbursed by the NHS include:

- *The cost of transportation to and from hospitals to access specialised services and care, parking charges, and overnight accommodation/meals*
  Daily trips to hospital for dialysis can be a significant burden on patients and their families/caregivers. The transportation cost per high-intensity haemodialysis visit is estimated to be £46, which equates to approximately £14,000 per year assuming that the patient requires six sessions per week.[256] Regular visits to hospital and highly specialist PH1 treatment centres for renal stone treatment and specialist consultations can also be a burden. UK clinical experts estimate that, regardless of age, patients with CKD 1–3b visit a specialist nephrologist once per year. Adult patients with CKD 4 or ESKD require two and three visits per year, respectively. The burden is greater for paediatric patients with late-stage disease; children with CKD 4 require eight visits per year, while those with ESKD require 13 visits per year (Appendix Table 11).

  For patients who live at a considerable distance, every visit may involve substantial travel time and transportation costs including overnight stays. The costs of the cumulative visits may be considerable and will be especially burdensome for patients and/or caregivers of patients with PH1 who are unable to work full-time due to time constraints imposed by disease management requirements.

- *The cost of adaptations to the home and appliances, adaptations to a vehicle, and other care equipment*
  As mentioned in Section 14.1, the inevitable consequences of untreated PH1 are likely to incur costs for mobility equipment, home equipment or adaptations, and travelling costs (i.e., adapted vehicles).

- *Loss of income for both the patient and the caregiver*
  As mentioned in Section 14.1, management of PH1 places a significant burden on patients and their caregivers, preventing many of them from working. Patients and caregivers who are able to work likely experience a substantial reduction in work capacity and loss of income. Most caregivers are females who are employed and in their prime working years.[96]

14.4 Estimates of caregiving time spent by family members

There is limited evidence in the literature on the time family members and caregivers spend taking care of patients with PH1, and no overall estimates for the UK. Caring for patients with PH1, from ensuring that young patients are hyperhydrated to accompanying patients on frequent trips to hospital for lengthy dialysis sessions, treatment of disease manifestations, and specialist visits, is assumed to place a significant burden on family members. Caregiver surveys [redacted]

[redacted] (Alnylam, Data on File).

14.5 Impact of lumasiran on the evidence base for clinical effectiveness of treatment

PH1 has a limited Level 1/2 evidence base to inform clinicians on its management. Most studies evaluating the management of PH1 with conservative treatment options (i.e., hyperhydration, crystallisation inhibitor use, and pyridoxine supplementation), renal replacement therapy, and transplantation have been retrospective and observational in design (refer to the SLR report in Appendix 1: Search strategy for clinical evidence). Based on communications with clinical experts, it is Alnylam's understanding that the OxalEurope PH1 treatment guidelines will be updated in the first half of 2022, and inclusion of lumasiran is anticipated.

The phase 3 ILLUMINATE trials of lumasiran in PH1 represent a major advance in research across patients with a range of ages and disease severity (Section 4.1).[8-11] The ILLUMINATE-A study is the first successful phase 3 RCT in PH1 and has demonstrated significantly improved outcomes with lumasiran treatment compared with ECM in patients older than 6 years of age with relatively intact renal function.[8] The open-label ILLUMINATE-B study has demonstrated the oxalate-lowering efficacy of lumasiran in patients younger than 6 years of age with relatively intact renal function.[9] In ILLUMINATE-C, involving patients of all ages with more advanced renal impairment due to PH1, treatment with lumasiran resulted in a reduction of 33.3% in plasma oxalate from baseline to Month 6 for patients not yet on dialysis and a reduction of 42.4% in predialysis plasma oxalate from baseline to Month 6 for patients on dialysis.[11]

Follow-up data from these ILLUMINATE trials and the phase 2 OLE are generating unique and high-quality data on the long-term safety and efficacy of lumasiran in PH1. Data from the longer running trials have demonstrated that patients with relatively preserved renal function have sustained lowering of oxalate levels, lower renal stone event rates, and reduced nephrocalcinosis severity, with no new safety signals, following at least 12 months of lumasiran treatment.[10,66]

14.6 Anticipated impact of lumasiran on innovation in the UK

Lumasiran is the third member of the RNAi drug class to be approved by European and US regulatory agencies.[73,257] Lumasiran strengthens the evidence base for using siRNA therapeutics to silence disease-causing genes and proteins in patients with rare and serious conditions. It is the first siRNA therapeutic to be studied, and shown to be safe and efficacious, in infants and young children. As such, it provides proof-of-principle evidence for using siRNA therapeutics in paediatric settings. The introduction of lumasiran in the UK is likely to inspire further research and clinical development of other siRNA drug candidates for diseases with an urgent need for effective therapies.

14.7 Patient registry or collection of clinical effectiveness data over the next 5 years

As described in Section 4.2, the UK National Renal Rare Disease Registry (RaDaR) is currently collecting data on patients with PH1.[92] A global, observational, longitudinal study with retrospective and prospective components (ALN-GO1-007, BONAPH1DE)[93] is currently underway and recruiting clinical sites, which are expected to include expert centres of the RDCN. The study will characterise the long-term real-world safety and efficacy of lumasiran, including in UK patients, and describe the natural history and progression of patients diagnosed with PH1, including during the course of pregnancy, births, and breast-feeding. Although BONAPH1DE will not be restricted to lumasiran treatment, it will be used to evaluate the development of infants born to women exposed to lumasiran during pregnancy. No data on treatments and outcomes are anticipated from RaDaR and BONAPH1DE within the next 12 months.

Multiple initiatives are also underway to analyse existing registry data to provide contextual background for understanding the benefits and risks of treatment with lumasiran.

A research collaboration has been initiated with the OHF PH Registry hosted by the RKSC at Mayo Clinic (Rochester, Minnesota, USA). The OHF/RKSC registry contains data from over 500 patients with PH, including over 400 patients with PH1.

As an initial priority, the collaboration involves retrospective analysis of the relationship between age and urinary oxalate:creatinine ratio in the subset of young children (<10 years of age) within the registry, to better understand whether the natural age-related decline in the urinary oxalate:creatinine ratio seen in healthy children is also observed in children with PH1.[122] An analysis of urinary oxalate:creatinine ratio data retrieved from the OHF/RKSC registry is ongoing. A second study (currently in the feasibility assessment stage) will describe the natural progression of disease manifestations such as nephrocalcinosis over time in patients with PH1; this study may provide useful context for outcomes observed with respect to these disease manifestations in patients treated with lumasiran in the clinical trial setting.

Other efforts include an investigator-initiated study to retrospectively analyse natural history data on clinical outcomes from the OxalEurope PH registry. This study has the potential to contextualise data on outcomes such as nephrocalcinosis, renal stone events, and systemic oxalosis across the lumasiran phase 3 trial programme.

Finally, the phase 2 OLE[66] and extension periods of the three ILLUMINATE trials[63,79,181] will continue to collect long-term evidence on the clinical effectiveness of lumasiran for the next 2 to 4 years.[87-90]

14.8 Review of clinical effectiveness of lumasiran

Lumasiran is approved for use in the EU,[73] US,[74] Brazil,[84] and Switzerland.[85] No review of the clinical effectiveness of lumasiran in the UK is planned outside of this submission.

14.9 Required level of expertise for the safe and effective use of lumasiran

As directed in the product label, lumasiran therapy should be initiated and supervised by a physician experienced in the management of hyperoxaluria.[73] Since there is no single Highly Specialised Service for PH1, patients with PH1 are currently managed by the leading paediatric and adult nephrology centres where genetic confirmation of the diagnosis is performed (Section 5.2). No additional expertise is anticipated to be needed for these centres to ensure the safe and effective use of lumasiran. A detailed patient care pathway is outlined in Section 8.3.

Hyperoxaluria has been designated by NHS England as a new Rare Disease Collaborative Network (RDCN) and this is anticipated to eventually lead to the formation of a Highly Specialised Service (Section 5.2).[65]

14.10 Additional infrastructure related to the safe and effective use of the technology

Treatment with lumasiran will be implemented through the RDCN expert centres at the Birmingham Women's and Children's NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Great Ormond Street Hospital, and the Royal Free. Clinical experts with experience in treating patients with PH1 have advised that the existing highly specialist consultant-led service, anchored around the regional centres of excellence, is effective in ensuring the delivery of care for the majority of the most severely affected patients with PH1. This is especially important for the predominantly paediatric population who may require regular, highly specialist hospital care. No additional infrastructure will be required to ensure the safe and effective use of the technology and equitable access for all eligible patients.

Section F - Managed Access Arrangements

15 Managed Access Arrangement

15.1 Level of engagement with clinical and patient groups to develop the MAA

No management access arrangement has been proposed at the time of this submission.

15.2 Details of the MAA proposal

Not applicable.

15.3 Effect of the MAA proposal on value for money

Not applicable.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The purpose of this SLR was to identify clinical efficacy and safety data for lumasiran (ALN-GO1) and established clinical management (ECM; hydration, vitamin B6 [pyridoxine], calcium oxalate crystallisation inhibitors [citrate, pyrophosphate, magnesium], haemodialysis, and combined/sequential liver–kidney transplantation or isolated kidney/liver transplant), and to identify any relevant cost, healthcare resource use, or utilities data in PH1.

Since the final NICE scope was unavailable when this SLR was conducted, the searches were kept intentionally broad, focusing on disease state and study designs. Interventions were not prespecified in the search strategy; rather, studies of specific interventions of interest (namely medicines or ECM) in PH1 were identified during study selection (screening).

17.1.1 The specific databases searched and the service provider used

A comprehensive literature search consisted of retrieving references from MEDLINE® (1946 to present; OVID), MEDLINE In-Process & Other Non-Indexed Citations (OVID), MEDLINE Epub Ahead of Print, Embase (1980 to present; OVID), Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (NLM) e-publications only, Econlit (1886 to present; EBSCO; economic SLR only), NHS Economic Evaluation Database (EED) and Health Technology Assessment (HTA; CRD), International HTA (INAHTA) database, Conference Proceedings Citation Index-Science (CPCI-S; 1990 to present; Web of Science, Clarivate Analytics), and the ScHARR Health Utilities Database (HUD).

No restrictions on language were applied in the searches, although records in languages other than English were recorded for future reference. For all cost and resource use publications, the region was recorded for future reference. The search strategy removed animal studies, in vitro studies, studies in healthy populations, investigational therapies, reviews, letters, comments, case reports, adherence studies, prognostic studies, epidemiological studies, and studies of treatment prescribing patterns.

17.1.2 The date on which the search was conducted

Original searches were conducted 20 June 2020, and updates were performed 13 April 2021 and 4 August 2021.

17.1.3 The date span of the search.

No date restrictions were placed on the database searches, except for conference abstracts that were searched in Embase or CPCI-S from 2018 to present.

17.1.4 The complete search strategies used, including all the search terms: textwords, subject index headings and the relationship between the search terms

Appendix Table 1 summarises the databases searched and hits retrieved for the original SLR search and the two subsequent updates.

Appendix Table 1. List of databases and hits retrieved

Database	Hits		
	Original search	**First update**	**Second update**
MEDLINE (all)	513	60	46
Embase	276	37	38
Cochrane (CENTRAL/CDSR)	48	54 (CENTRAL, 54; CDSR, 0)	9 (CENTRAL, 9; CDSR, 0)
PubMed (e-publications only)	92	37	36
Econlit	0	0	0
NHS EED	1	Not searched in this update	Not searched in this update
HTA Database	1	Not searched in this update	Not searched in this update
ScHARR HUD	0	0	0
International HTA Database	Not searched	1	0
Total	**1017**	**189**	**129**

CENTRAL=Cochrane Central Register of Controlled Trials; CDSR=Cochrane Database of Systematic Reviews; EED=Economic Evaluation Database; HTA=Health Technology Assessment; HUD=Health Utilities Database; NHS=National Health Service

The search terms used in the main database searches are described in full in the lumasiran SLR report attached below.

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database)

In addition to the database searches, a grey literature search was conducted, which included searches of ClinicalTrials.gov and the EU CTR, as well as select regulatory and HTA websites—NICE, the IQWiG, the US FDA, and the EMA. A manual search of reference lists of systematic reviews was planned, in order to identify any relevant primary publications. The study records returned from the grey literature search are summarised in Appendix Table 2 and Appendix Table 3.

Appendix Table 2. Study records retrieved from trial registers

Registry	Study records returned		
	Original search	**First update**	**Second update**
WHO ICTRP	Not available at time of review	Not searched in this update	Not searched in this update
ClinicalTrials.gov	75	82	84
EU Clinical Trials Register	21	23	23
Total	**96**	**105**	**107**

The WHO ICTRP was unavailable due to the COVID-19 pandemic.
EU=European Union; ICTRP=International Clinical Trials Registry Platform; WHO=World Health Organization

Appendix Table 3. Study records retrieved from web searches

Website	URL	N items returned		
		Original search	First update	Second update
NICE	https://www.nice.org.uk/ the general search function was used	1	1	1*
IQWiG	https://www.iqwig.de/en/projects-results/projects.1057.html the general search function was used	0	1	01
US FDA	https://www.accessdata.fda.gov/scripts/cder/daf/ the general search function was used to identify only medical reviews, statistical reviews, and other reviews. Records were downloaded if they a) appeared to relate to the correct population and b) were one of the three types of reviews specified above.	0	0	0
EMA	https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine the general search function was used. Records were downloaded if they a) appeared to relate to the correct population and b) were an EPAR.	10	1	01
Total		**11**	**3**	**13**

*Scope was not downloaded as it predated this search update.
EMA=European Medicines Agency; EPAR=European Public Assessment Report; FDA=Food and Drug Administration; IQWiG=Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE=National Institute for Health and Care Excellence; US=United States

Embase and CPCI-S databases were searched for relevant conference abstracts (Appendix Table 4).

Appendix Table 4. Conference abstracts retrieved

Database	Hits		
	Original search	First update	Second update
Embase	50	35	5
CPCI-S	35	6	0
Handsearch	111	12	0
Total	**196***	**53***	**5***

*Combined and not de-duplicated total.
CPCI-S=Conference Proceedings Citation Index-Science

17.1.6 The inclusion and exclusion criteria

The SLR selection criteria for published studies are summarised in Table C1

17.1.7 The data abstraction strategy

The number of reports identified by the literature search is provided in Appendix Table 2, Appendix Table 2, and Appendix Table 3. Search results were exported to EndNote X9 (Clarivate Analytics, Philadelphia, PA; available at: www.endnote.com). Study records were visually inspected and de-duplicated. All searches were fully documented, and results were saved in dedicated EndNote libraries. Search results were saved for each individual database. The full list of included studies is shown in Table C2. The full list of excluded studies is shown in the lumasiran SLR report (Appendix 17.1.4).

17.1.8 Quality assessment of clinical studies

Lumasiran studies

Refer to Section 9.5.1 for the quality assessment of phase 3 lumasiran clinical studies.

Reference:	**ALN-GO1-001**	
Study name	**Phase 1/2,[91] NCT02706886**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomisation (3:1) to either lumasiran or placebo in each dose-level cohort by computer-generated list generated by the contract research organisation biostatistician
Was the concealment of treatment allocation adequate?	Not clear	States block size was not known to the investigators but no details of allocation concealment
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Reported to be "generally balanced" but there are apparent differences in the mean age, proportion male, 24-h urinary oxalate:creatinine ratio and urine oxalate content across groups
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes (participants) No (care providers and outcome assessors)	Monthly dosed participants were blinded until Day 78, quarterly dosed participants were unblinded after postdose follow-up. Care providers and outcome assessors were not blinded (described as single-blind study). Masking between lumasiran and placebo was undertaken prior to treatments being taken to the clinic, no further details. Outcome measures were objective. Unclear if non blinding would have an impact on the risk of detection bias in the study, some concerns for definition and reporting of adverse events). High risk of performance bias
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No imbalance in drop-outs. Two participants withdrew consent. CONSORT diagram provided
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	Some exploratory outcomes are redacted from the publicly available trial protocol. Details re additional safety outcomes provided in the additional material
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	A safety analysis set was used (all participants that received at least one dose of study drug), however, there were different numbers included in the analysis groups over time and participant cross overs also occurred
Adapted from Centre for Reviews and Dissemination (2008) *Systematic reviews. CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination		

Reference	**ALN-GO1-002**	
Study name	**Phase 2 open-label extension,[66] NCT03350451**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Open-label extension to prior trial. All participants from Phase 1/2 were enrolled
Was the exposure accurately measured to minimise bias?	Yes	Treatment dosage details provided
Was the outcome accurately measured to minimise bias?	Not clear	Minimal safety and biomarker outcomes only reported in abstract, some without data points. Oxalate reduction data only provided in relative terms
Have the authors identified all important confounding factors?	No	No discussion of confounding factors

Have the authors taken account of the confounding factors in the design and/or analysis?	No	No discussion of confounding factors
Was the follow-up of patients complete?	Not clear	Data up to 22 months, unclear if all participants were followed-up and study described as 'ongoing'. Different number of participants are provided for different outcomes
How precise (for example, in terms of confidence interval and p values) are the results?	No	No precision estimates provided
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence: 12 questions to help you make sense of a cohort study		

17.2 Appendix 2: Search strategy for adverse events

The search strategy for AEs was identical to that outlined in Appendix 1.

17.3 Appendix 3: Search strategy for economic evidence

The search strategy for economic evidence was identical to that outlined in Appendix 1.

17.4 Appendix 4: Resource identification, measurement and valuation

The search strategy for resource identification, measurement, and valuation was identical to that outlined in Appendix 1.

17.5 Appendix 5: Supplemental data

Appendix Table 5. HRG and PbR cost codes used in the CE model, drug administration

Service code	Service description	Currency code	Currency description	Activity	National average unit cost	Total cost	No. data submissions
NURS	Nursing	N02AF	District Nurse, Adult, Face to face	26,642,008	£43.44	£1,157,317,097	83

CE=cost effectiveness; HRG=Healthcare Resource Group; No.=number; PbR=payment by results

Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 6. HRG and PbR cost codes used in the CE model, dialysis

Department code	Department description	Service code	Service description	Currency code	Currency description	No. sessions	National average unit cost	Total cost	No. data submissions
HAEMODIALYSIS									
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD02A	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	675,183	£163	£110,343,532	48
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD06A	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	1,104,877	£163	£171,162,824	40
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD10A	Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	81,996	£185	£15,160,964	38
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD02B	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 18 years and under	1,958	£606	£1,185,925	12
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD06B	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 18 years and under	234	£282	£66,004	6
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD10B	Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 18 years and under	2,001	£99	£198,902	2
PERITONEAL DIALYSIS									
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD11A	Continuous Ambulatory Peritoneal Dialysis, 19 years and over	323,416	£76	£24,423,029	43

Department code	Department description	Service code	Service description	Currency code	Currency description	No. sessions	National average unit cost	Total cost	No. data submissions
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD12A	Automated Peritoneal Dialysis, 19 years and over	536,269	£78	£41,581,897	44
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD13A	Assisted Automated Peritoneal Dialysis, 19 years and over	122,902	£88	£10,758,837	35
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD11B	Continuous Ambulatory Peritoneal Dialysis, 18 years and under	8,830	£133	£1,172,806	5
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD12B	Automated Peritoneal Dialysis, 18 years and under	16,335	£87	£1,415,026	10
RENALCKD	Renal dialysis for chronic kidney disease	RD	Renal dialysis at base	LD13B	Assisted Automated Peritoneal Dialysis, 18 years and under	1,919	£94	£179,522	1

Resource use was calculated as a weighted average based on observed activity within an age category for each currency description.
CE=cost effectiveness; HRG=Healthcare Resource Group; No.=number; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 7. HRG and PbR cost codes used in the CE model, renal stone events

Currency code	Currency description	Activity	Unit cost	Total cost
LB40C	Urinary Tract Stone Disease with Interventions, with CC Score 3+	1,086	£4,072	£4,422,431
LB40D	Urinary Tract Stone Disease with Interventions, with CC Score 0–2	1,761	£2,702	£4,757,765
LB40E	Urinary Tract Stone Disease without Interventions, with CC Score 6+	1,468	£1,586	£2,328,075
LB40F	Urinary Tract Stone Disease without Interventions, with CC Score 3–5	3,653	£884	£3,230,663
LB40G	Urinary Tract Stone Disease without Interventions, with CC Score 0–2	30,493	£534	£16,285,431

Resource use was calculated as a weighted average based on observed activity.
CE=cost effectiveness; HRG=Healthcare Resource Group; PbR=payment by results; RSE=renal stone event
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 8. HRG and PbR cost codes used in the CE model, systemic oxalosis complications

Complication	Annual cost	Year	Source	Annual cost inflated at 2021 price
Bone	£2,439.78	2017	Borgström et al. (2020)[233]; assumed equal to the annual cost of distal forearm fractures in the year following the fracture. EUR converted into GBP using the PPP at the year of costing	£2,626.34
Cardiac	£3,607.86	2016	Danese et al. (2016)[234]; assumed equal to the annual cost after an event of heart failure (Months 7–36 after the event)	£3,897.33
Cutaneous and vascular	£7,225.00	2015	Patel et al. (2020)[235]; assumed equal to the annual NHS & PSS cost in subsequent years to the first year from stroke occurrence	£7,874.93
Ophthalmologic	£1,201.06	2019	Galvin et al. (2020)[236]; assumed equal to the health-system cost of inherited retinal diseases in the UK (i.e., £25 million divided by 20,815 cases)	£1,251.54
Neurologic	£2,676.49	2012	Liedgens et al. (2016)[237]; assumed equal to the annual direct cost of neuropathic pain in the UK. EUR converted into GBP using the PPP at the year of costing	£3,026.48

CE=cost effectiveness; EUR=Euro; GBP=British pound sterling; HRG=Healthcare Resource Group; NHS=National Health Service; PbR=payment by results; PPP=purchasing power parities; PSS=Personal Social Services

Appendix Table 9. HRG and PbR cost codes used in the CE model, transplantation

Currency code	Currency description	Activity	Unit cost	Total cost
GA15A	Liver Transplant, 18 years and over	703	£20,827	£14,641,045
GA15B	Liver Transplant, between 2 and 17 years	58	£32,849	£1,905,245
GA15C	Liver Transplant, 1 year and under	18	£43,750	£787,494
LA01A	Kidney Transplant, 19 years and over, from Cadaver Non-Heart-Beating Donor	673	£14,448	£9,723,269
LA02A	Kidney Transplant, 19 years and over, from Cadaver Heart-Beating Donor	1,165	£13,774	£16,047,008
LA03A	Kidney Transplant, 19 years and over, from Live Donor	684	£12,837	£8,780,535
LA01B	Kidney Transplant, 18 years and under, from Cadaver Non-Heart-Beating Donor	9	£11,098	£99,883
LA02B	Kidney Transplant, 18 years and under, from Cadaver Heart-Beating Donor	33	£16,537	£545,723
LA03B	Kidney Transplant, 18 years and under, from Live Donor	65	£23,946	£1,556,470
LA11Z	Kidney Pre-Transplantation Workup of Live Donor	2,973	£363	£1,077,940
LA12A	Kidney Pre-Transplantation Workup of Recipient, 19 years and over	9,317	£387	£3,607,304
LA12B	Kidney Pre-Transplantation Workup of Recipient, 18 years and under	61	£440	£26,868
LA13A	Examination for Post-Transplantation of Kidney of Recipient, 19 years and over	89,099	£269	£24,004,132
LA13B	Examination for Post-Transplantation of Kidney of Recipient, 18 years and under	618	£270	£166,876
LA14Z	Examination for Post-Transplantation of Kidney of Live Donor	3,577	£280	£999,950
WH01A	Transplant Failure and Rejection, with Multiple Interventions	343	£10,982	£3,766,908
WH01B	Transplant Failure and Rejection, with Single Intervention	513	£5,335	£2,736,803
WH01C	Transplant Failure and Rejection, without Interventions, with CC Score 2+	801	£2,954	£2,365,762
WH01D	Transplant Failure and Rejection, without Interventions, with CC Score 0–1	1,297	£1,643	£2,131,343

Resource use was calculated as a weighted average based on observed activity within an age category for each currency description.
CE=cost effectiveness; HRG=Healthcare Resource Group; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 10. Monthly monitoring resources by health state

	Number of resources per month, by model health state										
	Paediatric population						Adult population				
	CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD		CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD
Lab tests											
24-h urinary oxalate	0.04	0.04	0.04	0.02	0.02		0.04	0.04	0.04	0.00	0.00
Full blood count	0.08	0.08	0.08	0.08	0.17		0.08	0.08	0.08	0.67	1.08
Spot urinary oxalate:creatinine ratio	0.04	0.04	0.04	0.02	0.00		0.04	0.04	0.04	0.00	0.00
Plasma oxalate	0.00	0.00	0.00	0.08	0.33		0.00	0.00	0.00	0.00	0.00
Serum creatinine	0.08	0.08	0.08	0.25	0.33		0.08	0.08	0.08	0.00	0.00
Electrolytes	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.67	1.08
Urea	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.67	1.08
Bone chemistry, calcium phosphate	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.67	1.08
Bone chemistry, parathyroid hormone level	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.67	1.08
Iron status	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.67	1.08
Bicarbonate (acid status)	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.67	1.08
Antibody screening tests from laboratory	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.33	0.33
Plasma creatinine	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.67	1.08
Procedures											
Renal ultrasound	0.04	0.04	0.04	0.08	0.08		0.04	0.04	0.04	0.04	0.04
Bone x-ray	0.01	0.01	0.02	0.00	0.00		0.01	0.01	0.02	0.02	0.04
Electrocardiogram	0.00	0.00	0.00	0.04	0.08		0.00	0.00	0.00	0.04	0.08
Echocardiogram	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.02	0.08
Fundoscopic eye examination	0.00	0.00	0.00	0.08	0.08		0.00	0.00	0.00	0.08	0.04
Skin/ muscle biopsy	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.02	0.03
CT scan	0.00	0.00	0.00	0.01	0.01		0.00	0.00	0.00	0.04	0.02
Visits											
Specialist consultation: nephrologist	0.08	0.08	0.08	0.67	1.08		0.08	0.08	0.08	0.17	0.25
Specialist consultation: nutritionist	0.02	0.02	0.02	0.17	1.08		0.02	0.02	0.02	0.03	0.08
Specialist nurse	0.00	0.00	0.00	0.17	1.08		0.00	0.00	0.00	0.04	0.14
Urologist (for stones)	0.08	0.08	0.08	0.25	0.25		0.08	0.08	0.08	0.03	0.03

	Number of resources per month, by model health state										
	Paediatric population						Adult population				
	CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD		CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD
Social worker	0.00	0.00	0.00	0.00	0.25		0.00	0.00	0.00	0.00	0.00
Psychologist	0.00	0.00	0.00	0.00	0.25		0.00	0.00	0.00	0.00	0.00

Adult values were used for paediatric visit resources as no data were provided.
CKD=chronic kidney disease; CT=computed tomography; ESKD=end-stage kidney disease
Source: UK clinical experts

Appendix Table 11. Annual monitoring resources by health state

	Number of resources per year, by model health state										
	Paediatric population						Adult population				
	CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD		CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD
Lab tests											
24-h urinary oxalate	0.50	0.50	0.50	0.50	0.00		0.50	0.50	0.50	0.50	0.25
Full blood count	1.00	1.00	1.00	1.00	8.00		1.00	1.00	1.00	1.00	1.00
Spot urinary oxalate:creatinine ratio	0.50	0.50	0.50	0.50	0.00		0.50	0.50	0.50	0.50	0.25
Plasma oxalate	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00	1.00
Serum creatinine	1.00	1.00	1.00	1.00	0.00		1.00	1.00	1.00	1.00	3.00
Electrolytes	0.00	0.00	0.00	0.00	8.00		0.00	0.00	0.00	0.00	0.00
Urea	0.00	0.00	0.00	0.00	8.00		0.00	0.00	0.00	0.00	0.00
Bone chemistry, calcium phosphate	0.00	0.00	0.00	0.00	8.00		0.00	0.00	0.00	0.00	0.00
Bone chemistry, parathyroid hormone level	0.00	0.00	0.00	0.00	8.00		0.00	0.00	0.00	0.00	0.00
Iron status	0.00	0.00	0.00	0.00	8.00		0.00	0.00	0.00	0.00	0.00
Bicarbonate (acid status)	0.00	0.00	0.00	0.00	8.00		0.00	0.00	0.00	0.00	0.00
Antibody screening tests from laboratory	0.00	0.00	0.00	0.00	4.00		0.00	0.00	0.00	0.00	0.00
Plasma creatinine	0.00	0.00	0.00	0.00	8.00		0.00	0.00	0.00	0.00	0.00
Procedures											
Renal ultrasound	0.50	0.50	0.50	0.50	1.00		0.50	0.50	0.50	0.50	0.50
Bone x-ray	0.10	0.10	0.10	0.25	0.00		0.10	0.10	0.10	0.25	0.25
Electrocardiogram	0.00	0.00	0.00	0.00	0.50		0.00	0.00	0.00	0.00	0.50

	Number of resources per year, by model health state										
	Paediatric population						Adult population				
	CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD		CKD 1–2	CKD 3a	CKD 3b	CKD 4	ESKD
Echocardiogram	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00	0.25
Fundoscopic eye examination	0.00	0.00	0.00	0.00	1.00		0.00	0.00	0.00	0.00	1.00
Skin/ muscle biopsy	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00	0.20
CT scan	0.00	0.00	0.00	0.00	0.10		0.00	0.00	0.00	0.00	0.50
Visits											
Specialist consultation: nephrologist	0.90*	0.90*	0.90*	0.90	8.0		0.90	0.90	0.90	0.90	2.00
Specialist consultation: nutritionist	0.20*	0.20*	0.20*	0.20	2.0		0.20	0.20	0.20	0.20	0.40
Specialist nurse	0.00*	0.00*	0.00*	0.00	2.0		0.00	0.00	0.00	0.00	0.50
Urologist (for stones)	1.00*	1.00*	1.00*	1.00	3.0		1.00	1.00	1.00	1.00	0.35
Social worker	0.00*	0.00*	0.00*	0.00	0.00		0.00	0.00	0.00	0.00	0.00
Psychologist	0.00*	0.00*	0.00*	0.00	0.00		0.00	0.00	0.00	0.00	0.00

Adult values were used for instances where details were not provided for the paediatric population.
CKD=chronic kidney disease; CT=computed tomography; ESKD=end-stage kidney disease
Source: UK clinical experts

Appendix Table 12. HRG and PbR cost codes used in the CE model, lab test and exam

Currency code	Currency description	No. tests	National average unit cost	Total cost	No. data submissions
DAPS03	Integrated Blood Services	49,520,134	£2	£89,758,547	28
DAPS04	Clinical Biochemistry	251,513,502	£1	£301,575,483	96
DAPS05	Haematology	50,860,393	£3	£129,952,635	96
DAPS06	Immunology	4,443,654	£7	£32,661,985	73
DAPS07	Microbiology	20,175,727	£8	£164,431,656	109
DAPS08	Phlebotomy	5,521,677	£4	£20,284,408	43
DAPS09	Other	4,320,689	£4	£15,440,641	40

CE=cost effectiveness; HRG=Healthcare Resource Group; No.=number; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 13. HRG and PbR cost codes used in the CE model, imaging

Department code	Department description	Currency code	Currency description	No. examinations	National average unit cost	Total cost	No. data submissions
IMAGDA	Imaging: Direct Access	RD40Z	Ultrasound Scan with duration of less than 20 minutes, without Contrast	1,941,493	£52	£101,900,765	120
IMAGOP	Imaging: Outpatient	RD40Z	Ultrasound Scan with duration of less than 20 minutes, without Contrast	174,777	£62	£10,904,052	29
IMAGOTH	Imaging: Other	RD40Z	Ultrasound Scan with duration of less than 20 minutes, without Contrast	6,649	£50	£333,521	8
IMAGDA	Imaging: Direct Access	RD41Z	Ultrasound Scan with duration of less than 20 minutes, with Contrast	14,618	£59	£863,472	36
IMAGOP	Imaging: Outpatient	RD41Z	Ultrasound Scan with duration of less than 20 minutes, with Contrast	4,075	£52	£213,411	10
IMAGOTH	Imaging: Other	RD41Z	Ultrasound Scan with duration of less than 20 minutes, with Contrast	2	£1,185	£2,370	1
IMAGDA	Imaging: Direct Access	RD42Z	Ultrasound Scan with duration of 20 minutes and over, without Contrast	408,097	£68	£27,912,023	82
IMAGOP	Imaging: Outpatient	RD42Z	Ultrasound Scan with duration of 20 minutes and over, without Contrast	38,181	£69	£2,629,849	19
IMAGOTH	Imaging: Other	RD42Z	Ultrasound Scan with duration of 20 minutes and over, without Contrast	1,685	£91	£152,720	6
IMAGDA	Imaging: Direct Access	RD43Z	Ultrasound Scan with duration of 20 minutes and over, with Contrast	3,951	£111	£436,789	10
IMAGOP	Imaging: Outpatient	RD43Z	Ultrasound Scan with duration of 20 minutes and over, with Contrast	342	£94	£32,238	3
IMAGOTH	Imaging: Other	RD43Z	Ultrasound Scan with duration of 20 minutes and over, with Contrast	823	£112	£92,291	1
IMAGOP	Imaging: Outpatient	PF	Plain Film	18,194	£34	£611,426	2
IMAGOTH	Imaging: Other	PF	Plain Film	9,467	£104	£987,689	2
IMAGDA	Imaging: Direct Access	RD51A	Simple Echocardiogram, 19 years and over	112,883	£99	£11,168,434	28
IMAGOP	Imaging: Outpatient	RD51A	Simple Echocardiogram, 19 years and over	22,665	£141	£3,185,180	11
IMAGOTH	Imaging: Other	RD51A	Simple Echocardiogram, 19 years and over				
IMAGDA	Imaging: Direct Access	RD51B	Simple Echocardiogram, between 6 and 18 years	799	£107	£85,565	19
IMAGOP	Imaging: Outpatient	RD51B	Simple Echocardiogram, between 6 and 18 years	223	£123	£27,509	4
IMAGOTH	Imaging: Other	RD51B	Simple Echocardiogram, between 6 and 18 years				
IMAGDA	Imaging: Direct Access	RD51C	Simple Echocardiogram, 5 years and under	512	£104	£53,127	5

Department code	Department description	Currency code	Currency description	No. examinations	National average unit cost	Total cost	No. data submissions
IMAGOP	Imaging: Outpatient	RD51C	Simple Echocardiogram, 5 years and under	44	£92	£4,059	2
IMAGDA	Imaging: Direct Access	RD20A	Computerised Tomography Scan of One Area, without Contrast, 19 years and over	178,623	£88	£15,729,793	119
IMAGOP	Imaging: Outpatient	RD20A	Computerised Tomography Scan of One Area, without Contrast, 19 years and over	82,628	£91	£7,529,493	28
IMAGOTH	Imaging: Other	RD20A	Computerised Tomography Scan of One Area, without Contrast, 19 years and over	2,128	£94	£201,035	6
IMAGDA	Imaging: Direct Access	RD20B	Computerised Tomography Scan of One Area, without Contrast, between 6 and 18 years	2,143	£159	£341,276	55
IMAGOP	Imaging: Outpatient	RD20B	Computerised Tomography Scan of One Area, without Contrast, between 6 and 18 years	2,172	£109	£236,397	13
IMAGOTH	Imaging: Other	RD20B	Computerised Tomography Scan of One Area, without Contrast, between 6 and 18 years	3	£323	£969	1
IMAGDA	Imaging: Direct Access	RD20C	Computerised Tomography Scan of One Area, without Contrast, 5 years and under	3,308	£104	£344,933	11
IMAGOP	Imaging: Outpatient	RD20C	Computerised Tomography Scan of One Area, without Contrast, 5 years and under	239	£188	£44,840	8
IMAGOTH	Imaging: Other	RD20C	Computerised Tomography Scan of One Area, without Contrast, 5 years and under				
IMAGDA	Imaging: Direct Access	RD21A	Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over	39,845	£124	£4,930,351	108
IMAGOP	Imaging: Outpatient	RD21A	Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over	21,323	£138	£2,947,236	21
IMAGOTH	Imaging: Other	RD21A	Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over	122	£103	£12,626	3
IMAGDA	Imaging: Direct Access	RD21B	Computerised Tomography Scan of One Area, with Post-Contrast Only, between 6 and 18 years	53	£148	£7,866	14
IMAGOP	Imaging: Outpatient	RD21B	Computerised Tomography Scan of One Area, with Post-Contrast Only, between 6 and 18 years	278	£238	£66,233	7
IMAGOTH	Imaging: Other	RD21B	Computerised Tomography Scan of One Area, with Post-Contrast Only, between 6 and 18 years				
IMAGDA	Imaging: Direct Access	RD21C	Computerised Tomography Scan of One Area, with Post-Contrast Only, 5 years and under	519	£141	£73,241	5
IMAGOP	Imaging: Outpatient	RD21C	Computerised Tomography Scan of One Area, with Post-Contrast Only, 5 years and under	250	£242	£60,490	4
IMAGOTH	Imaging: Other	RD21C	Computerised Tomography Scan of One Area, with Post-Contrast Only, 5 years and under				

Department code	Department description	Currency code	Currency description	No. examinations	National average unit cost	Total cost	No. data submissions
IMAGDA	Imaging: Direct Access	RD22Z	Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	1,308	£151	£197,300	29
IMAGOP	Imaging: Outpatient	RD22Z	Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	253	£185	£46,844	4
IMAGOTH	Imaging: Other	RD22Z	Computerised Tomography Scan of One Area, with Pre- and Post-Contrast				
IMAGDA	Imaging: Direct Access	RD23Z	Computerised Tomography Scan of Two Areas, without Contrast	12,593	£98	£1,237,506	101
IMAGOP	Imaging: Outpatient	RD23Z	Computerised Tomography Scan of Two Areas, without Contrast	3,589	£124	£444,677	19
IMAGOTH	Imaging: Other	RD23Z	Computerised Tomography Scan of Two Areas, without Contrast	107	£104	£11,119	4
IMAGDA	Imaging: Direct Access	RD24Z	Computerised Tomography Scan of Two Areas, with Contrast	52,999	£127	£6,708,336	108
IMAGOP	Imaging: Outpatient	RD24Z	Computerised Tomography Scan of Two Areas, with Contrast	15,829	£145	£2,300,981	20
IMAGOTH	Imaging: Other	RD24Z	Computerised Tomography Scan of Two Areas, with Contrast	132	£133	£17,544	3
IMAGDA	Imaging: Direct Access	RD25Z	Computerised Tomography Scan of Three Areas, without Contrast	5,850	£94	£550,931	81
IMAGOP	Imaging: Outpatient	RD25Z	Computerised Tomography Scan of Three Areas, without Contrast	2,565	£124	£317,911	14
IMAGOTH	Imaging: Other	RD25Z	Computerised Tomography Scan of Three Areas, without Contrast	18	£134	£2,414	1
IMAGDA	Imaging: Direct Access	RD26Z	Computerised Tomography Scan of Three Areas, with Contrast	40,617	£144	£5,836,743	106
IMAGOP	Imaging: Outpatient	RD26Z	Computerised Tomography Scan of Three Areas, with Contrast	42,519	£147	£6,269,355	20
IMAGOTH	Imaging: Other	RD26Z	Computerised Tomography Scan of Three Areas, with Contrast	2,045	£100	£204,003	5
IMAGDA	Imaging: Direct Access	RD27Z	Computerised Tomography Scan of more than Three Areas	21,392	£91	£1,940,497	86
IMAGOP	Imaging: Outpatient	RD27Z	Computerised Tomography Scan of more than Three Areas	4,191	£193	£809,234	18
IMAGOTH	Imaging: Other	RD27Z	Computerised Tomography Scan of more than Three Areas	72	£120	£8,633	4
IMAGDA	Imaging: Direct Access	RD60Z	Cardiac Computerised Tomography Scan	1,746	£254	£443,274	20
IMAGOP	Imaging: Outpatient	RD60Z	Cardiac Computerised Tomography Scan	6,607	£199	£1,311,514	9
IMAGOTH	Imaging: Other	RD60Z	Cardiac Computerised Tomography Scan				
IMAGDA	Imaging: Direct Access	RD61Z	Colon Computerised Tomography Scan	5,971	£162	£967,162	25

Department code	Department description	Currency code	Currency description	No. examinations	National average unit cost	Total cost	No. data submissions
IMAGOP	Imaging: Outpatient	RD61Z	Colon Computerised Tomography Scan	4,874	£161	£785,426	9
IMAGOTH	Imaging: Other	RD61Z	Colon Computerised Tomography Scan				

Resource use was calculated as a weighted average based on observed activity within an age category for each currency description.
CE=cost effectiveness; HRG=Healthcare Resource Group; No.=number; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 14. HRG and PbR cost codes used in the CE model, other imaging

Service code	Service description	Currency code	Currency description	Procedures	National average unit cost	Total cost	No. data submissions
259	Paediatric Nephrology	EC22Z	Electrocardiogram Monitoring or Stress Testing, for Congenital Heart Disease	4	£307	£1,229	4
361	Nephrology	EY51Z	Electrocardiogram Monitoring or Stress Testing	63	£504	£31,733	30
361	Non-Admitted Non-Face-to-Face Attendance, Follow-up	WF01C	Nephrology	28,438	£113	£3,204,262	49

Resource use was calculated as a weighted average based on observed activity within an age category for each currency description.
CE=cost effectiveness; HRG=Healthcare Resource Group; No.=number; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 15. HRG and PbR cost codes used in the CE model, specialist services

Service code	Service description	Activity	Unit cost	Total cost
130	Ophthalmology	4,332,277	£108	£466,658,806
216	Paediatric Ophthalmology	410,476	£103	£42,443,850
654	Dietetics	57,821	£322	£18,629,361
259	Paediatric Nephrology	912,496	£170	£155,015,601
361	Nephrology	793,847	£90	£71,429,611
656	Clinical Psychology	183,455	£201	£36,869,642
N02AF	District Nurse, Adult, Face to face	26,642,00	£43	£1,157,317,097

CE=cost effectiveness; HRG=Healthcare Resource Group; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 16. HRG and PbR cost codes used in the CE model, biopsy

Service code	Service description	Currency code	Currency description	Procedures	National average unit cost	Total cost	No. data submissions
120	ENT	YH32B	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 18 years and under	1	£67	£67	1
811	Interventional Radiology	YH32B	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 18 years and under	2	£94	£187	1
651	Occupational Therapy	YH32B	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 18 years and under	1	£27	£27	1
100	General Surgery	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	8	£679	£5,433	1
101	Urology	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£318	£318	1
110	Trauma & Orthopaedics	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	11	£157	£1,730	6
120	ENT	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	34	£124	£4,210	1
160	Plastic Surgery	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£5	£5	1
300	General Medicine	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£58	£58	1
303	Clinical Haematology	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£793	£793	1
308	Blood and Marrow Transplantation	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£59	£59	1
330	Dermatology	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£288	£288	1
340	Respiratory Medicine	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	5	£180	£899	2
341	Respiratory Physiology	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	2	£118	£237	2
400	Neurology	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£995	£995	1
410	Rheumatology	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	7	£70	£487	4
651	Occupational Therapy	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	7	£56	£391	1

Service code	Service description	Currency code	Currency description	Procedures	National average unit cost	Total cost	No. data submissions
658	Orthotics	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	1	£54	£54	1
800	Clinical Oncology (Previously Radiotherapy)	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	27	£881	£23,798	2
811	Interventional Radiology	YH32A	Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over	247	£106	£26,097	2

Resource use was calculated as a weighted average based on observed activity within an age category for each currency description.
CE=cost effectiveness; ENT=ear, nose, and throat; HRG=Healthcare Resource Group; No.=number; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 17. Social worker and nursing salaries

Healthcare professional	Annual salary	Weeks per year	Hours per week	Cost per hour
Social worker (adult services)	£34,982.00	40.9	37	£23.12
Social worker (children's services)	£36,400.00	41.4	37	£23.76
Nurse (GP practice)	£27,350.00	41.9	37.5	£17.41

GP=general practitioner
Source: Curtis and Burns (2020)[240]

Appendix Table 18. HRG and PbR cost codes used in the CE model, AEs

Currency code	Currency description	Activity	Unit cost	Total cost	No. data submissions
WH05Z	Allergy or Adverse Allergic Reaction	4,058	£267	£1,083,209	60
AA31E	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0–6	5,188	£403	£2,092,922	103
DZ22Q	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 0–4	1,037	£325	£336,964	76

AE=adverse event; CE=cost effectiveness; HRG=Healthcare Resource Group; PbR=payment by results
Source: National Schedule of NHS Costs 2019/20[229]

Appendix Table 19. Currency conversion

Year	EUR to GBP	Source
2012	0.907	Organisation for Economic Co-operation and Development (OECD)[258]
2017	0.950	Organisation for Economic Co-operation and Development (OECD)[258]

Appendix Table 20. Inflation indexes

Index	Reference year	Inflation indexes	Annual % increase on previous year	Source
HCHS Pay and Prices Index, PSSRU Unit Costs of Health and Social Care 2017	2003	213.70	0.00%	Until 2014/2015: Hospital & Community Health Service (HCHS) Pay and Prices Index, PSSRU Unit Costs of Health and Social Care 2017[259]
	2004	224.80	5.19%	
	2005	232.30	3.34%	
	2006	240.90	3.70%	
	2007	249.80	3.69%	
	2008	257.00	2.88%	
	2009	267.02	3.90%	
	2010	268.63	0.60%	
	2011	276.68	3.00%	
	2012	282.49	2.10%	
	2013	287.30	1.70%	
	2014	290.46	1.10%	
	2015	293.07	0.90%	
NHSCII Pay and Prices Index, PSSRU Unit Costs of Health and Social Care 2020	2016	295.71	0.35%	From 2015/2016: NHS Cost Inflation Index (NHSCII) Pay and Prices Index, PSSRU Unit Costs of Health and Social Care (Curtis and Burns 2020)[240]
	2017	296.74	2.12%	
	2018	303.03	1.16%	
	2019	306.55	2.31%	
	2020	313.32	2.21%	
	2021	319.43	1.95%	Average index between 2017 and 2020

HCHS=Hospital & Community Health Service; NHS=National Health Service; NHSCII=NHS Cost Inflation Index; PSSRU=Personal Social Services Research Unit

Appendix Table 21. National Life Tables

	Annual death probabilities			
Age (years)	Males	Females	Weighted probability	Per-cycle probability
0	0.0042	0.0035	0.0039	0.0020
1	0.0002	0.0002	0.0002	0.0001
2	0.0001	0.0001	0.0001	0.0001
3	0.0001	0.0001	0.0001	0.0000
4	0.0001	0.0001	0.0001	0.0000
5	0.0001	0.0001	0.0001	0.0000
6	0.0001	0.0001	0.0001	0.0000
7	0.0001	0.0001	0.0001	0.0000
8	0.0001	0.0001	0.0001	0.0000
9	0.0001	0.0001	0.0001	0.0000
10	0.0001	0.0001	0.0001	0.0000
11	0.0001	0.0001	0.0001	0.0000
12	0.0001	0.0001	0.0001	0.0000
13	0.0001	0.0001	0.0001	0.0001
14	0.0001	0.0001	0.0001	0.0001

Age (years)	Annual death probabilities		Weighted probability	Per-cycle probability
	Males	Females		
15	0.0002	0.0001	0.0001	0.0001
16	0.0002	0.0001	0.0002	0.0001
17	0.0003	0.0002	0.0002	0.0001
18	0.0004	0.0002	0.0003	0.0002
19	0.0004	0.0002	0.0003	0.0002
20	0.0005	0.0002	0.0004	0.0002
21	0.0005	0.0002	0.0004	0.0002
22	0.0005	0.0002	0.0004	0.0002
23	0.0005	0.0002	0.0004	0.0002
24	0.0005	0.0002	0.0004	0.0002
25	0.0005	0.0003	0.0004	0.0002
26	0.0006	0.0003	0.0004	0.0002
27	0.0006	0.0003	0.0005	0.0002
28	0.0006	0.0003	0.0005	0.0002
29	0.0007	0.0003	0.0005	0.0003
30	0.0007	0.0004	0.0006	0.0003
31	0.0008	0.0004	0.0006	0.0003
32	0.0008	0.0004	0.0006	0.0003
33	0.0009	0.0005	0.0007	0.0004
34	0.0009	0.0005	0.0008	0.0004
35	0.0010	0.0006	0.0008	0.0004
36	0.0010	0.0006	0.0009	0.0004
37	0.0013	0.0007	0.0010	0.0005
38	0.0012	0.0008	0.0010	0.0005
39	0.0014	0.0008	0.0011	0.0006
40	0.0015	0.0008	0.0012	0.0006
41	0.0016	0.0009	0.0013	0.0007
42	0.0017	0.0011	0.0014	0.0007
43	0.0019	0.0011	0.0016	0.0008
44	0.0021	0.0013	0.0018	0.0009
45	0.0023	0.0014	0.0019	0.0010
46	0.0024	0.0015	0.0021	0.0010
47	0.0026	0.0017	0.0022	0.0011
48	0.0028	0.0019	0.0024	0.0012
49	0.0031	0.0020	0.0027	0.0013
50	0.0034	0.0022	0.0029	0.0015
51	0.0037	0.0024	0.0031	0.0016
52	0.0039	0.0025	0.0033	0.0017
53	0.0043	0.0027	0.0036	0.0018
54	0.0046	0.0028	0.0039	0.0019
55	0.0049	0.0032	0.0042	0.0021
56	0.0054	0.0035	0.0046	0.0023
57	0.0059	0.0038	0.0050	0.0025
58	0.0065	0.0042	0.0056	0.0028
59	0.0070	0.0045	0.0060	0.0030

Age (years)	Annual death probabilities		Weighted probability	Per-cycle probability
	Males	Females		
60	0.0077	0.0050	0.0066	0.0033
61	0.0084	0.0054	0.0071	0.0036
62	0.0093	0.0062	0.0081	0.0040
63	0.0102	0.0066	0.0087	0.0044
64	0.0110	0.0071	0.0094	0.0047
65	0.0122	0.0078	0.0104	0.0052
66	0.0135	0.0085	0.0114	0.0057
67	0.0145	0.0092	0.0123	0.0062
68	0.0160	0.0103	0.0137	0.0069
69	0.0176	0.0110	0.0149	0.0075
70	0.0188	0.0124	0.0162	0.0081
71	0.0203	0.0132	0.0174	0.0087
72	0.0222	0.0150	0.0192	0.0096
73	0.0253	0.0168	0.0218	0.0110
74	0.0279	0.0191	0.0243	0.0122
75	0.0315	0.0210	0.0271	0.0137
76	0.0350	0.0237	0.0303	0.0153
77	0.0393	0.0272	0.0343	0.0173
78	0.0442	0.0305	0.0386	0.0195
79	0.0491	0.0349	0.0432	0.0219
80	0.0550	0.0387	0.0483	0.0244
81	0.0610	0.0438	0.0539	0.0273
82	0.0680	0.0492	0.0602	0.0306
83	0.0759	0.0560	0.0677	0.0345
84	0.0858	0.0638	0.0768	0.0391
85	0.0963	0.0726	0.0865	0.0442
86	0.1091	0.0832	0.0984	0.0505
87	0.1216	0.0945	0.1105	0.0568
88	0.1365	0.1066	0.1242	0.0641
89	0.1532	0.1200	0.1395	0.0724
90	0.1621	0.1347	0.1508	0.0785
91	0.1816	0.1517	0.1693	0.0885
92	0.1986	0.1696	0.1866	0.0981
93	0.2224	0.1882	0.2083	0.1102
94	0.2442	0.2059	0.2284	0.1216
95	0.2696	0.2282	0.2525	0.1354
96	0.2925	0.2517	0.2757	0.1489
97	0.3142	0.2771	0.2989	0.1627
98	0.3352	0.2985	0.3201	0.1754
99	0.3754	0.3193	0.3523	0.1952
100	0.3974	0.3488	0.3773	0.2109

Source: Office for National Statistics[216]

17.6 Appendix 6: Cost-effectiveness model

CE model:

CE model with confidential information identified:

17.7 Appendix 7: Budget impact model report

17.8 Appendix 8: Budget impact model

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies (HST)

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Company response to clarification questions

May 2022

File name	Version	Contains confidential information	Date
ID3765 Lumasiran HST Alnylam Response to Clarification Questions	V7.0	Yes	9 May 2022

Preamble

Alnylam would like to express our sincere appreciation for the careful review by the ERG and the technical team at NICE of our company submission (CS) for Lumasiran for treating primary hyperoxaluria type 1 (PH1). We welcome this opportunity to provide additional information to support an informed assessment of the value of lumasiran for patients with PH1 in the UK.

We hope that we have addressed each of the questions to the satisfaction of the ERG and the NICE technical team, and would be pleased to provide any additional information that may be required. We wish to note that some of our responses contain confidential information that has been marked accordingly.

Response to clarification questions

Section A: Clarification on effectiveness data

Literature searches

A1. Please provide the 'Date searched' for the MEDLINE search documented on page 106 of Appendix A of the Systematic Literature Review (SLR) report

Response: We wish to apologise for the typographic error in the SLR report. The date of the search was June 20, 2020. We have updated the SLR Report accordingly.

A2. Please explain the restrictions for conference abstracts searched in Embase or CPCI-S from 2018 to present (as outlined in the SLR report).

Response: The focus of our search approach, as it relates to conference abstracts, was handsearching the following conferences:

- American Society of Nephrology (ASN) Annual Meeting
- European Society for Paediatric Nephrology (ESPN) Annual Meeting
- International Society of Nephrology (ISN) World Congress of Nephrology (WCN)
- International Pediatric Nephrology Association (IPNA) Congress

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Presentations Database

Not applying the same date limits to the database searches for conference abstracts as were used for the conference handsearching had the potential to skew the database-retrieved records toward older non–peer-reviewed data. Date limits were used to align the database abstract searches to the handsearching time period to reduce the risk of bias that could arise by using two different time periods for the same type of record.

Decision problem

A3. Priority question. The population described in Table A1 of the submission does not specify age or severity of condition. Sections 6.1 and 13.1 of the submission state that *"clinical manifestations of PH1 typically first appear in childhood and persist into adulthood"* and that *"considering that lumasiran would only be used in patients who have not already undergone [liver transplant or combined liver–kidney transplant]…"*.

a. Please provide any lower or upper age limits or any other criteria for determining eligibility for treatment with lumasiran.

b. Please clarify that the population in the decision problem should be re-expressed as people with primary hyperoxaluria type 1 (PH1) who have not already undergone liver transplant or combined liver-kidney transplant.

c. Please state the proportion of patients who would be eligible for lumasiran which have advanced PH1.

Response: a. Due to more rapid progression of disease in patients identified in childhood,[1-4] all children with PH1 and elevated oxalate despite established conservative management who have not undergone liver transplant should be eligible for treatment with lumasiran. To address the question of whether a subgroup of adult patients with PH1 with preserved renal function and slowly progressing disease might be suitable for delayed initiation of lumasiran, Alnylam gathered clinical expert opinion from [redacted] on the criteria for

determining eligibility for treatment with lumasiran that may be applied in real-world practice in the UK, with reference to chronic kidney disease (CKD) stage.

[redacted] is a [redacted] and an [redacted] Alnylam posed the following questions:

> "We would like to understand likely clinical intentions to treat adult PH1 patients with lumasiran. Considering adult PH1 patients, you previously presented your perspective on potential approaches to initiating treatment with lumasiran during ERD 2021 [medical conference]. This suggested lumasiran may not be used in all early-stage adults.
>
> "Would UK clinicians intend to use lumasiran in all CKD 1-2 adult patients?
>
> "If not, which if any, CKD 1-2 adult patients would you intend to treat with lumasiran e.g., those with rapid progression?"

[redacted] noted there would need to be evidence of progression to justify use of lumasiran, outside of rare exceptions i.e., if the patient had severe co-morbidities or was approaching CKD stage 3.

For newly diagnosed patients, [redacted] indicated a watch-and-wait strategy would be used, to assess whether the patient was progressing based on oxalate increase or organ damage including kidney decline.

[redacted] suggested that in terms of a threshold for progression, an equal to or more than a 5-point decline/year in [estimated glomerular filtration rate] eGFR could be the approximate threshold to determine whether to introduce lumasiran.

Based on this response, Alnylam considers that UK clinicians may reserve initiating lumasiran for adult patients in later CKD stages—i.e., CKD3, CKD4, and end-stage kidney disease (ESKD)—with possible exceptions for patients in early CKD stages who show evidence of progression or severe comorbidities.

We wish to note that lumasiran has been studied in a broad selection of patients with PH1, largely representative of the diversity seen in clinical practice, including patients with relatively preserved renal function (ILLUMINATE-A[5] and ILLUMINATE-B[6]) and those with advanced renal disease (ILLUMINATE-C[7]). Patients in the ILLUMINATE studies ranged in age from infants as young as 3 months old[6] to adults as old as 60 years.[5]

b. Alnylam confirms that the population in the decision problem should be re-expressed as people with primary hyperoxaluria type 1 (PH1) who have not already undergone liver transplant or combined liver-kidney transplant. This change to the scope was proposed in the Company decision problem form submitted on 7 May 2021.

Because PH1 is caused by a deficiency of a liver-specific enzyme,[8] patients with PH1 who have already undergone liver transplant (with or without kidney transplant) would not require treatment with lumasiran, as the source of the excess oxalate production is eliminated by removal of the patient's liver in the transplant procedure.[9] Therefore, it is appropriate to exclude post-transplant patients from the target population for lumasiran.

c. Based on Alnylam's discussion with [redacted] as described above in our response to part a of question A3, it seems likely that most adult patients who would be eligible for lumasiran in the UK would have advanced PH1.

We wish to clarify that the terminology "advanced PH1" maps to patients with an estimated glomerular filtration rate (eGFR) ≤45 mL/min/1.73m^2 (which corresponds to chronic kidney disease [CKD] stages 3b, 4, and 5[10]) and plasma oxalate level (POx) ≥20 µmol/L; i.e., the enrolment criteria and subsequent patient population in ILLUMINATE-C.[7]

A4. Priority question. According to Table A1 of the submission, the comparator, established clinical management (ECM), includes a number of different treatments, i.e. pyridoxine, oxalate-controlled diet, liver transplant with a combined or sequential kidney transplant in patients with advanced PH1, haemodialysis and hyperhydration.

a. **Please provide the proportions of people with PH1 who would receive each of these treatments in National Health Service (NHS) clinical practice in England and Wales.**

b. **Please provide a full description of each of these treatments in terms of dosing and duration as they would be given to people with PH1 in NHS clinical practice in England and Wales.**

c. **Please compare the answers to questions a. and b. with the treatments administered in the ILLUMINATE trials. If there are any differences then please discuss the effect of these differences on all outcomes.**

Response: a. Alnylam has discussed with [redacted] and [redacted] (who is also a [redacted] and an [redacted]) the proportion of patients with PH1 who would receive the different components of ECM in NHS clinical practice in England and Wales. These experts' responses are reported in Table 1 below.

b. Alnylam also posed questions to these two clinical experts about the dosing and duration of use of the different components of ECM for patients with PH1 in NHS clinical practice in England and Wales. Their responses are presented in Table 1.

Table 1. Proportion of patients with PH1 in the UK receiving components of ECM

Intervention	Proportion of patients in ILLUMINATE trials receiving intervention at baseline	Alnylam estimation of portion of UK PH1 population receiving intervention currently	Expert comments *Does the stated Alnylam estimation reflect clinical practice in the UK? If not, please highlight UK clinical practice.* *If UK clinical practice varies from that observed in the ILLUMINATE trials would this affect the transposability of ILLUMINATE trial results on the UK population? If so, how?*	
			[redacted]	[redacted]
Pyridoxine	56%	Tried in ~90% of patients and continued in ~60% often including patients with <30% decrease in UOx Dosing: 5-20 mg/kg/day Duration: Lifelong as tolerated	Agreement with Alnylam estimation of the proportion of patients having used pyridoxine; dosing and duration of use assessed as being approximately accurate	Probably continued in about 75% of those with confirmed PH1 but patient compliance long term is poor so may be 50 – 60% in the end
Oxalate-controlled diet	Data not available	Not generally recommended or practiced in UK. Specific dietary recommendation in UK is same as for other patients with CKD	No dietary restrictions beyond avoiding foods very high in oxalate (i.e., they would be referred to and receive specific counselling from a dietician). Other recommendations consistent with general dietary recommendations made for patients with CKD	Not generally recommended as strict exclusion diet or practiced as such in UK. All PH1 patients do receive dietary advice to avoid excessive amounts of dietary oxalate and high doses of Vitamin C Specific dietary recommendation in UK for other patients with advancing CKD is given as standard national guidance for kidney function impairment [i.e., whether due to PH1 or other causes]
Hyperhydration	77% (proxied by 24-hour urine volume ≥1.5 L/m) excluding Illuminate C where hyperhydration status not available		Advise patients to urinate 2 liters a day proxied by 'as colourless urine as possible' Unknown how adherent patients are to this guidance	Advised for all patients but poor compliance. Better in young infants where tube feeding is provided. Harder to maintain hyper hydration in older children and adolescents, and [adherence is] often poor in adults

Intervention	Proportion of patients in ILLUMINATE trials receiving intervention at baseline	Alnylam estimation of portion of UK PH1 population receiving intervention currently	**Expert comments** *Does the stated Alnylam estimation reflect clinical practice in the UK? If not, please highlight UK clinical practice.* *If UK clinical practice varies from that observed in the ILLUMINATE trials would this affect the transposability of ILLUMINATE trial results on the UK population? If so, how?*	
			[redacted]	[redacted]
				Advised as 2.5 to 3 L per SA m^2 No national data is available on this at all.
Hemodialysis in CKD3b – 5 PH1 patients (excluding patients who have received a liver or combined/sequential liver and kidney transplant)	71%	76%	Agreed with Alnylam estimation	[No difference noted]

CKD = chronic kidney disease; ECM = established clinical management; PH1 = primary hyperoxaluria type 1; SA: (body) surface area; UOx = urinary oxalate.

c. Across the 78 patients in the ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C trials, 44 (56%) were receiving pyridoxine at baseline (Alnylam, data on file). The same number of patients (i.e., 44) were receiving hyperhydration at baseline, according to the data on hyperhydration status available for ILLUMINATE-A and ILLUMINATE-B (Alnylam, data on file). Hyperhydration status was not available for ILLUMINATE-C, but because fluid control is necessary for patients with advanced kidney disease, it is unlikely that any ILLUMINATE-C patients would be on hyperhydration.

Based on the expert clinician input presented above in Table 1, it appears that patterns of ECM use in the ILLUMINATE clinical trials were generally consistent with those seen in the UK PH1 population. Furthermore, Alnylam believes that any differences in the precise composition of ECM in the NHS vs in the ILLUMINATE studies are unlikely to have any meaningful impact on the interpretation of the clinical results of these studies or on how these outcomes are subsequently modelled in our CEA since (other than transplantation) the components of ECM have no high-quality data demonstrating an ability to reduce oxalate levels to normal/near-normal levels, and lumasiran was shown in the ILLUMINATE trials to be similarly efficacious at controlling oxalate across patients receiving different types of baseline ECM (e.g., use vs non-use of pyridoxine[5]).

A5. Priority question. Table A1 includes a list of outcomes which were "considered in the economic model".

a. Oxalate levels: According to page 60 of the submission , *"percent change in 24-h urinary oxalate excretion from baseline to Month 6 (corrected for BSA) (…) was chosen based on the pathophysiology of PH1, which is driven by excessive oxalate production by the liver and subsequent renal elimination of oxalate"*. On the same page, the submission provides some references in support of this endpoint.

However, the wording used in the clinical study report (CSR) for ILLUMINATE-C is more cautious and does not include any supporting references, namely [redacted]

[redacted].

Please explain how (well) the outcome "oxalate excretion" predicts other outcomes listed in the NICE scope, e.g. mortality and health-related quality of life. Please provide supporting evidence.

b. **Please provide an overview of all outcomes listed in the NICE scope and signpost the relevant results from the identified studies, e.g. in section 9 of the submission .**

Response: a. Oxalate excretion and other measures of hepatic oxalate production have been shown to predict mortality and health-related quality of life (HRQoL) in patients with PH1, with data to support this predictive relationship at a causal level, at a correlational level, and at an underlying, explanatory biological level.

At the causal level, published experience has shown that pre-emptive liver transplantation—an intervention that fully resolves oxalate overproduction by replacing the affected patient's native liver (bearing *AGXT* mutations that lead to excess oxalate synthesis) with a donor liver that does not bear pathogenic *AGXT* mutations—leads to improved outcomes in PH1. We refer to the published literature on pre-emptive liver transplantation because this intervention is the closest clinical analog to lumasiran treatment in this disease context and therefore serves as a plausible, likely model for the expected outcomes with lumasiran treatment.

In particular, a retrospective, single-centre study of 36 Israeli children with PH1 found that among those who presented prior to end-stage kidney disease (ESKD) (n=18), the 7 children who underwent pre-emptive liver transplantation had improved renal function over a follow-up period of 16–20 years post-transplant, with no patient reaching ESKD and no deaths.[11] In contrast, among the remaining 11 children who presented prior to ESKD but did not undergo pre-emptive liver transplant, dialysis was required at a median age of 20.7 years, and 2 deaths occurred during follow-up.

Consistent with this Israeli experience, other published reports (case series and individual case reports; total combined n=12) have shown that the majority of patients undergoing pre-emptive liver transplantation (prior to ESKD) experience stabilised or improved eGFR (relative to pre-transplant levels) over a follow-up duration ranging from 5 months to 8 years.[12-19]

At a correlational level, a positive predictive link has also been established between oxalate excretion and renal impairment in PH1. A retrospective study of 409 patients enrolled in the Mayo Clinic Rare Kidney Stone Consortium (RKSC) Registry found that in the 297 patients with PH (any subtype) who did not have ESKD at diagnosis, there was a significant positive association between 24-hour urinary oxalate (UOx) quartile and risk of incident ESKD, independent of sex, age, and baseline estimated glomerular filtration rate (eGFR) (HR: 4.2 for patients in Q4 versus Q1–Q3; 95% CI: 1.6–10.8).[20] The same study showed a positive association between post-index 24-hour UOx (captured as a continuous variable) and ESKD risk (HR: 1.8 [95% CI, 1.2 to 2.5] per 1-mmol/1.73 m^2 increase in 24-hour UOx).

Aside from oxalate excretion, other measures of oxalate burden have been shown to predict renal impairment in patients with PH1 as well. In a pooled analysis of baseline (pre-treatment) data across three separate randomized, placebo-controlled trials of an enteric-coated oral formulation of *Oxalobacter formigenes* for patients with primary hyperoxaluria (87% of whom had PH1), Milliner et al. (2021) found a statistically significant correlation wherein increased POx levels were associated with decreased eGFR ($p < 0.0064$).[21]

Similarly, an analysis of data from the Mayo Clinic RKSC registry found a predictive association between POx concentration and progression of renal impairment in patients with primary hyperoxaluria (the majority of whom had PH1).[22] In that analysis, within each CKD stage from CKD1 to CKD3b, patients' follow-up POx values (i.e., values ascertained >6 months after entry into the CKD stage of interest) were significantly and positively associated with ESKD risk, with each 1-µmol/L increase in follow-up POx concentration translating to a 12%–19% relative increase in hazard of ESKD ($p < 0.018$), depending on patients' starting CKD stage. In concordance with the observed association between POx and ESKD risk, an analysis of patients within the study cohort who had paired POx and eGFR

measurements available (i.e., POx and eGFR measurements obtained within 3 months of each other throughout follow-up) found that each 1-µmol/L increase in POx concentration was associated with a 1.27-mL/min/1.73 m^2 decrease in eGFR ($p < 0.001$).[22]

A third indicator of oxalate burden, nephrocalcinosis (i.e., accumulation of calcium salts such as calcium oxalate in the kidneys), has also shown an association with renal impairment in PH1. In an analysis of data from the Mayo Clinic RKSC Registry, Tang et al. (2015) investigated the association of nephrocalcinosis with renal decline in patients with PH who had available renal imaging data prior to the onset of ESKD (n=235, including 170 with PH1).[23] In that analysis, patients with nephrocalcinosis observed on 1 or more renal images exhibited a statistically significant, 1.7-fold elevation in hazard of ESKD (after adjustment for PH type, type of diagnosis [symptomatic vs. familial screening], and age at first renal image) relative to patients without nephrocalcinosis observed on renal imaging.

The causal role of oxalate in driving renal decline and the ability of multiple indices of oxalate burden to predict loss of renal function in PH1 can be traced to the biological effects of oxalate crystals on renal tissue. Accumulation of CaOx crystals in the kidney and urinary tract is known to cause a significant inflammatory response, with granuloma formation occurring around these crystals.[24] With continued accumulation, progressive tissue inflammation occurs and interstitial fibrosis develops within the kidneys.[25]

From this body of evidence, a clear picture emerges in which exposure of the kidneys to excess oxalate in PH1 leads to oxalate-mediated tissue damage, which in turn results in progressive loss of renal function and, ultimately, ESKD. Accordingly, measures of excess oxalate production, such as oxalate excretion and plasma oxalate concentration, are predictive of renal impairment and progression to ESKD, and successful inhibition of excess oxalate production has been shown to halt deterioration of renal function in PH1.

By extension, the occurrence of renal decline in association with excess oxalate production in PH1 can be linked to outcomes of interest in the NICE scope. Given that measures of oxalate production, such as oxalate excretion and plasma oxalate

concentration, are predictive of renal decline, it follows that these same measures are also positively associated with the HRQoL impairment and mortality risk that accompany renal decline. Numerous studies have shown that HRQoL decreases with progressive renal impairment, and that advanced renal impairment can have a profound negative effect on HRQoL, as affected patients experience a range of symptoms that lead to limitations in physical functioning and physical role.[26,27] This effect is especially pronounced in PH1, due to unique aspects of the disease and its management that are not present in other forms of renal impairment, particularly in later stages (e.g., the need for intensive haemodialysis, the occurrence of systemic oxalosis).[28,29] Likewise, progressive renal impairment carries with it a significant mortality risk, in line with the essential role of the kidney in various physiological processes. A retrospective database analysis of longitudinal eGFR data from >1 million adults found that mortality risk steadily increased with increasing CKD stage, such that patients in CKD3a, CKD3b, CKD4, and ESKD had 1.2-fold, 1.8-fold, 3.2-fold, and 5.9-fold increases, respectively, in mortality hazard relative to patients with eGFR ≥60 ml/min/1.73 m^2.[30]

In summary, oxalate excretion and other measures of excess oxalate production have been shown to predict renal impairment and the occurrence of ESKD in patients with PH1. Moreover, interventions that successfully halt excess oxalate production have been shown to modify this risk. As HRQoL impairment and increased mortality risk are fundamental consequences of renal impairment and ESKD, it follows that measures of oxalate production can be used to predict loss of HRQoL and mortality, in line with NICE scope.

b. The table below outlines the outcomes listed in the NICE scope and cross-references to the relevant results in the submission.

Outcome per NICE scope	Cross-reference	Specific page numbers
Oxalate levels in urine	Section 9.6.1	ILLUMINATE-A: pg 69-77
		ILLUMINATE-B: pg 81-84
		ILLUMINATE-C: pg 86, 88, 89
Oxalate levels in plasma	Section 9.6.1	ILLUMINATE-A: pg 69, 72, 77, 78
		ILLUMINATE-B: pg 81, 83, 85
		ILLUMINATE-C: pg 86-88
Change in eGFR	Section 9.6.1	ILLUMINATE-A: pg 73, 74, 78, 79
		ILLUMINATE-B: pg 81, 83, 85

Outcome per NICE scope	Cross-reference	Specific page numbers
Need for liver transplant with or without a kidney transplant	Section 9.4.6	ILLUMINATE-C: pg 67, 92
Mortality	Section 9.7.2	ILLUMINATE-A: pg 90
		ILLUMINATE-B: pg 91-92
		ILLUMINATE-C: pg 92
		Phase 2 open-label extension: pg 93
Adverse effects of treatment	Section 9.7.2	ILLUMINATE-A: pg 89-91
		ILLUMINATE-B: pg 91-92
		ILLUMINATE-C: pg 92
		Phase 2 open-label extension: pg 92-93
Health-related quality of life	Section 10.1.3	ILLUMINATE-A: pg 99

A6. Table A1 includes a list of subgroups which were *"considered in the economic model"*.

a. Results for other subgroups assessed in the identified studies are reported in the submission , e.g. in section 9.4.4. Please comment whether these were considered for the economic model. If not, please explain why this was not done.

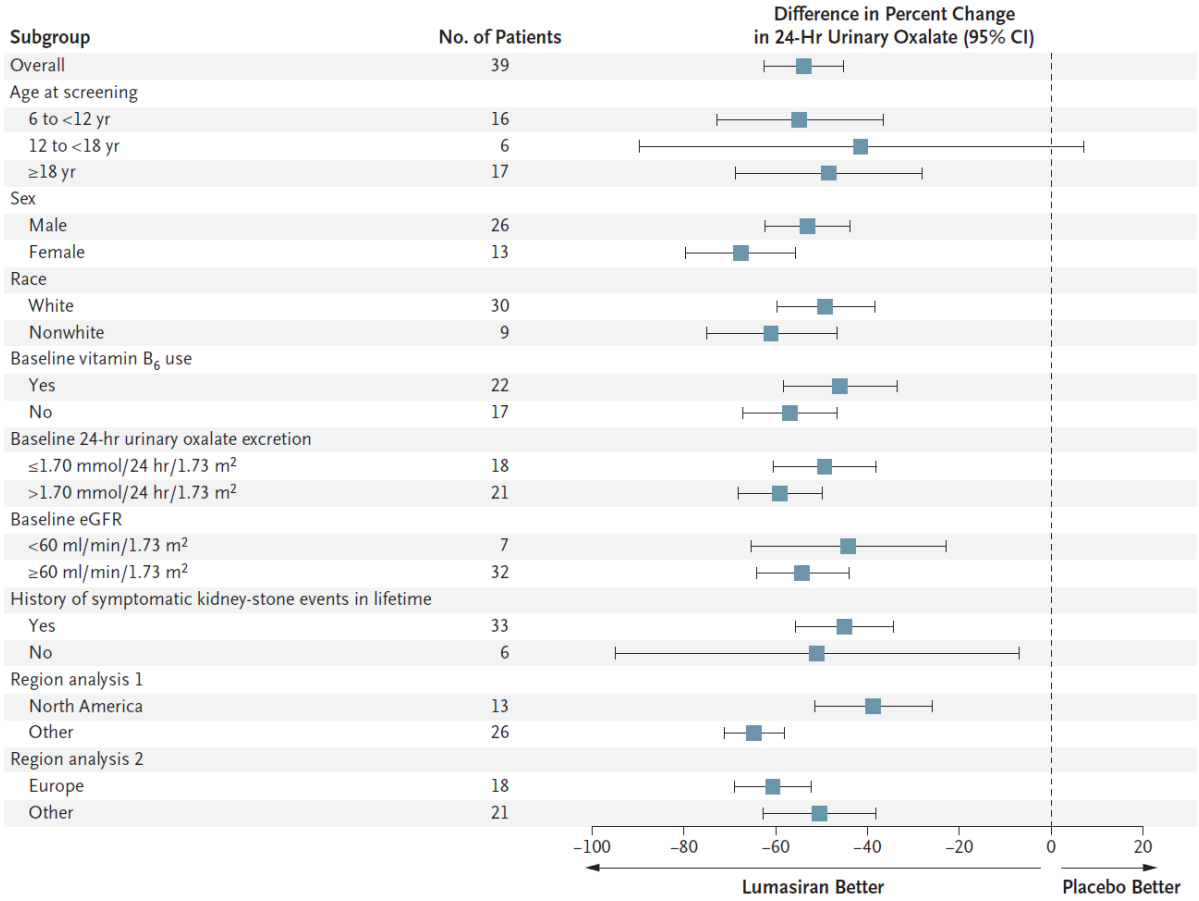
b. According to section 6.1.1 of the submission , "*there is evidence that a very small, genetically distinct subpopulation (G170R homozygotes) that accounts for approximately 5%–10% of the overall PH1 population retain some degree of AGT activity and have the potential to fully respond to pyridoxine, which may serve as a cofactor involved in AGT localisation"*. Please provide results for this subgroup. Were results considered for the economic model? If not, please explain why this was not done.

c. As per the NICE scope, infants with rapid and progressive disease should be considered as a relevant subgroup. However, the ILLUMINATE trial did not include this subgroup. Please confirm that no relevant data were gathered in this subgroup and discuss potential implications for the submission.

Response: a. Subgroup analyses were not conducted in the CEA because lumasiran demonstrated consistent benefit on UOx vs placebo across clinically relevant subgroups in ILLUMINATE-A (Figure 1).[5] Differences in the point estimates

in Figure 1 are likely attributable to small sample sizes in the subgroups, which would also reduce confidence in modelling the subgroups separately.

Figure 1. Subgroup analysis of the percent change from baseline to Month 6 in 24-hour urinary oxalate excretion in ILLUMINATE-A



Source: Garrelfs et al. 2021[5]

b. To provide context for our answer and explain why results for the G170R homozygote subpopulation are not provided, Alnylam asked [redacted] and another clinical expert, [redacted] (a [redacted]), about the extent of response to pyridoxine (vitamin B6) among G170R homozygotes. Although the quoted section of the CS mentions the theoretical possibility of a full response to pyridoxine among G170R homozygotes, the response from [redacted] pointed to the rarity of a full response even in this subpopulation, which he had never observed:

> "In the attached small clinical trial [Hoyer-Kuhn et al. (2014)[31]], 3 participants with homozygous G170R variants did not show full response to B6.

> “In our current experience of 17 children with PH1, two teenagers with homozygous G170R variants did not respond to B6, and one further patient had a partial reduction in UOx with B6
>
> “A reasonable clinical approach for children in whom there is no clinical urgency would be to try pyridoxine first. If patients have a full response to pyridoxine (normalisation/near normalisation of UOx), we would not use Lumasiran. However I have never seen a full response to pyridoxine in our clinical experience.
>
> “For patients with a progressive infantile phenotype for whom treatment is urgent, I would advocate starting Lumasiran ASAP with a view to assessing pyridoxine sensitivity at a later stage in childhood. This is because delaying an effective treatment would increase the risk of kidney failure and systemic oxalosis.”

[redacted] response addressed the question of her intended use of lumasiran in patients with a complete response to pyridoxine, as follows:

> “I wouldn’t immediately prescribe L[umasiran] in this group, unless with a lower GFR so if GFR falling I might consider it. But many B6 responsive patients lose this ability over time so can be unresponsive or less responsive some months to years later so still might require L in the future. At the time of completely normal U OX I would wait”

In summary, the clinical experts indicated that full responsiveness to pyridoxine is rare and transient, which suggests that this is not a key patient subgroup to model.

The current model already implicitly excludes G170R homozygotes who experience oxalate normalisation with pyridoxine treatment, as Phase 3 clinical trial entry criteria were such that only patients with elevated oxalate levels were included in these trials.

Please see also our response to question A13.

c. The Phase 3 clinical trial programme for lumasiran included 4 infants (<1 year of age at study entry): 2 patients in ILLUMINATE-B and 2 patients in ILLUMINATE-C.

By definition, infantile patients are those who have rapid and progressive disease. The results of treatment with lumasiran in these patients are summarised below in Table 2 to Table 4. Note that data on 24-hour UOx excretion were not available for these patients, as assessment of UOx excretion via 24-hour urine collection is not feasible in patients who are not toilet-trained. In addition, eGFR data are not available for these patients, as eGFR was not estimated in children <1 year of age in ILLUMINATE-B and ILLUMINATE-C.

Table 2. Spot UOx:Cr ratio in infants in Phase 3 clinical trials of lumasiran

		Spot UOx:Cr ratio (mmol/mmol)		
Patient	Trial	BL	% change at 6M	% change at 12M
A	ILLUMINATE-B	[redacted]	[redacted]	[redacted]
B	ILLUMINATE-B	[redacted]	[redacted]	[redacted]
C	ILLUMINATE-C (Cohort A)	[redacted]	[redacted]	[redacted]
D	ILLUMINATE-C (Cohort B)	[redacted]	[redacted]	[redacted]

BL = baseline; Cr = creatinine; M = month; UOx = urinary oxalate.
Cohort A = patients not requiring dialysis or kidney transplantation at study start; Cohort B = patients on haemodialysis at study start.

Table 3. Plasma oxalate concentration in infants in Phase 3 clinical trials of lumasiran

		POx concentration (µmol/L)				
			Absolute Change		% Change	
Patient	Trial	BL	6M	12M	12M	12M
A	ILLUMINATE-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B	ILLUMINATE-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C	ILLUMINATE-C (Cohort A)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	ILLUMINATE-C (Cohort B)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BL = baseline; M = month; POx = plasma oxalate.
Cohort A = patients not requiring dialysis or kidney transplantation at study start; Cohort B = patients on haemodialysis at study start.

Table 4. Renal stone events in G170R homozygotes in Phase 3 clinical trials of lumasiran

		Number of renal stone events by time period		
Patient	Trial	12M pre-treatment	BL to M6	M6 to M12
A	ILLUMINATE-B	[redacted]	[redacted]	[redacted]

Patient	Trial	Number of renal stone events by time period		
		12M pre-treatment	BL to M6	M6 to M12
B	ILLUMINATE-B	[redacted]	[redacted]	[redacted]
C	ILLUMINATE-C (Cohort A)	[redacted]	[redacted]	[redacted]
D	ILLUMINATE-C (Cohort B)	[redacted]	[redacted]	[redacted]

BL = baseline; M = month.
Cohort A = patients not requiring dialysis or kidney transplantation at study start; Cohort B = patients on haemodialysis at study start.

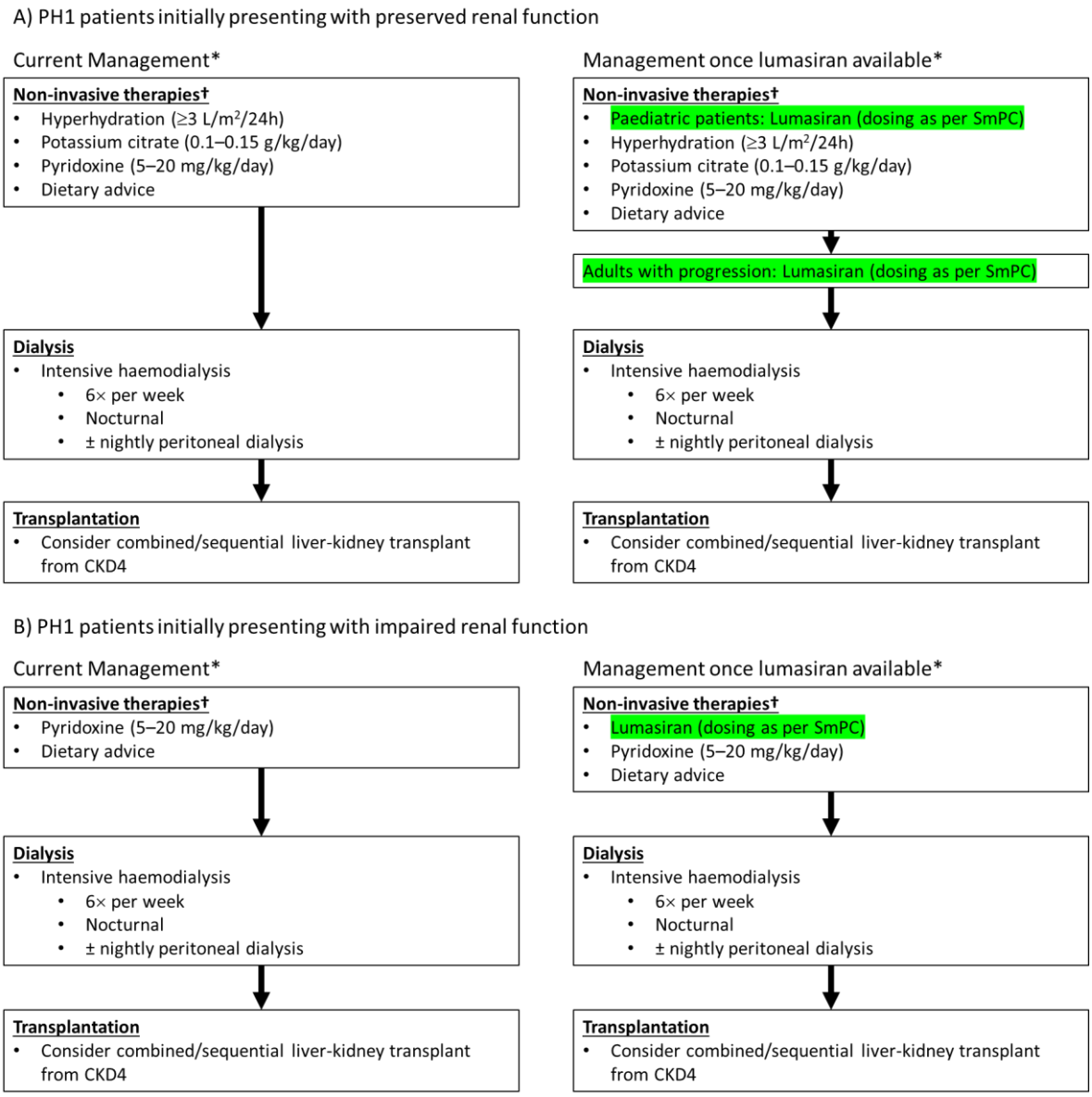
The results observed in infants in ILLUMINATE-B and ILLUMINATE-C were generally consistent with those observed in the broader patient populations in these trials. As a result, model inputs relating to the oxalate-lowering efficacy of lumasiran in the overall PH1 population were also applied to the infantile patient subgroup.

Clinical pathway

A7. Sections 8.2 and 8.3 of the submission summarise the current clinical pathway and proposed pathway of care respectively, for people with PH1. Please provide a figure showing the current clinical pathway for the treatment of people with PH1 in England and Wales and another figure showing the proposed place for lumasiran. Please provide supporting references.

Response: Alnylam has developed the requested figures based on individual consultations with clinical experts from the Hyperoxaluria RDCN, published expert commentary on the anticipated use of lumasiran (Hulton 2021[32]) and clinical practice guidelines for PH1 published prior to the development of lumasiran (Cochat et al. 2012[1]). As shown in Figure 2A, adult patients with preserved renal function would initiate lumasiran only with evidence of progression. Figure 2B indicates that patients presenting with impaired renal function would initiate lumasiran along with the applicable non-invasive therapies for this patient subpopulation.

Figure 2. Current clinical pathway for patients with PH1 in England and Wales and proposed place in therapy of lumasiran, for patients with A) preserved and B) impaired renal function.



CKD = chronic kidney disease (stage); PH1 = primary hyperoxaluria type 1; SmPC = Summary of Product Characteristics.
*Management directed at controlling oxalate level; does not include surgical management of urolithiasis.
†Refers to less invasive treatments compared with dialysis and transplantation (however, hyperhydration may require nasogastric or gastrostomy tube in infants).

Systematic literature review (SLR)

A8. Some aspects of the eligibility criteria for the SLR are unclear:

a. Please explain why studies with non-UK cost and resource use data were excluded

b. Please explain and provide supporting references as to why investigational therapies, including oxabact®, nedosiran, betaine, DCR-PH1, diacomit®, and ALLN-177 were excluded as per Table C1 of the submission..

c. Please expand on the information provided in Table C1 of the submission to further clarify which types of studies were included and excluded,. For example, surveys are listed as included but could be seen as a type of epidemiological study (which are listed to be excluded).

d. Please define adherence studies and studies of treatment prescribing patterns and explain why these study designs were not eligible.

Response: a. Per NICE HTA guidance,[33] interpretation of, and conclusions pertaining to, economic evidence should be subject to consideration of the relevance, or generalisability, of the analysis to clinical practice in England. Since non-UK cost and resource use data are not readily generalisable to the UK, the SLR was designed to preferentially identify UK-specific evidence in the literature to inform the UK cost-effectiveness analysis.

b. The SLR is aligned with the Final NICE Scope for lumasiran[34] with respect to the interventions included. The SLR was designed to identify data on established clinical management (including vitamin B6), liver/liver–kidney transplantation, haemodialysis, and hyperhydration. These are the treatments that are currently available to patients in the UK. Investigational therapies are not part of the treatment landscape and, therefore, are not relevant to current UK clinical practice.

c. Observational studies (both retrospective and prospective) were included to ensure that the SLR captured relevant clinical data in the literature. The SLR did not discriminate on the methodology for obtaining the observational data—surveys, chart reviews, registry studies, etc, were all included if they reported any of the clinical outcomes listed in Table C1. Studies that were solely focused on epidemiology, and that did not report on any of the outcomes of interest, were deemed to be epidemiological studies and were excluded. Studies that reported any of the outcomes of interest, even if alongside epidemiological data, were included.

d. Exclusion by study design was secondary to the outcomes inclusion criteria. Any study reporting an outcome of interest was included. The economic outcome

inclusion criteria were designed to identify relevant resource use and treatment cost data in the literature. Adherence studies and studies on treatment prescribing patterns that did not provide data on outcomes of interest were excluded.

A9. Section 2.5 in the SLR report states that data were extracted and validated by 2 investigators whereas page 2 of the same document states that *"data were extracted by one researcher (and validated by another)"*. Please specify which one applies. If it is the latter, please discuss the limitations and potential for bias.

Response: Data were extracted by one researcher and verified for accuracy by a second independent researcher. As recommended in the CRD guidance,[35] any disagreements between researchers were resolved by consensus. A third independent researcher was available to arbitrate; however, this additional step was not required during the execution of this SLR.

Although parallel extraction is generally considered the gold standard, it is limited by real-world constraints on time and resources and is not globally recommended in systematic review guidance.[35,36] The process implemented in the lumasiran SLR—single researcher extraction and validation by a second researcher—is an accepted minimum for systematic reviews. The CRD guidance states that, "As an accepted minimum, one researcher can extract the data with a second researcher independently checking the data extraction forms for accuracy and completeness".[35] To address potential limitations of single data extraction and validation (eg, human error, subjective decision-making), standardised data extraction forms that integrated drop-down lists to reduce the potential for data transcription errors, and that clearly defined the data to be extracted,[35] were developed. These standardised data extraction forms were then piloted by both researchers to improve consistency and to address any ambiguity. The piloted data extraction forms were then used to capture relevant data from the literature. The use of a standardised form and ensuring a piloting step is recommended to help ensure consistency and reduce bias during data extraction.[35,37]

Trials and data analysis

A10. According to section 9.3.1 of the submission, *"Lumasiran was evaluated in a phase 1/2, randomised, single-blind, placebo-controlled trial in 20 patients with PH1 (Part B),*[REF 91] *an ongoing phase 2 OLE,*[REF 66] *an ongoing phase 3 trial with a randomised placebo-controlled RCT period and associated extension phase (ILLUMINATE-A),*[REF 8] *and an ongoing phase 3 single-arm interventional open-label study (ILLUMINATE-B*[REF 67]*)"*. Four references are given in support, whereas section 9.4.1 of the submission lists 5 studies. Please resolve this apparent discrepancy, e.g. by clearly summarising the relevant evidence as well as relevant references.

Response: Section 9.3.1 summarises the clinical evidence retrieved and evaluated during the systemic literature review (SLR). As noted in the dossier, "*At the time of writing the SLR report, the ILLUMINATE-C clinical study had yet to report data and had not been captured in the search results*". Similarly, at the time of conducting the literature searches for the SLR (4 August 2021, see Section 17.1 Appendix 1), the ILLUMINATE-C study had yet to report data. Since ILLUMINATE-C data were first presented at the American Society of Nephrology Kidney Week 4–7 November, 2021, these data were not captured in the SLR search results and were not described in Section 9.3.1, but they were available in time for inclusion in Section 9.4.1 of the dossier, hence the discrepancy.

A11. According to section 9.7 of the submission, no severe adverse events were experienced by patients across the ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C trials.

a. Please provide tables of mild and moderate adverse events by preferred terms.

b. Please discuss hepatic adverse events associated with lumasiran in patients with PH1.

Response: a. Alnylam wishes to clarify that severe adverse events were reported in the ILLUMINATE trial programme, but none of these severe events were assessed as being related to lumasiran treatment. The requested adverse event data are presented in Table 5, Table 6, and Table 7 for ILLUMINATE-A, ILLUMINATE-B, and

ILLUMINATE-C, respectively. The sources for these data are the clinical study report appendices for the three studies.

Table 5. ILLUMINATE-A primary analysis period adverse events by system organ class, preferred term

System Organ Class Preferred Term	Placebo (n=13)			Lumasiran (n=26)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
At least 1 adverse event	7 (53.8)	2 (15.4)	0	15 (57.7)	7 (26.9)	0
Blood and lymphatic system disorders	0	0	0	1 (3.8)	0	0
Iron deficiency anaemia	0	0	0	1 (3.8)	0	0
Congenital, familial and genetic disorders	0	0	0	1 (3.8)	0	0
Thalassaemia beta	0	0	0	1 (3.8)	0	0
Ear and labyrinth disorders	0	0	0	1 (3.8)	0	0
Ear pain	0	0	0	1 (3.8)	0	0
Eye disorders	0	0	0	1 (3.8)	0	0
Vision blurred	0	0	0	1 (3.8)	0	0
Gastrointestinal disorders	1 (7.7)	0	0	3 (11.5)	1 (3.8)	0
Abdominal discomfort	1 (7.7)	0	0	1 (3.8)	0	0
Abdominal pain	0	0	0	2 (7.7)	0	0
Abdominal pain lower	0	0	0	1 (3.8)	0	0
Abdominal pain upper	0	0	0	2 (7.7)	0	0
Constipation	0	0	0	1 (3.8)	0	0
Nausea	0	0	0	0	1 (3.8)	0
General disorders and administration site conditions	0	0	0	10 (38.5)	1 (3.8)	0
Chest pain	0	0	0	1 (3.8)	0	0
Fatigue	0	0	0	0	1 (3.8)	0
Injection site discomfort	0	0	0	1 (3.8)	0	0
Injection site erythema	0	0	0	3 (11.5)	0	0
Injection site pain	0	0	0	3 (11.5)	0	0
Injection site reaction	0	0	0	6 (23.1)	0	0
Immune system disorders	0	0	0	1 (3.8)	0	0
Hypersensitivity	0	0	0	1 (3.8)	0	0
Infections and infestations	4 (30.8)	1 (7.7)	0	7 (26.9)	4 (15.4)	0
Fungal skin infection	0	0	0	1 (3.8)	0	0
Infected bite	0	0	0	1 (3.8)	0	0
Kidney infection	0	0	0	0	1 (3.8)	0
Nasopharyngitis	0	0	0	1 (3.8)	0	0
Otitis media acute	1 (7.7)	0	0	0	0	0
Pharyngitis	0	0	0	1 (3.8)	0	0
Pneumonia	0	0	0	1 (3.8)	1 (3.8)	0

System Organ Class Preferred Term	Placebo (n=13) Mild n (%)	 Moderate n (%)	 Severe n (%)	Lumasiran (n=26) Mild n (%)	 Moderate n (%)	 Severe n (%)
Rhinitis	2 (15.4)	0	0	2 (7.7)	0	0
Tonsillitis	0	0	0	0	1 (3.8)	0
Tooth infection	0	1 (7.7)	0	0	0	0
Upper respiratory tract infection	2 (15.4)	0	0	2 (7.7)	0	0
Urinary tract infection	0	0	0	0	2 (7.7)	0
Injury, poisoning and procedural complications	2 (15.4)	0	0	1 (3.8)	1 (3.8)	0
Contusion	1 (7.7)	0	0	0	0	0
Foot fracture	0	0	0	1 (3.8)	0	0
Gastrostomy tube site complication	1 (7.7)	0	0	0	0	0
Tibia fracture	0	0	0	0	1 (3.8)	0
Metabolism and nutrition disorders	1 (7.7)	0	0	1 (3.8)	0	0
Iron deficiency	1 (7.7)	0	0	0	0	0
Vitamin D deficiency	0	0	0	1 (3.8)	0	0
Musculoskeletal and connective tissue disorders	2 (15.4)	0	0	5 (19.2)	0	0
Back pain	1 (7.7)	0	0	2 (7.7)	0	0
Flank pain	0	0	0	1 (3.8)	0	0
Groin pain	0	0	0	1 (3.8)	0	0
Musculoskeletal chest pain	0	0	0	1 (3.8)	0	0
Musculoskeletal pain	0	0	0	1 (3.8)	0	0
Pain in extremity	1 (7.7)	0	0	0	0	0
Nervous system disorders	2 (15.4)	1 (7.7)	0	6 (23.1)	1 (3.8)	0
Disturbance in attention	0	0	0	0	1 (3.8)	0
Dizziness	0	0	0	1 (3.8)	0	0
Headache	2 (15.4)	1 (7.7)	0	3 (11.5)	0	0
Hypoaesthesia	0	0	0	1 (3.8)	0	0
Restless legs syndrome	0	0	0	1 (3.8)	0	0
Psychiatric disorders	0	0	0	1 (3.8)	2 (7.7)	0
Anxiety	0	0	0	1 (3.8)	0	0
Fear of injection	0	0	0	0	1 (3.8)	0
Irritability	0	0	0	0	1 (3.8)	0
Renal and urinary disorders	0	0	0	1 (3.8)	1 (3.8)	0
Polyuria	0	0	0	1 (3.8)	0	0
Renal pain	0	0	0	0	1 (3.8)	0
Respiratory, thoracic and mediastinal disorders	2 (15.4)	0	0	2 (7.7)	0	0
Cough	0	0	0	1 (3.8)	0	0

System Organ Class Preferred Term	Placebo (n=13)			Lumasiran (n=26)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Nasal congestion	1 (7.7)	0	0	1 (3.8)	0	0
Oropharyngeal pain	1 (7.7)	0	0	1 (3.8)	0	0
Skin and subcutaneous tissue disorders	0	0	0	2 (7.7)	1 (3.8)	0
Alopecia	0	0	0	1 (3.8)	0	0
Eczema	0	0	0	1 (3.8)	0	0
Erythema	0	0	0	1 (3.8)	0	0
Pruritus	0	0	0	0	1 (3.8)	0
Rash erythematous	0	0	0	1 (3.8)	0	0
Vascular disorders	0	0	0	1 (3.8)	0	0
Hypertension	0	0	0	1 (3.8)	0	0

Based on MedDRA version 21.1.
Patients who experienced >1 event in a given category are counted only once in that category according to the maximum severity.

Table 6. ILLUMINATE-B primary analysis period adverse events by system organ class, preferred term

System Organ Class Preferred Term	<10 kg (n=3)			10 to <20 kg (n=12)			>= 20 kg (n=3)			All lumasiran treated (N=18)		
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
At least 1 adverse event	1 (33.3)	2 (66.7)	0	11 (91.7)	1 (8.3)	0	1 (33.3)	2 (66.7)	0	13 (72.2)	5 (27.8)	0
Blood and lymphatic systemdisorders	0	2 (66.7)	0	0	0	0	0	0	0	0	2 (11.1)	0
Anaemia	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0
Iron deficiency anaemia	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0
Congenital, familial and genetic disorders	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Factor XII deficiency	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Ear and labyrinth disorders	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Ear pain	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Gastrointestinal disorders	0	2 (66.7)	0	5 (41.7)	0	0	1 (33.3)	0	0	6 (33.3)	2 (11.1)	0
Abdominal pain	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Anal pruritus	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0

System Organ Class Preferred Term	<10 kg (n=3)			10 to <20 kg (n=12)			>= 20 kg (n=3)			All lumasiran treated (N=18)		
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
Aphthous ulcer	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Diarrhoea	0	0	0	2 (16.7)	0	0	0	0	0	2 (11.1)	0	0
Mouth ulceration	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Nausea	0	0	0	1 (8.3)	0	0	1 (33.3)	0	0	2 (11.1)	0	0
Teething	0	2 (66.7)	0	0	0	0	0	0	0	0	2 (11.1)	0
Vomiting	0	1 (33.3)	0	2 (16.7)	0	0	1 (33.3)	0	0	3 (16.7)	1 (5.6)	0
General disorders and administration site conditions	1 (33.3)	2 (66.7)	0	5 (41.7)	0	0	1 (33.3)	1 (33.3)	0	7 (38.9)	3 (16.7)	0
Influenza like illness	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0
Injection site reaction	0	0	0	2 (16.7)	0	0	1 (33.3)	0	0	3 (16.7)	0	0
Pyrexia	1 (33.3)	1 (33.3)	0	4 (33.3)	0	0	0	1 (33.3)	0	5 (27.8)	2 (11.1)	0
Infections and infestations	1 (33.3)	1 (33.3)	0	10 (83.3)	1 (8.3)	0	1 (33.3)	1 (33.3)	0	12 (66.7)	3 (16.7)	0
Asymptomatic bacteriuria	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Bronchitis	0	0	0	0	1 (8.3)	0	1 (33.3)	0	0	1 (5.6)	1 (5.6)	0
Conjunctivitis bacterial	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Croup infectious	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Ear infection	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Gastroenteritis	0	0	0	2 (16.7)	0	0	0	0	0	2 (11.1)	0	0
Influenza	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Nasopharyngitis	1 (33.3)	0	0	0	0	0	1 (33.3)	0	0	2 (11.1)	0	0
Oral herpes	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Pharyngitis	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Pneumonia	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Rhinitis	0	1 (33.3)	0	3 (25.0)	0	0	0	0	0	3 (16.7)	1 (5.6)	0
Tonsillitis	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Upper respiratory tract infection	1 (33.3)	0	0	2 (16.7)	0	0	0	1 (33.3)	0	3 (16.7)	1 (5.6)	0
Urinary tract infection	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Viral infection	0	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0
Viral pharyngitis	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0

System Organ Class Preferred Term	<10 kg (n=3)			10 to <20 kg (n=12)			>= 20 kg (n=3)			All lumasiran treated (N=18)		
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
Injury, poisoning and procedural complications	2 (66.7)	0	0	0	0	0	1 (33.3)	0	0	3 (16.7)	0	0
Arthropod bite	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Arthropod sting	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Fall	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Investigations	0	0	0	1 (8.3)	0	0	0	1 (33.3)	0	1 (5.6)	1 (5.6)	0
Blood creatinine increased	0	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0
Urine analysis abnormal	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Metabolism and nutritiondisorders	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Iron deficiency	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Nervous system disorders	0	0	0	0	0	0	2 (66.7)	0	0	2 (11.1)	0	0
Headache	0	0	0	0	0	0	2 (66.7)	0	0	2 (11.1)	0	0
Psychiatric disorders	1 (33.3)	0	0	0	0	0	1 (33.3)	0	0	2 (11.1)	0	0
Behaviour disorder	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Irritability	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Renal and urinary disorders	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Haematuria	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Reproductive system and breast disorders	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Gynaecomastia	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Respiratory, thoracic andmediastinal disorders	1 (33.3)	1 (33.3)	0	3 (25.0)	0	0	1 (33.3)	0	0	5 (27.8)	1 (5.6)	0
Cough	0	1 (33.3)	0	1 (8.3)	0	0	0	0	0	1 (5.6)	1 (5.6)	0
Nasal congestion	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Oropharyngeal pain	0	0	0	2 (16.7)	0	0	0	0	0	2 (11.1)	0	0
Rhinorrhoea	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Skin and subcutaneous tissue disorders	1 (33.3)	0	0	1 (8.3)	0	0	1 (33.3)	0	0	3 (16.7)	0	0
Eczema	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0

System Organ Class Preferred Term	<10 kg (n=3)			10 to <20 kg (n=12)			>= 20 kg (n=3)			All lumasiran treated (N=18)		
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
Rash	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Rash maculo-papular	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0

Adverse events are coded using MedDRA version 23.0.
Patients who experienced > 1 event in a given category are counted only once in that category according to the maximum severity.
Severe AEs include both severe events and events with missing severity.
System organ class and preferred terms within a system organ class are sorted alphabetically.

Table 7. ILLUMINATE-C primary analysis period adverse events by system organ class (preferred term)

System Organ Class Preferred Term	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
At least 1 adverse event	4 (66.7)	1 (16.7)	0	4 (26.7)	3 (20.0)	6 (40.0)	8 (38.1)	4 (19.0)	6 (28.6)
Blood and lymphatic system disorders	0	0	0	0	1 (6.7)	1 (6.7)	0	1 (4.8)	1 (4.8)
Anaemia	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Blood loss anaemia	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Spontaneous haematoma	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Endocrine disorders	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Hyperparathyroidism tertiary	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Gastrointestinal disorders	1 (16.7)	1 (16.7)	0	5 (33.3)	2 (13.3)	0	6 (28.6)	3 (14.3)	0
Abdominal pain	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Abdominal pain upper	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Constipation	1 (16.7)	0	0	1 (6.7)	0	0	2 (9.5)	0	0
Diarrhoea	1 (16.7)	0	0	3 (20.0)	0	0	4 (19.0)	0	0
Gastritis	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Pancreatitis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Peptic ulcer	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Vomiting	0	1 (16.7)	0	1 (6.7)	0	0	1 (4.8)	1 (4.8)	0
General disorders and administration site conditions	2 (33.3)	0	0	8 (53.3)	1 (6.7)	1 (6.7)	10 (47.6)	1 (4.8)	1 (4.8)
Catheter site swelling	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Device related thrombosis	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Injection site reaction	1 (16.7)	0	0	4 (26.7)	0	0	5 (23.8)	0	0
Pyrexia	1 (16.7)	0	0	6 (40.0)	1 (6.7)	0	7 (33.3)	1 (4.8)	0
Swelling	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Hepatobiliary disorders	0	0	0	1 (6.7)	1 (6.7)	0	1 (4.8)	1 (4.8)	0

System Organ Class Preferred Term	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
Cholecystitis acute	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Cholelithiasis	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Infections and infestations	2 (33.3)	0	0	2 (13.3)	4 (26.7)	0	4 (19.0)	4 (19.0)	0
Candida nappy rash	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Catheter site infection	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Clostridium difficile colitis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Conjunctivitis	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Device related infection	0	0	0	0	2 (13.3)	0	0	2 (9.5)	0
Ear infection	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Paronychia	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Roseola	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Sepsis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Upper respiratory tract infection	1 (16.7)	0	0	1 (6.7)	0	0	2 (9.5)	0	0
Urinary tract infection	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Injury, poisoning and procedural complications	2 (33.3)	0	0	1 (6.7)	2 (13.3)	1 (6.7)	3 (14.3)	2 (9.5)	1 (4.8)
Arteriovenous fistula thrombosis	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Burns second degree	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Clavicle fracture	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Fibula fracture	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Head injury	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Humerus fracture	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Limb injury	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Radius fracture	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Skin scar contracture	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Upper limb fracture	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Investigations	1 (16.7)	0	0	3 (20.0)	2 (13.3)	0	4 (19.0)	2 (9.5)	0
Alanine aminotransferase increased	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Aspartate aminotransferase increased	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Blood phosphorus increased	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Blood potassium increased	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Blood uric acid increased	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
General physical condition abnormal	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
International normalised ratio increased	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Liver function test increased	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
SARS-CoV-2 test positive	0	0	0	2 (13.3)	0	0	2 (9.5)	0	0
Staphylococcus test positive	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0

System Organ Class Preferred Term	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
Metabolism and nutrition disorders	3 (50.0)	0	0	1 (6.7)	0	0	4 (19.0)	0	0
Carnitine deficiency	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Hyperkalaemia	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Hypokalaemia	1 (16.7)	0	0	1 (6.7)	0	0	2 (9.5)	0	0
Iron deficiency	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Metabolic acidosis	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Vitamin D deficiency	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Nervous system disorders	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.8)	0	1 (4.8)
Paraesthesia	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Seizure	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Product issues	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Thrombosis in device	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Psychiatric disorders	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Insomnia	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Renal and urinary disorders	2 (33.3)	0	0	0	0	0	2 (9.5)	0	0
Proteinuria	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Renal impairment	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Cough	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Surgical and medical procedures	0	0	0	0	0	5 (33.3)	0	0	5 (23.8)
Arteriovenous fistula operation	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Dialysis device insertion	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Renal and liver transplant	0	0	0	0	0	2 (13.3)	0	0	2 (9.5)
Renal transplant	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Vascular disorders	0	0	0	2 (13.3)	1 (6.7)	0	2 (9.5)	1 (4.8)	0
Dialysis hypotension	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Haemorrhage	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Hypotension	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Jugular vein thrombosis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0

Adverse events with missing severity are considered severe.
Adverse events are coded using MedDRA version 23.0.
Cohort A = patients not requiring dialysis or kidney transplantation at study start; Cohort B = patients on haemodialysis at study start.

b. Hepatic events were infrequent during the lumasiran clinical development programme (Alnylam, data on file). On laboratory analysis, there have been no notable changes in liver function test (LFT) parameters related to lumasiran treatment. No elevations in LFT values had led to treatment interruption or discontinuation. Based on these results, there have been no hepatic safety concerns in clinical studies of lumasiran.

A12. The ILLUMINATE-A trial had a very small sample size (n=39) and the majority of patients were of white ethnicity (76.9%). Please discuss implications for generalisability to England and Wales; and outline effectiveness in other race/ethnicity groups, e.g. by adding all relevant results divided by these and other relevant subgroups.

Response: As shown above in Figure 1, there was no indication of a difference by race in the impact of lumasiran on oxalate in ILLUMINATE-A: the 95% CIs for white and nonwhite patients overlapped, and the 95% CI for nonwhite patients included the point estimate for white patients.[5]

The proportion of patients of white ethnicity in ILLUMINATE-A, 77%, is essentially the same as in the population of England and Wales, where 85% of people identified as white in 2019.[38] With the small sample size in this trial (which is a reflection of the rarity of PH1), an additional 3 white patients would have yielded 85% of the trial population of white ethnicity. Thus, we consider that the ILLUMINATE-A trial population is generalisable to England and Wales.

There were no deaths in ILLUMINATE-A,[5] so it is not possible to assess racial differences in the potential impact of lumasiran on mortality. Similarly, eGFR remained stable in both treatment arms of the 6-month ILLUMINATE-A trial,[5] a result that was expected given the natural history of PH1, in which eGFR declines gradually, so ILLUMINATE-A is not informative about whether or not there might be racial differences in the impact of lumasiran in the evolution of eGFR over the long term.

A13. According to section 10.2.2. of the CSR, pyridoxine use was reported by 56.4% of patients at study entry. Please indicate if this has been adjusted for in the analyses.

Response: As shown above in Figure 1, there was no indication of a difference by pyridoxine (vitamin B6) use in the impact of lumasiran on oxalate in ILLUMINATE-A: the 95% CIs for users and nonusers of pyridoxine overlapped, and the 95% CI for users included the point estimate for nonusers.[5] Since the clinical effect of lumasiran was not influenced by pyridoxine use, we did not adjust for pyridoxine use in the analyses.

A14. According to Appendix G in the SLR report, the quality of the included studies was assessed to be low. Please discuss the implications of this for clinical decision making.

Response: The quality appraisal conducted for this SLR was comprehensive and the researchers were fully independent of the manufacturer. Only records that were identified in the SLR were subjected to quality appraisal (i.e., the manufacturer did not supply any additional evidence to address any gaps in the literature), which resulted in some uncertainty in the assessment of the lumasiran studies, particularly for ILLUMINATE-B which was only reported in a conference abstract.

Furthermore, the eligibility criteria for clinical effectiveness allowed the inclusion of all study designs, which ensured that all available evidence was identified. However, observational study designs inherently have limitations and more potential biases than RCTs, with biases due to selection of participants or confounding being particularly important.[37] Most of the studies included in the SLR were retrospective observational studies, and key details were often not reported. Through the quality assessment process, several limitations in the evidence were noted, such as selection bias, differing treatment exposure, inadequate detail on assessment of outcomes, and lack of appropriate consideration of important confounding factors. Limitations such as these increase uncertainty for clinical decision-making.

Alnylam is conducting extensive research in the PH1 population, with the goal of improving outcomes for patients with this disease. Although the existing literature on current established clinical management is hindered by a dearth of prospectively designed studies, the lumasiran clinical trial programme is robust. Many of the lumasiran studies are ongoing and will contribute valuable data that can improve clinical decision-making.

Evidence synthesis

A15. Priority question. According to section 9.8.1 of the submission , *"no meta-analyses or indirect comparisons were feasible due to the lack of RCTs for any comparator to lumasiran"*.

The NICE final scope defined 4 comparators: established clinical management without lumasiran, including vitaminB6 and an oxalate-controlled diet; liver transplant with or without a combined/ sequential kidney transplant; haemodialysis; and hyperhydration.

Please demonstrate that there are currently no placebo-controlled comparative studies for any of these comparators that could have been used in an indirect treatment comparison, e.g. by providing details of a relevant SLR.

Response: All studies evaluating established clinical management without lumasiran were observational in design, as described in the Lumasiran SLR Report and listed in Table 8 below. No placebo-controlled studies of the four comparators outlined in the Final NICE Scope were identified in the literature.

Table 8. Studies for comparators identified in SLR

Comparator	Cross-reference in Lumasiran SLR report	Description of studies identified
Established clinical management without lumasiran (including vitamin B6 and an oxalate-controlled diet)	Section 3.2, Table 6	• No placebo-controlled studies were identified • All studies were observational in design – One prospective survey – One prospective case series – One retrospective database analysis – One retrospective cohort study – Four retrospective case series • Studies did not mention oxalate-controlled diet
Liver transplant with or without a combined or sequential kidney transplant	Section 3.4, Table 14	• No placebo-controlled studies were identified • All studies were observational in design: – One survey – Four retrospective case series – Four retrospective cohort studies – Eleven retrospective analyses of registries or databases

Comparator	Cross-reference in Lumasiran SLR report	Description of studies identified
Haemodialysis	Section 3.3, Table 10	• No placebo-controlled studies were identified • Two studies were identified; both were observational and retrospective in design
Hyperhydration	Section 3.2, Table 6	• No placebo-controlled studies were identified • All studies were observational in design: – One prospective survey – One retrospective database analysis – One retrospective cohort study – Three retrospective case series

SLR = systematic literature review.

Section B: Clarification on cost-effectiveness data

Conceptual model

B1. Priority question. To derive transition probabilities for the model, a regression coefficient from Shah et al. 2020 is used, indicating that 1 unit increase in oxalate leads to a 1.27 unit decrease in estimated glomerular filtration rate (eGFR).

For the ECM group, transitions are calculated based on the small increase in oxalate level during 6 months, which is converted into a decrease in eGFR using Shah et al. 2020. This is then used to estimate the time until the patient will move to the next chronic kidney disease (CKD) class. Using this logic, if oxalate level does not change over 6 months, eGFR does not change and patients will remain in the current CKD class. It appears that this does not reflect the disease very well, where continuous exposure to a constant high level of oxalate leads to decreasing eGFR, or, in other words, no change in oxalate level is required for eGFR to decrease if the oxalate level is high enough.

Similarly, for the lumasiran group, it is assumed that patients will remain in their CKD class as long as they are on treatment, since the oxalate level dropped by almost 50% over 12 months during the randomised controlled trials (RCTs) which would, according to Shah's regression

coefficient lead to an increase in eGFR. However, if the 50% reduction of oxalate leads to a level of oxalate that is still outside the normal range, it seems very plausible that patients still move to a worse CKD class, albeit slower.

Based on the above, please justify the current approach of modelling transitions between CKD 1-2, CKD 3a, CKD 3b, i.e. based only on change in oxalate level, rather than including also exposure to above-normal levels of oxalate.

Response: Evidence on the natural disease history in PH1 suggests that higher oxalate levels are associated with worsening in kidney function, leading to ESKD.[39] The current model defines progression of the disease at early stages (CKD1–3b) by simulating transitions to the next-worse CKD stage driven by increasing oxalate level.

We appreciate the conceptual issue being raised by the ERG, which suggests that, to some degree, the extent of the patient's elevation in absolute oxalate levels (i.e., degree of exposure to above-normal levels of oxalate) should inform their progression to a worse CKD class, rather than progression being solely based on the trajectory of change in oxalate (i.e., the slope of change) over time. We consider that our modelling approach in the CS was the best possible solution given the available evidence from the literature, but we acknowledge that it may have limitations. In principle, we would have liked to be able to stratify patients' risk of progression based on the degree of exposure to above-normal levels of oxalate but the evidence in this condition is unavailable. The paucity of data on this topic is detailed in our SLR, and there are significant limitations in the literature that precluded us from implementing a model design as proposed:

(1) No pharmacologic ECM interventions have been able to show a reduction in the degree of exposure to oxalate to normal or near-normal levels; e.g. PH1 patients generally fail to achieve a full or durable response to pyridoxine as noted by [redacted] and [redacted] (see our response to part b of Question A6). The relationship between achievement of such levels with drug treatment and rate of disease progression has never been shown before, so it is impossible for us to use any pre-existing

evidence to inform how a patient's risk of progression might change as a function of the extent of normalisation.

(2) The vast majority of relevant studies examining the relationship between oxalate and renal function are cross-sectional in nature and therefore are unable to capture the complex relationship between oxalate and eGFR dynamics, which does not allow for an assessment of how risk associated with above-normal oxalate translates to a worsening in CKD stage.

Therefore, the problem is two-pronged in that no pharmacologic intervention has ever been able to normalise oxalate exposure and, as a result, available publications have only ever shown that the degree of oxalate is ever-increasing and that the CKD stage is ever-worsening. Therefore, it is not possible for us to quantify how holding a patient's level of oxalate constant mediates their long-term risk of CKD-stage progression.

Importantly, our proposed approach relied on the study by Shah et al. (2020) to allow modelling of these CKD stage transitions as a function of oxalate levels because it is the only study that has established a longitudinal relationship between oxalate levels and eGFR[22]; other available studies are strictly cross-sectional in nature, which leads to important limitations in how one interprets the validity of this relationship over the disease course. The study reported by Shah et al. (2020) suggests that higher oxalate levels are associated with lower eGFR; on average the eGFR decreased by 1.27 mL/min/1.73 m^2 per 1 µmol/L increase in POx ($p < 0.001$).[22] This longitudinal link in the relationship between these parameters explains the rationale behind the current modelling approach.

Nevertheless, we have undertaken exploratory analyses to stratify the risk of progression through CKD stages in the model based on data from the ILLUMINATE studies, and have a preliminary version of this model ready to share. The ILLUMINATE studies are the only suitable dataset for these analyses, since lumasiran is the only intervention to compellingly demonstrate an ability to reduce the level of circulating oxalate in the body.

This revised exploratory approach partitions the CKD1–3b cohort into two separate strata: (1) one corresponding to patients with normal or near-normal oxalate levels

and (2) the other corresponding to patients with “above-normal” oxalate levels; the transition probabilities between CKD stages are differentiated for each stratum. In this way, decreases in eGFR with exposure to a constant high level of oxalate can be modelled specifically within the “above-normal” oxalate stratum. For the purposes of this approach, normalisation/near-normalisation were based on UOx levels, using the pre-specified UOx normalisation/near-normalisation thresholds defined as part of the ILLUMINATE trial protocol and endpoint structure: ≤ upper limit of normal (ULN) and ≤1.5 × ULN, respectively. Combining of normal and near-normal oxalate levels is appropriate because near-normalisation is expected to predict clinical benefit in patients with PH1 according to the evaluation of clinical outcomes and endpoints for the approval of new therapies for PH1 from the Kidney Health Initiative (KHI) and Oxalosis and Hyperoxaluria Foundation (OHF).[39] Due to the use of different methods for measuring UOx, ILLUMINATE-A and ILLUMINATE-B data could not be pooled, and therefore the modelling of differential progression based on UOx stratum was informed by data from ILLUMINATE-A (lumasiran arm).

To ensure full representation of the progression of renal decline based on UOx normalisation level, each of the CKD1–3b health-states was partitioned into two substates: 1) above-normal UOx and 2) normal/near-normal UOx. Within each CKD-based health state, at simulation start 100% of the cohort is assigned to the above-normal UOx substate (as a simplification since there was only 1 patient with near-normal UOx and none with normal UOx in ILLUMINATE-A at baseline); the transition probabilities of these patients from the above-normal UOx substate to the normal/near-normal UOx substate is based on observations over the first 12 months of data from the lumasiran arm of ILLUMINATE-A. Observations between baseline and Month 6 (Table 10) were used to estimate the transition probabilities in the first model cycle, while observations between Month 6 and Month 12 (Table 10) were used to estimate the transition probabilities from the second model cycle onwards, assuming recycling of last observed probabilities. The approach described here resulted in the following transition probabilities:

- Probability of reaching normal/near-normal UOx at month 6 if UOx was above-normal at baseline, applied in the first cycle of the analysis = [redacted] (i.e., [redacted] out of [redacted] patients at risk)

- Probability of reaching normal/near-normal UOx at month 12 if UOx was above normal at Month 6, applied from the second cycle of the analysis = [redacted] (i.e., [redacted] out of [redacted] patients at risk). None of the patients with normal/near-normal UOx level reverted to above-normal UOx level at month 6 or at month 12, and therefore a probability of 0 was applied for transition from the normal/near-normal UOx substate to the above-normal UOx substate at any model cycle.

Table 9. Shift table—baseline to Month 6, number of patients by UOx normalisation level, patients randomised to lumasiran in ILLUMINATE-A

From/to	Above-normal	Normal/Near-normal	Total
Above-normal	[redacted]	[redacted]	[redacted]
Normal/Near-normal	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

UOx = urinary oxalate.

Table 10. Shift table—Month 6 to Month 12, number of patients by UOx normalisation level, patients randomised to lumasiran in ILLUMINATE-A

From/to	Above-normal	Normal/Near-normal	Total
Above-normal	[redacted]	[redacted]	[redacted]
Normal/Near-normal	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

UOx = urinary oxalate.

Consistent with all available published data, the placebo arm in ILLUMINATE-A (i.e., ECM in the model) shows that any degree of normalisation with available care management strategies cannot be demonstrated. Therefore, it was not necessary to add substates in the ECM arm of the model since there would be 0% of the cohort in the normal/near-normal UOx substate.

While UOx-based thresholds were used to define how lumasiran changes patients' exposure to elevated oxalate levels (i.e., transition between above-normal and normal/near-normal substates within the CKD1-3b health states), we still needed to apply assumptions about the long-term trajectory of these patients' eGFR decline, due to the previously noted absence of data to inform expectations about this trajectory. As a conservative assumption, we assume that these patients (i.e., those in the above-normal UOx substate) experience progression commensurate with those patients in the ECM arm of the model. We hope this assumption sufficiently

addresses the ERG's suggestion that patients who experience an elevated, above-normal level of UOx should be expected to experience CKD stage progression.

The estimated per-cycle probabilities of CKD stage progression based on oxalate increase in the ECM arm, which were applied to the proportion of the cohort with above-normal UOx levels in the lumasiran arm, are reported in Table 11.

Table 11. Health-state transition probabilities (per cycle) in above-normal UOx substates, any cycle.

From/to	CKD1-2	CKD3a	CKD3b	CKD4
CKD1–2	[redacted]	[redacted]	[redacted]	[redacted]
CKD3a	[redacted]	[redacted]	[redacted]	[redacted]
CKD3b	[redacted]	[redacted]	[redacted]	[redacted]

CKD = chronic kidney disease (stage); UOx = urinary oxalate.

Accompanying this response, we are providing a version of the model incorporating this new approach (see *Lumasiran PH1 in CKD1-5 CEM UK_v11.0_with Luma progression_AiC-CiC.xlsm*).

B2. In the paper by Cochat et al. 2013, it is stated that *"measurement of plasma levels of oxalate should be reserved for patients with stage 3b chronic kidney disease (estimated GFR, 30 to 45 ml per minute per 1.73 m^2), since plasma levels remain relatively normal until kidney function is substantially impaired"*. Based on the above, please explain why the company uses changes in plasma oxalate to estimate transition between CKD 1-2, CKD 3a and CKD 3b.

Response: Multiple different measures can be used to assess oxalate overproduction or otherwise evaluate disease activity in PH1, depending on patient type and other contextual factors. In the interest of model simplicity, however, it is desirable to make use of a single, common measure that can meaningfully track oxalate overproduction and disease activity across the entire spectrum of patient types. POx fulfils this requirement as a unifying measure that predicts disease progression and morbidity across all patient ages and all levels of disease progression. As such, it allows the use of POx alone to model disease progression in earlier stages of disease (CKD1–3b) and to model disease progression, resource use, and risk of systemic oxalosis complications in later stages of disease (CKD4 / ESKD), while eliminating the need for a more complex model implementation involving separate UOx- and POx-based modules.

The ability of plasma oxalate to predict disease morbidity (and, thus, associated resource use) in patients with PH1 who have advanced renal impairment has long been recognized, as suggested by Cochat and Rumsby and elaborated upon by Milliner et al. (representing the KHI and OHF in the US) in a review of clinical trial endpoints in PH1.[28,39] Since the 2013 publication by Cochat and Rumsby, however, there has been substantial evolution in understanding of the prognostic value of POx levels in earlier stages of renal impairment associated with PH1. As noted in the Sponsor's response to question A5, recent studies have demonstrated the prognostic value of POx in patients with PH1 and CKD stage 1–3b, as evidenced by the following:

- Milliner et al. (2021) identified a statistically significant inverse correlation between POx levels and eGFR in a pooled analysis of baseline data across three separate clinical trials of *O. formigenes* (enteric-coated oral formulation) for patients with primary hyperoxaluria (87% of whom had PH1)[21]; of note is that these trials were restricted to patients with eGFR > 40 mL/min/1.73 m^2, corresponding to CKD that was no more advanced than stage 3b
- Shah et al. (2020) reported a predictive association of POx concentration with progression of renal impairment and ESKD risk in patients with primary hyperoxaluria (the majority of whom had PH1)[22]; of note is that this analysis focused on patients with CKD stage 1-3b

These recent findings, taken together with established understanding of the clinical significance of POx levels in later-stage renal impairment associated with PH1, support the value of POx concentration as a prognostic indicator across all stages of PH1.

The value of POx concentration in this regard is unique, as the role of UOx excretion as an indicator of disease activity in PH1 is largely limited to early-stage patients. Due to the advanced renal impairment exhibited in later stages of PH1, patients with late-stage disease typically do not clear their entire hepatic oxalate output in urine or are fully anuric, such that UOx excretion is no longer a meaningful measure of hepatic oxalate production in these patients.[28] Moreover, even among early-stage patients, different methods for UOx measurement (with different quantitative outputs) are required for patients of different ages. In general, 24-hour UOx (i.e., aggregate

UOx excretion over all urine voids collected during a 24-hour period, measured in units of mmol/L per day and normalized to a body surface area of 1.73 m^2) is the recommended method to assess oxalate excretion in urine; however, single-void UOx (i.e., UOx excretion from a single urine void, measured in units of mg or mmol UOx per mg or mmol urine creatinine, reflecting normalisation of UOx excretion to creatinine excretion to account for possible differences in urine dilution from one urine void to the next) is often necessary for younger patients who are not toilet-trained and in whom 24-hour urine collection may therefore be infeasible.[40]

Given these challenges in applying UOx as a meaningful indicator of disease activity and prognostic variable across the entire PH1 population, the decision was made to incorporate POx into the Sponsor's economic model to allow modelling of disease via a common, unifying measure with prognostic value in all stages of disease and in patients of all ages.

Population and model structure

B3. Priority question. On page 121 of the submission, it is stated that *"it is currently unknown whether clinicians in real-world practice will initiate lumasiran in patients with early-stage disease without rapid signs of progression; furthermore, it is unknown how clinical practice will vary by patient characteristics (e.g., age, age at disease onset)"*.

- **a. Please elaborate on the possible reasons for why clinicians would not initiate treatment in patients with early-stage disease without rapid signs of progression.**
- **b. Please indicate clearly which model health states are considered to reflect early-stage disease, what defines progression in this context, and when signs of progression are considered as rapid or not.**
- **c. Please elaborate on the possible variations in clinical practice and how this translates to variations in health care resource use.**
- **d. Please explain how both sources of uncertainty were addressed in the model.**

e. **Please provide options in the model, i.e. by means of drop-down boxes, to select whether and when treatment with lumasiran is initiated in patients with early-stage disease or not.**

f. **Please provide options in the model to reflect relevant variations in clinical practice in relation to varying patient characteristics.**

Response: a. Based on input from [redacted] reported above in our response to question A3.a, it appears that clinicians would consider it appropriate to take a watch-and-wait approach in adult patients with early-stage disease to see if they are experiencing disease progression, which would justify initiating lumasiran.

b. Early-stage disease is reflected by minimal level of kidney impairment (eGFR >59 mL per minute per 1.73 m^2), which therefore corresponds to model health-state CKD1–2.[10] Progression in this context is defined by progressive impairment of kidney function and progression to worse CKD stages. Given that the underlying pathology of PH1 is present from birth, typically leading to early age of disease onset,[2] patients who still have minimal kidney impairment in adulthood are likely to be considered as non-rapid progressors. Infantile onset is a recognised sign of rapid progression and the model accounts for this by applying a hazard ratio of ESKD progression of 6 versus the overall PH1 population rate of ESKD progression. The subgroup of patients with infantile onset is included as a modelled scenario.

c. Although Alnylam was unable to obtain precise information on possible variation in use of lumasiran in clinical practice in the UK, based on the input received from Hyperoxaluria RDCN experts there could be variation in the use of lumasiran in G170R homozygotes and adult patients in early CKD stages. Per the proposed treatment pathway presented in Figure 2, all early-stage patients would be expected to use the healthcare resources and incur the costs associated with the non-invasive components of ECM whether or not they received lumasiran.

d. The submitted model included two scenario analyses to explore the impact on the model results if lumasiran were to be administered in subgroups with faster progression: 1) 100% paediatric cohort at model start and 2) 100% infant cohort at model start, the latter being the subgroup with fastest progression. An additional scenario has been added which excludes adults with early-stage disease from the eligible population at simulation start (see response to point e.) The results from

these three scenarios address the impact of changes in healthcare resource use resulting from possible variations in the population treated, since the model considers clinical practice differences between paediatric and adult patients in terms of:

- Access to transplant and transplant-related healthcare resources
- Dialysis patterns and associated costs
- Monitoring healthcare resource use differing by CKD stage

e. An option was added to run the simulation excluding adult patients in CKD1–2, which are defined as those with early-stage disease. This option can be selected from the dropdown selector "Treatment eligibility" in the Results sheet (2nd option). The distribution for the adult cohort at the simulation start was estimated based on the Singh et al. data after excluding patients in the CKD1–2 health state (Table 12). The resulting ICER is £[redacted]/QALY, which represents a [redacted] compared with the base-case ICER of £[redacted]/QALY (estimated after correcting the transplantation rate as noted in the answer to question B9).

Table 12. Distribution of adult cohort at model start after removing early-stage disease (CKD1–2)

CKD stage	% cohort at model start
CKD1–2	0%
CKD3a	20%
CKD3b	20%
CKD4	16%
CKD5	45%
TOTAL	100%

CKD = chronic kidney disease (stage)

f. As mentioned in the response to question d) under this topic, the model already considers clinical practice differences between paediatric and adult patients and by CKD stage. Therefore, by adjusting the distribution of the cohort at start of the simulation to exclude the CKD1–2 adult patients, in whom expectations regarding initiation of lumasiran treatment are uncertain, relevant variations in the clinical practice are taken into consideration.

B4. Priority question. In Table D23 of the submission it is noted that the consultant paediatric nephrologist clarified that in the specific subpopulation of patients with infantile onset of PH1 in the UK, the

distribution of CKD stages is skewed more heavily toward later CKD stages (0% in CKD1–3b, 10% in CKD4, and 90% in ESKD). However, the model only uses the distribution of CKD stages as reported by Singh et al. 2021.

Please include the option in the model to use a distribution of CKD stages for the paediatric population that is in line with the estimates from the consultant paediatric nephrologist.

Response: As requested, an option was added in the existing dropdown "Distribution of CKD stages at start" (3rd option in the dropdown) to run the model considering a CKD health-state distribution for the paediatric cohort based on the consultant paediatric nephrologist opinion (0% in CKD1–3b, 10% in CKD4, and 90% in ESKD). Following this change the ICER is [redacted] by approximately [redacted] compared to the ICER obtained from applying the Singh et al. (2020) distribution to the paediatric cohort.

B5. According to section 12.1.3 of the submission, "t*he model structure and the definition of the health states were validated by UK clinical experts"*. Please provide details regarding the number of experts and the nature of their expertise, the questions that were asked and the answers that were provided as well as the methods used, e.g. individual interviews, focus groups, or Delphi procedure.

Response: As described in Section 12.2.5 of the CS, in 2021 Alnylam solicited expert opinion to validate key model inputs and assumptions, from clinicians:

- Who are members of the PH1 Rare Disease Collaborative Network (RDCN),
- Whose experience, in totality, spanned the full spectrum of ages over which patients may be impacted by PH1, from infancy to adulthood, and
- Who had been investigators in the ILLUMINATE study programme, to obtain their insights into how lumasiran would be utilised in clinical practice based on their hands-on experience using the drug in these trials

Two UK-based clinical experts meeting all of these criteria were approached to participate in individual, web-based interviews. Both clinical experts agreed to these interviews.

One interview was conducted with the first clinical expert, a consultant paediatric nephrologist. Two interviews were conducted with the second clinical expert, a consultant nephrologist.

The information provided by Alnylam and verbalised during interviews as background for discussion consisted of an overview of the modelling assumptions in this submission, along with data from Jamieson et al. (2005),[41] Singh et al. (2021),[42] and the transplant rates from the NICE appraisal of Tolvaptan for treating autosomal dominant polycystic kidney disease [TA358].[43]

Clinical advisers' feedback on key model inputs and assumptions as discussed in these interviews are summarised in Table 13.

Table 13. Clinical validation of the CE model assumptions and methodology

Parameters/inputs	Details
Plasma oxalate threshold indicative of disease control	The clinical experts validated the use of a plasma oxalate threshold of 50 µmol/L as being indicative of meaningful disease control, resulting in improved health status, improved suitability for transplantation, and more favourable prognosis post-transplant for patients achieving plasma oxalate levels below this threshold relative to patients with higher plasma oxalate levels.
Correspondence of plasma oxalate control to clinical states defined by Jamieson et al. (2005)[41]	The clinical experts noted that patients with plasma oxalate levels below the threshold of 50 µmol/L can be expected to correspond to those categorised as having *Very Good* or *Good* overall clinical status in the analysis conducted by Jamieson et al. to assess the relationship between pretransplantation clinical status and post-transplant survival in patients undergoing combined liver–kidney transplantation for PH1, while patients with plasma oxalate levels above this threshold can be expected to correspond to those categorised as having *Fair* or *Poor* clinical status in the same analysis.

Parameters/inputs	Details
Transplant eligibility for patients with controlled plasma oxalate levels	The clinical experts confirmed that all patients with plasma oxalate levels below the threshold indicative of disease control would, by virtue of their improved post-transplant outlook, be considered eligible for transplantation if they were sufficiently fit, such that their rate of advancement to combined liver–kidney transplantation would be limited only by the availability of suitable donor organs (and not by PH1-specific concerns relating to patients' oxalate burden and its impact on post-transplant outcomes). Accordingly, the clinicians validated the assumption that transplant rates for patients with controlled plasma oxalate levels would match the rates observed in the general population of patients requiring transplantation for reasons unrelated to PH1. The clinical experts suggested using transplantation rates from annual transplantation reports published by the NHS.
Relationship between plasma oxalate control and prevalence of systemic oxalosis complications	The clinical experts agreed that the prevalence of systemic oxalosis complications is lower for patients with controlled plasma oxalate levels than for those with uncontrolled plasma oxalate levels. The assumption that complications of systemic oxalosis would be [redacted] less prevalent in patients in the former group vs. those in the latter group aligned with clinical opinion.
Dialysis practices specific to PH1	The consultant paediatric nephrologist estimated that among paediatric patients with PH1 who are receiving intensive dialysis for management of systemic oxalosis and/or ESKD, 100% would be expected to receive daytime haemodialysis and that smaller percentages would also receive night-time peritoneal dialysis 7 days per week (~60%) or night-time haemodialysis 6 days per week (20%).
CKD stage distribution of patients with PH1 in the UK	The clinical experts confirmed that at the level of the overall population, the distribution of CKD stages reported by Singh et al. (2021)[42] for patients with PH1 in the RKSC PH registry is consistent with the distribution observed in the prevalent PH1 population in the UK. Nonetheless, the consultant paediatric nephrologist clarified that in the specific subpopulation of patients with infantile onset of PH1 in the UK, this distribution is skewed more heavily toward later CKD stages (0% in CKD1–3b, 10% in CKD4, and 90% in ESKD).

CKD=chronic kidney disease; ESKD=end-stage kidney disease; NHS=National Health Service; PH=primary hyperoxaluria; PH1, primary hyperoxaluria type 1; RKSC=Rare Kidney Stone Consortium.

Clinical parameters

B6. Section 12.1.3 of the dossier reads *"Since the distribution of the Harambat et al. study population leaned more towards CKD 3 than CKD 4, the ESKD-free survival curves reported by Harambat et al. were used to model the transition of patients from CKD 4-OxU to ESKD-OxU"*. Please explain why the fact that the

distribution leaned more towards CKD3 leads to the decision to use the curves to model the transition from CKD4-OxU to ESKD-uncontrolled oxalate levels (OxU).

Response: We would like to clarify that the sentence included in the dossier had a typographical error, such that “CKD 3 and CKD 4” should replace “CKD 3 than CKD 4”. In fact, the distribution in the Harambat et al. (2010) study population leaned more towards CKD3 and CKD4 (73% in CKD3 and CKD4 at diagnosis) as opposed to earlier CKD stages, and the specific percentages in CKD1 and CKD2 are not mentioned.[3] Thus, it would not have been appropriate to apply the probability of ESKD obtained from time-to-ESKD data from the Harambat et al. study to model progression to ESKD directly from early disease health states of the model, as this would have likely overestimated the risk of ESKD (i.e., fast progression to ESKD in the BSC arm). As an alternative approach, the model was built based on the relationship between oxalate and eGFR to define transitions between CKD1–4 health states, and the ESKD-free survival curve from Harambat et al. was applied to define only the transition from CKD4 to ESKD. This is a conservative approach since the population at risk in the Harambat study included also patients with CKD3 who would have had a lower risk of ESKD than CKD4 patients, such that rates of progression determined from Harambat et al. would underestimate the true rate in patients in CKD stage 4.

B7. According to Table D2, “*oxalate is central to PH1 pathophysiology* [and] *patients with oxalate levels being held below the threshold for control (50 µmol/L) have disease stabilisation and do not transition to the corresponding ESKD health state”*.

Cochat et al. 2013 stated that *“if preemptive transplantation is not feasible, therapeutic strategies that include short daily sessions of high-flux dialysis, nocturnal dialysis, or combinations of hemodialysis and nocturnal peritoneal dialysis are needed to keep predialysis levels of plasma oxalate below 30 to 45 µmol per liter”*.

Please explain why the company considers 50 µmol/litre to be the correct threshold for oxalate control and how it would impact the results if a lower threshold was used.

Response: Cochat and Rumsby (2013) propose a POx level of <30–45 µmol/L as a criterion for oxalate control in patients with PH1 and advanced renal impairment.[28] This target POx level reflects a high degree of caution, as there is evidence that a less stringent threshold of 50 µmol/L is similarly indicative of clinically meaningful oxalate control and also more realistically achievable than a threshold as low as 30 µmol/L.

In terms of clinical significance, the 30-µmol/L threshold is suggested by findings from Hoppe et al. (1999) and Ogawa et al. (2006) that plasma CaOx supersaturation, the key risk factor for systemic oxalosis, occurs at POx values above 30 µmol/L in patients with PH1.[44,45] However, these findings contrast with those of Marangella et al. (1993), who reported CaOx saturation in association with POx levels of 44–46 µmol/L and thus proposed a POx threshold of 50 µmol/L as a critical benchmark in establishing candidacy for transplantation.[46] This 50-µmol/L threshold is likely to be a more realistic target, as reduction of POx to levels substantially lower than 50 µmol/Lis often unachievable with dialysis in the setting of PH1 (i.e., pathologically elevated hepatic oxalate production) with advanced renal impairment. Even in studies involving ESKD cohorts without PH1, plasma oxalate levels are significantly elevated, falling in the range of 35 to 55 µmol/L, due to impaired renal clearance of normal physiologic levels of hepatic oxalate output.[47-52] Application of an oxalate control threshold substantially lower than 50 µmol/L could therefore exclude a substantial proportion of patients from transplant eligibility even in the absence of clear evidence that these patients' systemic oxalosis risk profile would make them suboptimal candidates for transplantation.

For the reasons outlined here, an oxalate control threshold of 50 µmol/L was incorporated into the Sponsor's model. Use of a lower threshold, consistent with the lower bound of the range described by Cochat and Rumsby (2013), would modestly delay the transition of patients in the lumasiran arm from the CKD4-OxU and ESKD-OxU model states to the corresponding controlled oxalate states.

B8. According to page 139 of the submission, in the ECM arm 100% of the CKD 4 and 100% of the ESKD health states receive high-intensity dialysis. In the lumasiran arm 0% of the CKD 4 health state receive normal-intensity dialysis and 100% of the ESKD health states receive normal-intensity dialysis.

a. Please justify the assumption that kidney function in CKD4 is severely impaired in patients receiving ECM and normal in patients receiving lumasiran.
b. Please justify the assumption that treatment with lumasiran is 100% effective in controlling oxalate and treatment with ECM is 0% effective in controlling oxalate.
c. Unless there is evidence available in support of these assumptions, please provide options in the model that reflect more conservative assumptions for these aspects.

Response: a. The assumptions in the model regarding the prevalence of dialysis use are based on consideration of the different purposes of dialysis in patients with PH1 at different CKD stages. As described in Section 8.2.1 of the HST submission (page 39), dialysis is used in advanced stages of renal decline to slow the build-up of systemic oxalate and, in patients with ESKD, to provide some of the key function normally carried out by the kidney.[1,53,54]

However, the rate of oxalate production in PH1 patients greatly surpasses the ability to remove it through dialysis, since oxalate is sequestered in organs and re-enters the plasma following dialysis.[55] Patients with PH1 require high-intensity dialysis schedules since conventional (i.e, normal-intensity) dialysis is typically insufficient for lowering oxalate levels.[55] However, even intensified schedules are inadequate to consistently lower oxalate.[55,56]

ECM does **not** normalise oxalate in patients with PH1. This is evident from the literature[31,55] and from the placebo arm of the ILLUMINATE-A trial,[5] where participants were required to continue their ECM with hyperhydration, crystallisation inhibitors, and/or pyridoxine and yet no normalisation of oxalate was observed.

In ILLUMINATE-A (PH1 patients aged ≥6 years with relatively preserved renal function), none of the patients in the placebo (i.e., ECM) arm achieved near-normalisation (≤1.5×ULN) or normalisation (≤ ULN) of urinary oxalate, compared with 84% and 52% of lumasiran-treated patients, respectively.[5] Lumasiran significantly lowered urinary oxalate (percent change: −65.4% vs. −11.8%; $p<0.001$) and plasma oxalate (percent change: −39.8% vs. −0.3%; absolute change: −7.5 vs. 1.3 µmol/L;

p<0.001 for both comparisons) from baseline to Month 6, compared with the placebo arm.

In ILLUMINATE-B (PH1 patients aged <6 years with PH1 and relatively preserved renal function), treatment with lumasiran resulted in substantial reductions in urinary oxalate (−72.0%) and plasma oxalate (−31.7%) from baseline to Month 6.[6]

In ILLUMINATE-C (PH1 patients of any age with advanced kidney disease), lumasiran led to reductions in plasma oxalate from baseline to Month 6 in patients not yet on dialysis (−33.3%) and in patients on dialysis (−42.4%).[7]

Since lumasiran has the ability to normalise or near-normalise oxalate overproduction, it is assumed that 0% of the lumasiran cohort in the CKD 4 health state receives dialysis, either for the purpose of replacing renal function or removing oxalate from the blood, since the kidney is functioning in CKD 4 and oxalate is controlled by lumasiran. It is assumed that 100% of the lumasiran cohort in the ESKD health state receives normal-intensity dialysis (but not higher-intensity dialysis to control oxalate), since there is a need to replace some of the key function normally carried out by the kidney but oxalate is controlled by lumasiran.

Since ECM does **not** have the ability to normalise oxalate overproduction, it is assumed that 100% of the ECM cohort in the CKD 4 and ESKD health states receive high-intensity dialysis to delay oxalate accumulation and (in the case of ESKD) replace renal function.

b. Alnylam acknowledges that the assumption that treatment with lumasiran is 100% effective in controlling oxalate and treatment with ECM is 0% effective in controlling oxalate is subject to some uncertainty. These values were selected as a simplifying assumption in the absence of definitive data to inform these values. Nevertheless, we believe these values are plausible, for several reasons:

- As described in the response to Question B8a, ECM does not normalise oxalate in patients with PH1, as acknowledged in the literature[31,55] and demonstrated in the placebo arm of the ILLUMINATE-A trial.[5]
- Large changes from baseline urinary oxalate and plasma oxalate were observed with lumasiran.[5]

- None of the patients in the placebo arm achieved near-normalisation/normalisation of urinary oxalate overproduction, while in the lumasiran arm, 84% achieved near-normalisation and 52% achieved normalisation at Month 6.[5]
- The oxalate-lowering effect of lumasiran is maintained through 12 months; 87.5% of patients treated with lumasiran in the double-blind period and who remained on lumasiran for a further 6 months achieved near-normalisation of urinary oxalate overproduction.[57]
- A comparable proportion of patients randomized to placebo who received 6 months of lumasiran from Month 6 achieved near-normalisation (77%).[57]

Alnylam believes that this is sufficient evidence to support the assumption that treatment with ECM is 0% effective in controlling oxalate and that treatment with lumasiran is effective in controlling oxalate in most patients. Nevertheless, we have provided a new version of the model in which these values can be changed by the ERG and NICE technical team.

c. A scenario analysis was added where 100% of CKD4 and ESKD patients in the lumasiran cohort would receive high-intensity dialysis, in line with the assumption in the ECM arm. This scenario can be selected from the dropdown selector added in the Results sheet: “Dialysis in Lumasiran cohort” (2nd option). This scenario was run by applying both costs and utilities associated with high-intensity dialysis to 100% of the lumasiran cohort in the CKD4-controlled oxalate (OxC), CKD4-uncontrolled oxalate (OxU), ESKD-OxC and ESKD-OxU health-states. Table 14 below presents the inputs used to run the scenarios, in line with the inputs applied in the ECM arm and presented in the original dossier along with the source and calculation method. The resulting ICER is [redacted]/QALY, which represents [redacted] compared with the base-case ICER of £[redacted]/QALY (estimated after correcting the transplantation rate as noted in the answer to question B9).

Table 14. Inputs used to run the high-intensity dialysis scenario in the lumasiran arm

Parameter name	Model inputs
CKD4-OxU, paediatric	-0.08
CKD4-OxC, paediatric	0.42
ESKD-OxU, paediatric	-0.18
ESKD-OxC, paediatric	0.22
CKD4-OxU, adults	0.23
CKD4-OxC, adults	0.45
ESKD-OxU, adults	-0.13
ESKD-OxC, adults	0.25
Cycle cost of high-intensity dialysis, adults (£)	32,371.95
Cycle cost of high-intensity dialysis, paediatric (£)	83,632.63

CKD = chronic kidney disease; ESKD = end-stage kidney disease; OxC = controlled oxalate; OxU = uncontrolled oxalate.

Transplantation

B9. Priority question. According to Table D14 of the submission, there is a 100-fold difference in the probability of transplantation for patients in CKD4-OxC and ESKD-controlled oxalate levels (OxC) versus CKD4-OxU and ESKD-OxU. The probability for the CKD4-OxC and ESKD-OxC patients is a conditional probability, i.e. it gives the probability of a transplant given that patients are in CKD4 or ESKD. However, for the uncontrolled patients in CKD4 and ESKD, the probability is unconditional, or simply conditional on being a PH1 patient.

Please provide a conditional probability of transplantation for the uncontrolled group.

Response: To estimate the conditional probability of transplant for patients in CKD4-OxU and ESKD-OxU, we multiplied the total number of PH1 patients (n=250) over the period of observation, by the proportion of CKD4 and ESKD in line with the Singh et al. (2020) study, which is used to define the distribution of the cohort at the start of the simulation. Based on this source, 38% of PH1 patients have CKD4 or ESKD. The resulting transplant probability per year therefore is 0.0113 = 1-(1-33/(250*0.38))^(1/31), where 33 is the number of liver kidney transplants; 250 is the total number of PH1 patients, which is then multiplied by the proportion of CKD4 and ESKD patients, 0.38; and 31 is the total follow-up period in years, i.e. from 1979 to

2010). The probability adjusted into cycle length is 0.007. This was adjusted in the new version of the model and resulted in an updated ICER (discounted) of £[redacted]/QALY, which represents [redacted] compared to the ICER in the submitted dossier.

B10. Priority question. The re-transplantation rate was estimated using data from France in the period 1979 to 2010, as reported by Compagnon et al. 2014. Please comment on the representativeness of these data for current re-transplantation rates in the UK.

Response: Re-transplantation in patients with PH1 is a rare event, which likely explains why we were unable to identify a UK-specific source and thus needed to refer to the unique long-term study by Compagnon et al.[58] We have no reason to expect that there should be meaningful differences between the UK and France in re-transplantation rates for these patients. This assumption was supported by [redacted], who informed us that, "Due to this study being conducted in in France and the length of follow-up it is reasonable to think this would be representative for the UK. There would be no reason to think otherwise."

Notably, the re-transplantation rate does not have a major impact on the ICER.

B11. Please justify the assumption that 100% of patients in CKD4- OxC and ESKD-OxC would be placed on the waiting list for transplantation.

Response: Transplantation is currently the only cure for PH1. The assumption that 100% of patients with controlled CKD Stage 4 or 5 would be placed on the list for transplantation was adopted as a simplifying assumption in the absence of hard data, but it is clinically realistic for two interrelated reasons.

First, current guidelines for the treatment of PH1 recommend that patients with CKD4 or 5 receive combined or sequential liver–kidney transplantation, according to the patient's condition.[1] Pre-emptive organ transplantation planning at CKD3b is recommended to avoid the complications of systemic oxalosis.

Second, experts treating patients with PH1 are aware that the clinical status of the patient immediately prior to transplantation has a significant impact on their post-transplantation survival. In a European study of 127 liver transplants performed in

117 patients over a 20-year period, the clinical status of a patient with PH1 immediately prior to transplantation was found to have a significant impact on post-transplantation survival.[41] Five-year survival was only 45% in patients with poor clinical status and advanced systemic oxalosis, compared with 73% in patients with a fair clinical status and 100% in patients with very good or good status. Plasma oxalate levels are a key component of a patient's clinical status prior to transplantation, to define the risk of systemic oxalosis and determine if a patient with PH1 is a candidate for transplantation.[56,59,60]

Given the guideline-recommended consideration of patients in CKD4 and ESKD for transplant and the demonstrated ability of lumasiran to control oxalate, which should position patients for better outcomes, fewer complications, and longer survival post-transplantation, it is plausible that 100% of patients in CKD4-OxC and ESKD-OxC would be placed on the waiting list for transplantation.

B12. Please explain if the probability of receiving a transplant would alter if, through treatment with lumasiran, the number of patients eligible for transplant increases.

Response: Alnylam does not anticipate that the probability of receiving a transplant would change meaningfully if the proportion of patients with PH1 who are eligible for transplant increases due to lumasiran treatment controlling their oxalate levels, for two main reasons:

- PH1 is such a rare disease that even major changes in the percentage of patients eligible for transplant would have negligible impact in the context of the much larger number of patients with other diseases on the transplant waiting list. To put the comparative numbers in context, 771 liver transplants were carried out in the UK from 1 April 2020 to 31 March 2021 and there were 602 patients on the UK liver transplant list on 31 March 2021,[61] compared with an estimate of only [redacted] patients with PH1 (in any CKD stage) who are currently eligible for lumasiran treatment (see Section 13.1 of the CS).
- With the adoption of the "opt out" organ donation legislation in England and Wales, the supply of donor organs is predicted to become even less limiting than it has been previously.[62]

Health related quality of life

B13. Priority question. Please provide the source for the prevalence rates for the various combinations of systemic oxalosis manifestations and justify why the same values are used for paediatric and adult patients.

Response: The prevalence for each manifestation was obtained from a third-party survey conducted with UK clinical experts.[63] Systemic oxalosis in late-disease patients is known to impact multiple organ systems and therefore manifestations in multiple organs may be observed simultaneously.[64] Nevertheless, to minimize complexity, the survey queried the prevalence of each condition separately, rather than the proportion of patients with any combination of systemic oxalosis manifestations. To estimate the combined impact on HRQoL from systemic oxalosis manifestations, it was necessary to estimate the proportion of the cohort with none, one, two, three, four, or all of the systemic oxalosis complications. A multiplicative, permutation-based approach was used to estimate the probability of each unique combination of systemic oxalosis manifestations. The underlying assumption of this approach is that the likelihood of occurrence of systemic oxalosis manifestations in one organ system is independent from the likelihood of occurrence of systemic oxalosis manifestations in any other organ system. Some examples are provided below:

- the proportion of the cohort with bone manifestation but not the other manifestations was calculated as follows, in which P signifies prevalence: P_bone_only = P_bone X (1 – P_cardiac) X (1 – P_cutaneous) X (1 – P_ophtalmologic) X (1 – P_neurological)
- The proportion of the cohort in a given health state with bone and cardiac conditions was calculated as P_bone&cardiac = P_bone X P_cardiac X (1 – P_cutaneous) X (1 – P_ophtalmologic) X (1 – P_neurological)
- The proportion of the cohort with all manifestations was given by P_all = P_bone X P_cardiac X P_cutaneous X P_ophtalmologic X P_neurological

Both a paediatric and an adult nephrologist were included in the survey and therefore provided a set of prevalence estimates of systemic oxalosis manifestations for paediatric and adult patients separately. The prevalence rates of systemic oxalosis manifestations obtained from the survey split by paediatric and adults are

presented Table 15 below. The average prevalence rates between those reported by the adult and the paediatric nephrologist were applied in the model in an attempt to reduce complexity in the analysis and since overall, they appeared rather similar. In fact, splitting the prevalence rates by paediatric and adults in the model would result in separate prevalence rates for each of five systemic oxalosis manifestations for CKD4 vs ESKD, OxC vs OxU and paediatric vs adult (total of 40 prevalence rates). This in turn would make the estimation of HRQoL more complex since the total utility decrement associated with systemic oxalosis manifestations would need to be estimated separately for paediatric and adults in all health-states.

Table 15. Prevalence by systemic oxalosis manifestation obtained from the third-party survey with UK clinical experts.

	Paediatric nephrologist	Adult nephrologist	Average
CKD4			
Bone	0.30	0.30	0.30
Cardiac	0.00	0.30	0.15
Cutaneous and vascular	0.20	0.10	0.15
Ophthalmologic	0.30	0.05	0.18
Neurological	0.20	0.15	0.18
ESKD			
Bone	0.80	0.80	0.80
Cardiac	0.20	0.60	0.40
Cutaneous and vascular	0.40	0.30	0.35
Ophthalmologic	0.60	0.20	0.40
Neurological	0.40	0.40	0.40

CKD = chronic kidney disease (stage); ESKD = end-stage kidney disease

B14. Priority question. Please provide a scenario analysis where time trade-off (TTO) values are used whenever the vignettes are part of the health state utility value (HSUV) estimation. Please alter the Excel model so that this scenario can be easily selected.

Response: As requested, we added a scenario with TTO utilities obtained from the vignette study to estimate the impact on the HRQoL of the cohort in the model. The scenario can be run by selecting the second option in the dropdown selector added in the Results sheet “Utility from vignette study”. The resulting ICER is £[redacted]/QALY, which represents [redacted] compared with the

base-case ICER of £[redacted]/QALY (estimated after correcting the transplantation rate as noted in the answer to question B9).

Nevertheless, it is important to note that the company does not believe this TTO scenario should be considered of relevance since NICE guidance clearly states that the EQ-5D is the preferred measurement method to measure HRQoL, given the need for consistency across evaluations.[65,66] Thus, using TTO values would not fit the purpose for assessment by NICE as well as our current approach.

B15. For patients with multiple systemic oxalosis manifestations a multiplicative approach was used to estimate the utility.

a. Please justify why a multiplicative approach was used.

b. Please provide a scenario in which an additive approach is used instead.

Response: a. A multiplicative approach was adopted instead of an additive approach in order to pre-empt concerns that quality-of-life deductions assigned to systemic oxalosis manifestations might be overestimated. We used a multiplicative method developed in consultation with John Brazier and the health-economic experts at Sheffield University. The multiplicative approach was developed by Ara and Brazier (2017),[67] and is recommended by the International Society for Pharmacoeconomics and Outcomes Research Good Practices for Outcome Research Task Force.[68] We applied this method by multiplying the utility in the absence of a given condition by the product of the ratios of the utilities for individuals with the conditions to the utility of individuals in the general population.

b. The multiplicative approach was chosen as preferred for the estimation of the combined impact of multiple systemic oxalosis manifestation on the HRQoL of patients since it is less likely to overestimate the incremental disutility of each additional condition. This is because it multiplies utilities from the single conditions, and thus has a relative effect for each additional systemic oxalosis manifestation. On the other hand, the additive method applies the combined absolute disutility from the single conditions on the baseline, and thus assumes a constant absolute decrement on the baseline utility independently of the number of prevalent conditions. As requested, a scenario was run estimating the disutilities of systemic oxalosis

manifestations using the additive approach. Table 16 shows that there is a small difference in the resulting disutilities between the multiplicative and the additive approach, with the multiplicative approach disutilities being slightly smaller than the additive approach disutilities, as expected. The resulting ICER is £[redacted]/QALY, which represents [redacted] compared with the base-case ICER of £[redacted]/QALY (estimated after correcting the transplantation rate as noted in the answer to question B9).

Table 16. Differences in disutilities of systemic oxalosis manifestation estimated using the multiplicative vs additive method

	Total systemic oxalosis manifestation disutility	
	Multiplicative approach	Additive approach
CKD4-OXu, all	-0.101	[redacted]
ESKD-OXu, all	-0.233	[redacted]
Cardiac and neurological complications in CKD4-OXu, children	-0.056	[redacted]
Cardiac and neurological complications in ESKD-OXu, children	-0.131	[redacted]
Cardiac, ophthalmologic and neurological complications in ESKD-OXu, adults	-0.145	[redacted]
CKD4-OXc, all	-0.081	[redacted]
ESKD-OXc, all	-0.190	[redacted]

CKD = chronic kidney disease (stage); ESKD = end-stage kidney disease; OXc = oxalate controlled; OXu = oxalate uncontrolled

Resource use and costs

B16. Priority question. It is assumed that lumasiran is only available in vials of 94.5 mg, with the consequence that on average very large and costly quantities of lumasiran are wasted with each administration.

a. Please explain whether it has been considered to provide lumasiran in smaller quantities per vial to enhance flexibility in dosing and reduce wastage.

b. In case it is possible to provide vials with smaller quantities, then please include this as an option in the model.

c. Please provide calculations in the model that demonstrate exactly how much lumasiran is wasted per administration and per cycle, including the corresponding wastage costs.

Response: a. Alnylam is currently not able to share any plans to provide lumasiran in smaller quantities per vial.

b. We have not provided this option in the model as providing vials with smaller quantities will not be possible.

c. The model base case assumes no vial sharing; i.e., the content of a vial not fully used is wasted. Table 17 below shows how many vials are wasted per administration and per cycle, for the adult and paediatric cohorts, and the associated wastage cost. Based on average paediatric and adult weight in the ILLUMINATE trials, the dose is 3 mg/kg with 3 administrations in the loading quarter (i.e., 3-month period) and 1 administration per quarter for maintenance treatment. Lumasiran vial strength is 94.5 mg.

To address this request and make the impact of vial wastage fully transparent in the model, an option has been added to run the analysis including the possibility of vial sharing. This option can be selected by choosing the second option of the dropdown selector “Vial sharing” added in the Results sheet. If vial sharing is included, the resulting ICER would be £[redacted]/QALY, which represents [redacted] compared with the base-case ICER of £[redacted]/QALY (estimated after correcting the transplantation rate as noted in the answer to question B9).

Table 17. Lumasiran wastage estimation

	Paediatric	Adult
Weight, kg	[redacted]	[redacted]
Dose per administration (loading or maintenance), mg	[redacted]	[redacted]
Wastage per administration (loading or maintenance)		
N vials with vial sharing	[redacted]	[redacted]
N vials with no vial sharing	[redacted]	[redacted]
Wastage in mg	[redacted]	[redacted]
Wastage in cost	[redacted]	[redacted]
Wastage in cycle 1 (one quarter of loading and 1 quarter maintenance admin)		
N vials with vial sharing	[redacted]	[redacted]
N vials with no vial sharing	[redacted]	[redacted]
Wastage in mg	[redacted]	[redacted]
Wastage in cost	[redacted]	[redacted]
Wastage from cycle 2 (maintenance)		
N vials with vial sharing	[redacted]	[redacted]
N vials with no vial sharing	[redacted]	[redacted]
Wastage in mg	[redacted]	[redacted]
Wastage in cost	[redacted]	[redacted]

B17. Priority question. Please provide details and documentation of all clinical expert opinion that was used to inform and validate the cost-effectiveness model. This includes:

- **annual resource use of laboratory tests, procedures, and visits that was obtained from a survey completed by UK clinical experts;**
- **the third-party survey with UK clinical experts on the prevalence of systemic oxalosis complications in CKD4 and ESKD with uncontrolled oxalate and reductions relative to those with controlled oxalate;**
- **expert opinion that was used to validate key model inputs and assumptions from a clinical perspective.**

Response: Expert clinical opinion informing health care resource utilisation (i.e., annual resource use of laboratory tests, procedures, and visits) and the prevalence on systemic oxalosis complications was obtained through a study led by Tolley Health Economics and commissioned by Alnylam.[63] We are enclosing the report for this study with our response.

The methodology selected by Tolley Heath Economics for this study was a structured expert exercise (SEE), using a modified version of the SEE framework developed by the Centre for Health Economics, University of York, UK to account for the ultra-rare context of PH1.[63] A total of 3 UK experts participated in this study (an adult nephrologist, a paediatric nephrologist, and a transplant surgeon). All experts had recent experience in treating patients with PH1 in the UK and were considered to have the relevant, up-to-date, knowledge and experience of PH1.

An elicitation protocol was developed consisting of a semi-structured discussion guide with questionnaire.[63] These were sent to each expert with a request to provide responses prior to a video conference interview, with both mailing of the questionnaires and interviews taking place in September 2020.

In addition to this, expert clinical opinion was used to validate key model inputs and assumptions from a clinical perspective. This is described in section 12.2.5 of the CS. A web-based interview with the paediatric nephrologist was conducted on 21 September 2021, whilst two web-based interviews with the adult nephrologist were

conducted on 8 October and 1 December 2021. These validation interviews were not recorded in a structured fashion but instead informal notes were taken, and thus no study reports are available.

B18. Priority question. In Table D23 of the submission it is noted that the consultant paediatric nephrologist estimated that among paediatric patients with PH1 who are receiving intensive dialysis for management of systemic oxalosis and/or ESKD, 100% would be expected to receive daytime haemodialysis and that smaller percentages would also receive night-time peritoneal dialysis 7 days per week (~60%) or night-time haemodialysis 6 days per week (20%).

a. Please explain whether and, if so, how this information was used in the model.

b. If this information was not used in the model, then please provide the option to use it.

Response: a. The submitted model assumes that 100% of the paediatric cohort receives daily haemodialysis alone based on the third-party survey with UK expert clinicians.[63] The interview with the consultant paediatric nephrologist suggested that a proportion of paediatric patients receives nocturnal (home) dialysis in combination with diurnal haemodialysis. However, to be conservative this was not included in the submitted base-case scenario since there was some uncertainty on the actual prevalence reported by the clinician.[63]

b. As requested, a scenario was added to the model which estimates the average cost of high-intensity dialysis per cycle based on the dialysis patterns suggested by the consultant paediatric nephrologist in the UK.[63] The scenario can be run by selecting the second option in the dropdown selector “Dialysis in paediatric cohort” added in the Results sheet. The inputs used to run this scenario are fully aligned with the paediatric dialysis scheme suggested by the consultant paediatric nephrologist in the UK and are presented in Table 18. Considering that 20% of the paediatric cohort would receive diurnal haemodialysis alone (6 x week), 60% diurnal haemodialysis (6 x week) + nocturnal haemodialysis (6 x week) and 20% would receive diurnal haemodialysis (6 x week) + nocturnal peritoneal dialysis (7x week), the estimated average cost per model cycle for paediatric dialysis is £84,288. This average cost

per cycle is slightly higher than the average cost used in our base-case analysis based on 100% daily diurnal haemodialysis alone (£83,633). The resulting ICER is £[redacted]/QALY, which represents [redacted] compared with the base-case ICER of £[redacted]/QALY (estimated after correcting the transplantation rate as noted in the answer to question B9).

Table 18. Inputs to model high-intensity dialysis in paediatric cohort in line with advice from consultant paediatric nephrologist in the UK

	% paediatric cohort	N sessions/ week	Unit cost / session	Source of unit cost	Cost per cycle
HD diurnal	100%	6	£458	NHS Reference Cost 2019/20,[69] Renal dialysis for chronic kidney disease, Weighted average of tariffs LD02B, LD06B, LD010B	£71,685
HD nocturnal (add-on to HD diurnal)	20%	6	£99	NHS Reference Cost 2019/20,[69] Renal dialysis for chronic kidney disease, Tariff LD010B	£15,559
PD nocturnal (add-on to HD diurnal)	60%	7	£87	NHS Reference Cost 2019/20,[69] Renal dialysis for chronic kidney disease, Tariff LD12B	£15,819

HD = haemodialysis; PD = peritoneal dialysis

B19. According to page 150 of the submission, costs were inflated using the Consumer Price Index (CPI) for the UK, but no reference is provided.

Please confirm that the CPI refers to the UK NHS Cost inflation Index (NHSCII; as provided in Table 20 in Appendix 5) or explain which source was used.

Response: Until 2014/15, the model used the Hospital & Community Health Service (HCHS) pay and prices Index.[70] From 2015/16 the model used the NHS cost Inflation Index (NHSCII) pay and prices Index.[71]

B20. The cost of systemic oxalosis complication 'bone' was assumed equal to the annual cost of distal forearm fractures from Borgström et al. 2020 and converted into GBP.

a. Please justify the plausibility of this assumption and relevance of these costs to the UK.

b. Please consider the use of UK cost estimates, for example as used in NICE technology appraisal (TA) 464.

Response: a. The study by Borgström et al. 2020 reported the burden and management of fragility fractures in 6 countries in the European Union, including the UK.[72] The study therefore reports country-specific estimates for the UK and therefore can be trusted as representative of the cost of bone disorders in the UK. Costs are reported in Euros to allow cost comparison between the 6 European countries included in the study, which was one of the main objectives. Nevertheless, this should not indicate the cost estimates are less relevant for the UK.

b. As mentioned in the answer to part A, the UK cost reported in Borgström et al. 2020 was estimated specially based on UK healthcare resource use and unit costs and therefore it is relevant for the analysis from the perspective of the UK. Nevertheless, we also reviewed the documentation associated with the appraisal TA464, as requested. We could not identify a cost estimate that would be representative of all resource use associated with bone complications, as provided in the study by Borgström et al.. For this reason, we could not run an alternative scenario based on this appraisal. Please note, that an earlier study by Borgström was also referenced in this appraisal "Borgstrom F., Strom O., Coelho J., Johansson H., Oden A., McCloskey E.V. et al. The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX. *Osteoporosis International* 2010; 21(3):495-505".

B21. Please justify the plausibility of the assumption that the cost of systemic oxalosis complication 'cutaneous and vascular' was assumed equal to the annual cost of stroke.

Response: The definition of stroke is an abrupt onset of neurological deficit secondary to a vascular event. Thus, the origin of the disease is due to a vascular alteration. In fact, the treatment cost for stroke is expected to be similar to the cost of other vascular disorders due to vascular occlusion or hyper-coagulability states such as peripheral artery disease, carotid and vertebral artery disease (extracranial segments) or vascular stenosis. These disorders involve hospitalisation in acute phases (including laboratory testing, vascular imagining techniques to assess the severity of the occlusion and location), and ongoing treatment with antithrombotic therapy, endovascular management or open surgery (depending on the characteristics and the severity of the vascular damage) with recurrent visits/examinations to assess disease control and reduce the risk of cardiovascular events by a multidisciplinary team.[73]

B22. Please justify the plausibility of the assumption that the cost of systemic oxalosis complication 'neurologic' was assumed equal to the cost of neuropathic pain.

Response: Neuropathic pain is defined as pain caused by a lesion or disease of the nervous system (somatosensory), so the origin of the pain is from a neurological alteration. The management of neurologic conditions such as trigeminal neuralgia which is a close proxy to cranial nerve involvement (common findings in PH1 neurologic manifestations), is comparable to the management of neuropathic pain, with use of anticonvulsants, opioid analgesic, nonsteroidal anti-inflammatory drugs, serotonin-noradrenalin reuptake inhibitors and tricyclic antidepressants.[74]

B23. Please justify the choice of always using a value of 10% of the base-case value when standard errors were not available, rather than taking the amount of natural variation into account.

Response: A conventional 10% was applied to estimate the standard error in cases where no additional data were available to infer a more specific value. This approach is in line with the method used in NICE HST10 and HST16 and accepted by the ERG and Committee.

B24. Please could you confirm if any of the drug costs in the model would fall under a primary care setting?

Response: Alnylam considers the cost of pyridoxine and potassium citrate could fall under a primary care setting.

B25. Please compile a table which lists all the treatments that have been modelled in your base case results and all other analyses, making sure to include:

a. the intervention, comparators, any subsequent treatments, concomitant or pre-medications (as appropriate)

b. the strength, form/mode of administration, pack size, list price (and source) for each treatment included in the table.

Response: a. – b. Table 19 below includes the list of treatments modelled with the requested information.

Table 19. Information on treatments included in the model

	Strength	Form/mode of administration	Pack size	List pack price	Source
Lumasiran - Oxlumo (Intervention)	94.5mg/0.5ml solution for injection in vial	Subcutaneous administrations Loading dose: • kg<10: 6mg/kg, 3 administrations/quarter • 10≤kg<20: 6mg/kg, 3 administrations/quarter • kg≥20: 3mg/kg, 3 administrations/quarter Maintenance dose: • kg<10: 3mg/kg, 3 administrations/quarter • 10≤kg<20: 6mg/kg, 1 administration/quarter • kg≥20: 3mg/kg, 1 administration/quarter	1 vial	£61,068.98	MIMS, accessed 12/2021
Vitamin B6-Pyridoxine (Concomitant treatment / part of established clinical management)	50mg tablet	Oral administration Dose: 8mg/kg administered daily	28 tablets	£21.93	MIMS, accessed 11/2021
Prednisolone (Medication post-transplant)	10mg tablet	Oral administration Dose: 16.5mg administered daily	28 tablets	£9.66	MIMS, accessed 11/2021

Section C: Textual clarification and additional points

C1. Please clarify what is meant by *"A pragmatic filter to identify systematic reviews or meta-analyses"*.

Response: We did not use an acknowledged search filter to identify these publication types. The search approach was based on the combination of controlled indexing terminology (MeSH or Emtree) or free-text search terms. Systematic reviews (SRs) and meta-analyses (MAs) were not eligible for inclusion in the SLR but handsearching of SR/MA bibliographies was planned for any relevant records in order to identify eligible studies not found via the other search methodologies. The SLR did not identify any relevant SRs or MAs for manual handsearching.

C2. In the SLR report, Table 1 states that there were English language restrictions, whereas page 2 of the document states that no restrictions were imposed. Please explain this discrepancy.

Response: Both statements are accurate. The statement on page 2 pertains to the searches. The searches were broad and did not incorporate any language restrictions. Table 1 details the PICOS criteria that were used during the study selection stage. At the study selection stage, studies published in languages other than English were excluded. Studies excluded based on language are recorded in Appendix F: List of excluded publications.

C3. For the ILLUMINATE A trial, only paediatric patients aged 6 years and older were eligible; whereas Table C1 of the submission states that : "Adult and paediatric patients of any age were eligible". Please explain the discrepancy and discuss the implications for the estimation as well as for generalisability to the NHS setting in England and Wales.

Response: Table C1 in the CS refers only to the search strategy used in the SLR, in which no studies were excluded based on patient age distribution. The actual age ranges for the patient populations in the different ILLUMINATE studies are reported in the respective study result sections.

C4. As per Table C7 of the submission, plasma oxalate, mean (SD), µmol/litre seems to range significantly from mean standard deviation (SD) 13.24 (6.500) to [redacted]. Please clarify whether these values are within the normal range.

Response: The variation in POx levels documented in CS Table C7 corresponds to differences in population of interest across the different Phase 3 studies of lumasiran and is reflective of the relationship between POx and renal function. As expected given the relationship between increased POx and decreased eGFR, mean POx levels were higher in the ILLUMINATE-C study ([redacted]), which involved patients with advanced CKD—primarily CKD4 and ESKD—and considerably lower in ILLUMINATE-A (14.8 µmol/L in the lumasiran arm and 15.5 µmol/L in the placebo arm) and ILLUMINATE-B (13.24 µmol/L), both of which involved patients with relatively intact renal function. POx concentrations in healthy adults and children have been reported to fall within the range of 1–5 µmol/L,[75] such that the mean POx concentration observed in the ILLUMINATE-C study population was well above the normal range, while mean POx concentrations in the ILLUMINATE-A and ILLUMINATE-B study populations were also above the normal range, albeit to a lesser extent.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Metabolic Support UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Metabolic Support UK is a non-profit patient umbrella organisation, supporting patients and families worldwide living with Inherited Metabolic Disorders. Metabolic Support UK receives it's funding from corporation, community fundraising and grants, trusts and giving. Metabolic Support UK supports over 2000 members worldwide.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered from an online survey issued via social media channels and direct mailing. This survey was designed by Metabolic Support UK, along with input from the Oxalosis and Hyperoxaluria Foundation (OHF) and Rare QOL, to support the response to this submission. Information has also been gathered via a broad search on social media to identify further commentary from patients and families regarding the use of Lumasiran and via 1:1 patient interview, conducted by Metabolic Support UK.
Living with the condition	
6. What is it like to live with the condition? What do carers	Primary Hyperoxaluria is characterised by excessive amounts of oxalate in the blood and urine. There are three forms of this disorder. Type 1 is caused by a fault in the AGXT gene which leads to a deficiency of a liver enzyme called AGT. This causes the liver to produce too much oxalic acid which the body cannot get rid of and it forms crystals. With time oxalosis can occur

experience when caring for someone with the condition?	which is when the oxalate crystals are deposited in other organs such as the eyes, skin, muscle, and heart. . Primary Hyperoxaluria Type 1 is a very rare and debilitating disease, people living with PH1 experience the following symptoms. - Cardiac issues - Visual impairment - Swelling in hands and feet - Failure to thrive (infancy) - Decreased kidney function including frequent kidney stones - Kidney failure - Continual pain and fatigue - Hypermobility - Weakness of joints - Frequent Urinary Tract or Kidney infections (Pyelonephritis) - Loss of appetite. - excessively dry skin - slow bowel motility/irritable bowel syndrome The physical and psychosocial impact of living with PH1 is significant. In a recent survey conducted by MSUK, OHF and Rare QOL, a majority of respondents rated their quality of life as 'poor'. We asked patients and parent/carers to indicate which of their daily activities have been most impacted or they unable to do, as a result of Primary Hyperoxaluria type 1, the top three activities were attending school or work, socialising, and travelling and participating in planned events and activities. Renal failure in patients living with PH1 often results in the patient requiring dialysis and eventually a transplant. Without effective treatment kidney failure occurs in patients at a young age and reduce life expectancy. Even with treatment, the above symptoms mean that attendance at school is challenging due to ill health, giving limited opportunity to be able to eventually gain full time employment. The psychosocial aspects of this condition can be devastating, and every aspect of life is challenging and has a significant impact for both patients and caregivers. The support required for daily living demands an arduous regime, a cycle of medication administration alongside navigating the impact that those medicines have on the patient. Children rely on their parents or carers to support them to manage and administer medicines. We interviewed a young adult living with PH1 who advised that their parents struggled to understand and manage the condition and when they reached adulthood they sought help from a peer support group. Due to the nature and complexities of the condition, despite being

	eligible for transition to adult care, the patient remains under the care of paediatrics. There was a general consensus amongst those we interviewed that living with PH1 is physically and emotionally draining and has a detrimental impact on the patient's ability to socialise and take part in activities, in some cases this has led to bullying and deterioration in mental health. People living with PH1 are often under the care of a nephrologist, urologist and genetic/metabolic specialist and required to attend multiple hospital appointments, this in itself impacts school and work attendance. ***Case Study 1 (Anonymised)*** Parent/carer X has two children living with PH1, patient Y and patient Z. Patient Y was diagnosed with severe infantile PH1 when seven months old and experienced severe renal failure. Patient Z was diagnosed at the age of two, with less severe PH1 and as a result of genetic testing, following patient Y's diagnosis. Patient Z required emergency kidney stone surgery following a scan and has been advised that they will require a liver transplant when they reach teenage years. Patient Z suffers from multiple stomach aches and recurrent kidney stones. Patient Y is currently dialysis dependent and has received a liver transplant, the parent/carer describes the patients bones as 'fragile and wrecked' and patient Y also experiences deposits in their eyes.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most patients manage their condition via prescription medications such as Vitamin b-6, diuretics, and baclofen. 50% of patients who took part in our survey stated prescription medication is often followed by a kidney or liver transplant as a form of treatment and condition management. A majority of the patients and carers we surveyed, indicated that they feel current treatment options enable them to control the condition and symptoms well, however 7% stated their treatment plan does not help them control the condition or symptoms at all. The biggest drawbacks of current treatment and care are having to intake a 'demanding' number of fluids alongside continuous medication, an increased amount of hospital visits and admissions as the disease progresses, having to rely on transplant organs or consider the possibility of future transplants which comes with its own risks and challenges such as anxiety regarding rejection, surgical complications, and further medication. Dialysis is a long time consuming and life debilitating process which makes it difficult to try other treatment plans. In summary, patients and carers often find the current treatment for PH1 debilitating, anxiety inducing and onerous, with much uncertainty or hope for the future. The top two priorities regarding future treatments are stopping or slowing disease progression and preventing the formation of kidney stones.

	Case Study 1 (continued) Current treatment regime for Patient's Y and Z includes daily potassium citrate and pyridoxine to prevent kidney stones. Parent/carer X advised they have issues with adherence and described the treatment as "*a vile medicine which you have to drink and it's like pure lemon juice, very difficult to get a child to take it".* Drinking lots of fluids is also part of the current treatment regime for patient Y and Z and this in itself impacts quality of life. Patient Z received a ureteroscopy when they were younger and as a result, high intake of fluids results in frequent incontinence, patient Z is currently aged 10. Parent/Carer X advised *"there has been a battle at school who don't understand why it is necessary for her to leave the classroom so often for the toilet".* Parent/Carer X advises they want to avoid dialysis or future transplants in reference to Patient Z, having experienced a transplant with patient Y they believe transplants are 'life-altering' and 'hugely disruptive', they also raised concerns regarding immunosuppression and the longevity of how long a transplant will work. -
8. Is there an unmet need for patients with this condition?	Yes, there are several unmet needs for patients with this condition. 1. There is a lack of understanding amongst general health practitioners resulting in patients becoming 'stuck' in incorrect systems and risks of misdiagnosis. 2. Limited treatment options result in the patient suffering from kidney stones and often requiring surgery at a young age, impacting their quality of life. The current treatment regimen requires patients to intake a demanding number of fluids alongside medication, which is onerous and also impacts adherence, particularly for younger patients. 3. There is a lack of psychosocial support for patients with this condition and their mental and social needs often go unmet due to a lack of understanding.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and carers believe Lumasiran provides the following advantages. - It prevents further build-up of oxalate throughout the body by stopping or reducing the overall production. - It prevents the need for future liver or kidney transplants - Administration of treatment is easier and less onerous, requiring only one injection per month instead of continuous pills and fluids which have little to no impact. - It improves quality of life - It would slow/stop disease progression leading to a 'normal life'

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients and carers think the disadvantages of Lumasiran are the eligibility criteria, those who are on long term dialysis are ineligible, administration via injection could prove difficult especially with young children and there is concern regarding unknown side effects of the treatment. **Case Study 1 (continued)** Patient Z has a significant needle phobia, and this is a barrier for her and parent/carer X, when considering new treatments such as Lumasiran. Patient Z was on a clinical trial for Lumasiran but didn't finish the treatment due to an inability to undergo blood tests as a result of patient Z's needle phobia. However, parent/carer X advised should the benefits outweigh the negatives and patient Z's pain begins to ease and quality of life improve, it would be much easier to consider future treatments such as Lumasiran as a form of treatment. Patient Z expressed they would like to 'feel more normal' and parent/carer X feels this medicine may give them the chance to.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is our view that all current and future patients living with PH1 and eligible for this treatment will benefit from the technology. Younger patients will benefit as the treatment has the potential to reduce or remove the need for kidney surgery or transplants, improving overall quality of life.
Equality	
12. Are there any potential equality issues that should be considered when considering this condition and the technology?	No, providing the commissioning of this technology follows the NHS Equality and Diversity guidelines, we do not envisage any potential issues in regard to equality or equity, with this technology.

Other issues	
13. Are there any other issues that you would like the committee to consider?	None.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The psychosocial and physical impact of living with PH1 is significant, with a majority of patients rating their quality of life as 'poor'.
- Current treatment options often involve surgery and are onerous, difficult to adhere to and significantly impact quality of life. Patients are required to intake large volumes of fluid alongside medication and often struggle to do this.
- Patients believe lumasiran offers multiple advantages including a simplified treatment regime, improved quality of life and reduced risk/need for kidney surgery.
- Some parents/carers are concerned treatment could result in needle phobia, however MSUK and other patient organisations are working with the NHS to develop resources regarding this. This is a fear amongst many rare disease parent/carers where administration of treatment via injection is the only option.
- There are multiple unmet needs for people living with this condition, many of these are beyond NICE's scope and remit but unmet needs should be taken into consideration during the evaluation process, as the technology has the potential to improve and address some of these.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	The Renal Association (now known as the UK Kidney Association) • Also on behalf of Metabolic Kidney Stones Unit, Royal Free Hospital

3. Job title or position	Consultant Nephrologist and Honorary Associate Professor
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK Kidney Association (formerly known as the Renal Association) is the main professional body for the UK renal community including doctors, nurses and scientists. It is a charity and funded by its members as well as grants for specific projects. RADAR (the national renal rare disease registry) is an NIHR portfolio clinical research registry with secure data storage of more than 26000 patients over 15 years.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To stop progression of systemic oxalate deposition in primary hyperoxaluria type 1 (PH1). For an individual patient, this may be manifested as stabilisation/reduction in kidney stone formation (e.g. in less severely affected patients), stabilisation of kidney function (e.g. in more severely affected patients), or stabilisation of organ/skin/eye damage (e.g. in the most severely affected paediatric patients).

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In adults, stabilisation of kidney function (eGFR) measured over at least 2-3 years; reduction in kidney stone formation (measured by imaging or symptoms) over at least 2-3 years; and potentially, avoidance of need for liver transplantation in PH1 patients transplanted with kidney alone (measured over at least 2 years).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The only other disease-modifying drug in PH1 is pyridoxine, which is clinically effective in less than 25% of all PH1 patients, depending on genetic mutation. Therefore there is no currently available treatment for pyridoxine non-responders with progressive disease. Allowing the disease to progress untreated often leads to severe clinical end-organ damage, which can lead to the need for transplantation, which is expensive, difficult for the patient, and has generally unfavourable long-term outcomes as it affects the whole body not just the kidneys.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Pyridoxine (vitamin B6) is attempted where possible but often does not produce a clinical effect. Supportive measures include hyperhydration and potassium citrate but these do not affect the course of the disease to any great extent. There are no useful dietary treatments. Also see question (8) above.
• Are any clinical guidelines used in the treatment of the	Most recent published guidelines are from 2012 and now out of date (PMID: 22547750 DOI: 10.1093/ndt/gfs078). New European guidelines written by a committee of OxalEurope (I am a co-author) have been submitted for publication to Nature Reviews Nephrology (Jan 2022; in confidence), and these

condition, and if so, which?	reflect European consensus views, including recommendations on the use of RNAi drugs (such as lumasiran) using or extrapolating from published data as of late 2021.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Care pathway until the point of considering new therapies is reasonably defined. One major problem is that PH1 diagnosis in adults often occurs very late, often resulting in the immediate need for renal replacement therapy with few other therapeutic options outside clinical trials. However, there is mostly consensus regarding treatment plans among clinical experts in PH and informal discussions about patient care by phone and email have taken place for many years. We are now trying to formalise this via the NHS Rare Disease Collaborative Network for Hyperoxaluria (https://ukkidney.org/rare-renal/patient/hyperoxaluria-0#collapse9 bottom tab) and plans for the pathway are outlined in Objective 1: "Creation of a virtual clinical pathway which is nationally available", planned for 2022.
• What impact would the technology have on the current pathway of care?	It is likely to change it considerably. The benefits may best be realised by early deployment of RNAi in many cases. This would require (a) improved efforts and faster mechanisms for diagnosis of suspected cases (b) formalisation of the clinical pathway so that advice, treatment and monitoring are all provided in a timely fashion and response to treatment is monitored.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, its use will be very different. Unless pyridoxine-sensitive (<25%), there is no current disease modifying therapy. The RNAi drugs are the second therapy (after pyridoxine) to potentially do so.
• How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	All aspects of care of PH1, including diagnostics, treatment and monitoring should be supervised by clinical experts. This has always been the case, even though mechanisms until now have been informal. Therefore the technology should be authorised and monitored via national specialist clinics. We think that there is a good opportunity to provide this service virtually, e.g. specialist review occurring via videoconference MDT (as outlined in https://ukkidney.org/rare-renal/patient/hyperoxaluria-0#collapse9). The actual administration of the drug could then occur locally, most likely via a secondary care clinic or even at home (as we are doing with clinical trials now), supervised by the patient's local hospital team.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Specialist review by national expert committee. This would allow clinical oversight and monitoring of effect. NHS resources to convene and formalise such an MDT at national level would be required. Fortunately, much of the required infrastructure is already running in the renal community, so this function could be added in at low cost. Mechanisms for secure data capture (national RADAR database hosted by UK Kidney Association, functional for 15 years and has data on >20,000 UK patients) and models of national clinical decision making (e.g. National Amyloidosis Centre and National Complement Therapeutics Centre) already exist and have excellent track records in terms of cost effectiveness and international reputation. We strongly recommend utilising these resources for NHS clinical oversight and monitoring, as part of the establishment of a virtual national specialist centre for hyperoxaluria, building on the NHS Rare Disease Collaborative Network established in 2021. The UK is in an excellent position to lead internationally on this.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, when used in appropriate patient groups the data show that there is potential to stabilise the condition. If so, this could result in a reduced rate of kidney stone formation (and hence reduced need for urological operations) and slower progression to endstage renal disease (hence delaying the need for renal replacement therapy). These benefits are already realised in pyridoxine-sensitive patients with PH1.
• Do you expect the technology to increase length of life more than current care?	Yes, especially in the paediatric patient group. Patients diagnosed very early in life stand to benefit the most in terms of prolongation of life.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes, see (11) above.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The treatment is subcutaneous injection monthly/every three months which is easy to administer in hospitals or community. Published data show that injection-related adverse events are mild. The majority of the monitoring required is therefore for effectiveness rather than safety (although long term safety is yet to be established). This is best facilitated by concurrent national decision making and monitoring systems as outlined in (10) above. Patient groups such as Metabolic Support UK, the Oxalosis and Hyperoxaluria Foundation and PH-Europe are active in promoting new treatments and informing clinicians and industry about patient acceptability, and they would be in a good position to contribute to this.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start rules: See (9) and (10) above. (a) It is essential that expert review occurs as described above, e.g. to prevent misdiagnosis and hence inappropriate treatment with this expensive new technology e.g. exclusion of enteric hyperoxaluria. (b) European guidelines are in press, but these will need to be adapted to a UK context. Stop rules: we need to build the clinical evidence base for outcomes from NHS/renal community rather than purely via industry-sponsored long term follow up studies. This is the only way that clinically-led stop decisions can be validated. Current industry-sponsored studies have no stop mechanism unless for safety. National data collection and ongoing validation can be easily achieved at minimal cost via existing RADAR and RDCN mechanisms described above, and we strongly recommend their utilisation.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Publicity about the availability of the technology may increase the referral rate for metabolic work up of stones, which may increase the numbers diagnosed with PH1 and hence treated. It will also lead to the diagnosis of other rare stone-forming disorders, many of which are treatable using currently available treatments.

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. The published data show a very profound and impressive initial clinical effect. This technology has the potential to be revolutionary. It is one of the few major breakthroughs in the prevention of kidney stones in the last few years. The current management with transplantation is suboptimal and survival is poor. siRNA therapy has proven to be similarly beneficial in other disease areas e.g. hereditary amyloidosis.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Major unmet need is pyridoxine non-responders who until now have had no disease-modifying treatment available.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Published data and our clinical and research experience show mainly minor side effects so this is unlikely to be a problem.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	There is no precedent for RNAi drug usage in this condition. However the patient population in the trials reflected the likely major subsets of future UK clinical usage. In fact other criteria for usage, such as peri-transplantation, may also be clinically indicated in some cases but have not yet been tested in clinical trials. Other criteria, such as patients already on dialysis, are the subject of ongoing clinical trials. Data will also be available, in 2022 or 2023, from the competitor product nedosiran.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Rate of eGFR decrease; kidney stone formation. There were attempts to measure these as secondary outcomes in published and ongoing trials. However 6-12 months is not a long enough time period to convincingly show an effect for either of these outcomes. Therefore the lack of effect demonstrated in published trials should not be taken as evidence of lack of efficacy in the longer term.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	All published trials have used urine oxalate excretion as the primary outcome measure. This is an internationally agreed surrogate marker in PH1 (PMID: 32165440). There is less controversy about this in PH1 than for PH types 2 and 3, as there is a higher correlation between urine oxalate excretion and longterm clinical outcomes in PH1.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	Alnylam are collecting data on patients taking lumasiran via its EAMS scheme. Treatment decisions are made by an expert clinician independent of clinical trials and therefore it is used in situations where there is urgent/severe clinical need but no trial is available or criteria are not met. This represents real-world use to an extent (e.g. for the extended indications given in 18a above), and data from these could be sought from the company.
Equality	

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Ease of access for patients from all areas of the country to have suitable diagnostics as the initial step in the care pathway. Possibly the greatest inequality risk would be those that have clinical features of primary hyperoxaluria but are not referred for assessment to a specialist centre because of distance or inadequate referral pathways. Virtual pathways, as outlined in (9) above, can help with this. Industry support for increased diagnostics across the population (especially funding for diagnostic genetics) would be helpful. There is a precedent for this e.g. enzyme replacement in Fabry disease, where industry sponsors diagnostic testing and educates clinicians. Data from RADAR and clinical experience nationally suggests a disproportionately high incidence in certain families of non-white ethnicity and especially where there is consanguinuity, and extra efforts are needed to allow these patients to be diagnosed.
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- This technology represents a step-change in the treatment of a life threatening condition, and meets an area of clinical need.
- We recommend that clinical oversight of treatment decisions and monitoring should be in the hands of the UK renal community rather than industry, using existing infrastructure that has proven effective: clinical networks (RDCN), a secure registry (RADAR) and experience of managing high-cost renal drugs in the NHS (national amyloid and complement centres)
- As part of this appraisal, equal attention should be given to diagnostics (upstream of the proposed care pathway), ensuring that clinical services are in place to identify patients early so that the technology can be used to prevent accumulating end-organ damage.

Thank you for your time.

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Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation NHS England & Improvement

Please indicate your position in the organisation: Medical Advisor, Highly Specialised Services, NHSEI

- Department of Health or Welsh Government in general?
- commissioning services for the Department of Health or Welsh Government specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)?
- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There are no NHSEI national clinical commissioning policies for the treatment of this condition. Use of the drug to date has been through trials.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

The treatment of these patients is currently undertaken in adult specialist renal services, adult renal transplant centres and specialist renal services for children. NHSEI is the responsible commissioner for these services.
Two adult and two paediatric specialist renal centres are members of the Hyperoxaluria Rare Disease Collaborative Network (RDCN). RDCNs are made up of providers with an interest in a particular rare disease and are committed to working together to progress research, increase knowledge and improve patient experience and outcomes. These are not commissioned services but would provide a structure through which the drug could be distributed if it were approved by NICE.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

If the technology were recommended this would represent a step-change in the care of these patients.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

Please see previous response.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

The budget impact has not been estimated. Factors to be considered are the list price, the current and future patient population and the effectiveness of the drug in preventing long term complications.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

There may be reduced need for dialysis and organ transplantation specifically for patients with hyperoxaluria. However, given the small number of patients with the condition and the high volume of need for both these interventions for other clinical indications this will not have a material impact.

Would there be any need for education and training of NHS staff?

If the drug were approved there may need to be awareness raising amongst referrers. No additional training is required.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No additional considerations

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

No other issues

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Wesley Hayes
2. Name of organisation	British Association for Paediatric Nephrology

NICE National Institute for Health and Care Excellence

3. Job title or position	Consultant paediatric nephrologist, Great Ormond Street Hospital, London
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. To prevent kidney stone formation 2. To ameliorate/prevent progression to kidney failure 3. To prevent systemic oxalosis (calcium oxalate damage to eyes, skin, bone marrow, heart)
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An accepted surrogate marker of kidney failure risk is urinary oxalate excretion in patients with urine output. A reduction on urinary oxalate excretion to normal or near normal reference limits for age would be highly clinically significant.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Some children with PH1 progress to kidney failure, currently treated with liver and kidney transplant. Infantile oxalosis has a high mortality risk in the first year of life. Whilst a minority of patients with PH1 respond to pyridoxine, for the majority of patients with PH1 there was no effective treatment prior to siRNA therapies.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Operative procedures to remove recurrent kidney stones. Dialysis for kidney failure followed by liver and kidney transplantation. Pyridoxine treatment for a small minority who respond to this. High fluid intake, and potassium citrate to inhibit calcium oxalate crystal agglomeration in the urine.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	I am not aware of a current clinical guideline.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	PH1 is a rare condition, so delays in diagnosis are common. Paediatric patients are generally managed in specialist centres.
• What impact would the technology have on the current pathway of care?	Lumasiran siRNA treatment has the potential to significantly reduce the number of kidney stone procedures, delay or stop progression to kidney failure, and remove the need for liver and kidney transplantation.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	In current NHS clinical practice, approximately 8 children are treated with Lumasiran via the early access medicines scheme, with 4 children receiving Lumasiran within open label extension phases of 3 clinical trials. Lumasiran treatment differs markedly from current care. It is administered by subcutaneous injection 1-3 monthly. Current treatment: Potassium citrate and pyridoxine taken by mouth at home, kidney stone procedures undertaken during brief hospital admissions with subsequent follow up ultrasound scans and

	clinic reviews, kidney failure treated with haemodialysis 5 – 6 sessions per week, liver and kidney transplant require extensive specialist hospital admissions and regular outpatient follow up.
• How does healthcare resource use differ between the technology and current care?	As above – resource use for the technology is day-case or homecare subcutaneous injections every 1-3 months. Current care resource to manage complications of PH1 are extensive (kidney stone procedures undertaken during brief hospital admissions with subsequent follow up ultrasound scans and clinic reviews, kidney failure treated with haemodialysis 5 – 6 sessions per week, liver and kidney transplant require extensive specialist hospital admissions and regular outpatient follow up). In small children, nasogastric tubes or gastrostomy insertion is sometimes required for high fluid intake to reduce kidney calcium oxalate deposition.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	For children with PH1, specialised paediatric nephrology services should manage PH1 care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Pharmacy storage and distribution of the siRNA treatment. Administration is routine subcutaneous injection.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Results from clinical trials indicate clinically significant reduction in urinary oxalate excretion for adults and children with PH1 treated with Lumasiran. This is consistent with clinical experience managing 12 children with PH1 receiving Lumasiran treatment. The full clinical benefit will be determined with long term follow up, however short term benefits of reduced kidney stone events, stabilisation/improvement in kidney function are apparent. A significant long term benefit is very likely given the observed improvement in urinary oxalate excretion in children and adults with PH1.

• Do you expect the technology to increase length of life more than current care?	Yes. Increased life expectance has been observed in 2 infants with infantile oxalosis phenotype treated with Lumasiran on the early access medicines scheme. Given that kidney failure and systemic oxalosis are life limiting conditions, all patients with PH1 treated with Lumasiran are expected to have longer life expectancy.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes: - reduced kidney stone events with associated pain, and hospital admission for operative procedures - reduced progression to kidney failure requiring dialysis - reduced need for liver and kidney transplant
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with PH1 who respond to pyridoxine (vitamin B6) may experience adequate improvement in urinary oxalate excretion without Lumasiran, but this requires formal evaluation in a clinical trial.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Easier than standard care. Standard care includes dialysis treatment, transplantation, and management of complications of systemic oxalosis. Practical implications are arrangements for 1 – 3 monthly subcutaneous injections (hospital or homecare administration?).

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Additional blood test monitoring of liver enzymes will be required with the technology.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Suggest that genetic confirmation of Primary Hyperoxaluria type 1 with pathogenic variant(s) in AGXshould be a pre-requisite for starting siRNA treatment.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patient experience: current standard of care includes oral potassium citrate to inhibit calcium oxalate crystal agglomeration in the kidney. This medication is poorly tolerated in children due to sour taste, leading to frequent non-concordance. Achieving a high fluid intake can also be challenging for families with small children. Less need for potassium citrate and high fluid intake, and less need for gastrostomy insertion for some infants, are quality of life considerations that may not be quantified in the QUALY calculation.

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Lumasiran is innovative, in that it is the first siRNA treatment with clear evidence of efficacy in clinical trials. Clinical trial data, and clinical experience with 12 children treated with Lumasiran, suggest that it has a high probability of transforming outcomes in Primary Hyperoxaluria type 1. The observed reduction in urinary oxalate excretion is likely to substantially ameliorate long term kidney damage and progression to kidney failure, significantly reduce the number of kidney stone procedures required, and reduce/remove the need for dialysis treatment and kidney and liver transplantation in this condition.
• Is the technology a 'step-change' in the management of the condition?	Yes, for the above reasons.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – the unmet need of an effective treatment that substantially ameliorates long term complications.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In clinical trial results, and clinical experience, injection site reactions were a relatively frequent side effect in around 20% patients. These were self-limiting and needed no specific treatment. All patients chose to continue receiving the treatment, and did not impact patients' quality of life.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the trials reflect UK paediatric practice, and several children from UK centres participated.
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Urinary oxalate excretion is a widely accepted marker of kidney stone risk and long term kidney failure risk in patients with PH1 passing urine. Plasma oxalate levels are helpful in anuric patients. Both urine and plasma oxalate levels were measured in clinical trials. Long term follow up data is being collected to determine the effect on long term kidney function.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes - published registry data demonstrate a clear link between urinary oxalate levels and long term kidney failure risk.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any in our experience of 12 children with PH1 treated with Lumasiran, nor from ongoing clinical trial safety alerts.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes – We have anecdotal evidence of benefit in an infant with PH1 and kidney failure treated with Lumasiran. Results of the relevant clinical trial in adults and children with severely reduce kidney function have not been published at the time of submitting this statement.
21. How do data on real-world experience compare with the trial data?	Real world data from children treated via the Early Access Medicines Scheme reflects clinical trial data with normalisation/near-normalisation of urinary oxalate excretion, stabilisation of kidney function, and substantially reduced number of kidney stone events.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	PH1 is an autosomal recessive disorder, and therefore more common in cultures where consanguineous marriage is more widely practised.
22b. Consider whether these issues are different from issues with current care and why.	This affects both the technology and current care in a similar way.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- There is a clear unmet need for patients with PH1, with no effective treatment option for most patients
- PH1 reduces life expectancy, with some children dying in early infancy from systemic oxalosis
- Lumasiran is a novel siRNA treatment with clinical trial data which reflect real world treatment experience
- Experience with infants and children with PH1 suggests significantly improved clinical course with Lumasiran treatment
- Long term follow up data are being collected to determine if the anticipated long term benefits are observed

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 21/03/2022

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number NIHR 13/37/05.

Declared competing interests of the authors None.

Acknowledgements

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

O'Meara S, Al M, Wetzelaer P, Abraham K, Danopoulos E, Perry M, Posadzki P, Ahmadu C, Stirk L, Armstrong N, Corro Ramos I, Kleijnen J, Wolff R. Lumasiran for treating primary hyperoxaluria type 1 [ID3765]: a Highly Specialised Technology Evaluation. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors

Susan O'Meara and Robert Wolff acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Pim Wetzelaer, Kathi Abraham, Charlotte Ahmadu, Nigel Armstrong, and Isaac Corro Ramos acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Evangelos Danopoulos, Mark Perry, and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse effect, adverse event
AGT	Alanine-glyoxylate aminotransferase
AiC	Academic in confidence
AIC	Akaike information criterion
ALT	Alanine transaminase
ASN	American Society of Nephrology
AST	Aspartate transaminase
AUC	Area-under-the-curve
BIC	Bayesian information criterion
BL	Baseline
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CaOx	Calcium oxalate
CASP	Critical Appraisal Skills Programme
CBA	Cost-benefit analysis
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in Confidence
CKD	Chronic kidney disease
cLKT	Combined liver–kidney transplantation
CMA	Cost-minimisation analysis
CMH	Cochran-Mantel-Haenszel
CPCI-S	Conference Proceedings Citation Index-Science
CRD	Centre for Reviews and Disseminations
CS	Company submission
CSR	Clinical study report
CUA	Cost-utility analysis
DALY	Disability-adjusted life-year
DB	Double blind
DP	Decision problem
DSU	Decision Support Unit
EAS	Efficacy analysis set
ECM	Established clinical management
EED	Economic Evaluation Database
EGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 dimensions
EQ-5D-5L	European Quality of Life-5 dimensions-5 levels
EQ-5D-Y	EuroQol 5-Dimension - Youth version
ERG	Evidence Review Group
ESHPM	Erasmus School of Health Policy & Management
ESKD	End-stage kidney disease
ESPN	European Society for Paediatric Nephrology
EU	European Union
EUCTR	European Union Clinical Trials Register
EUR	Erasmus University Rotterdam

EUR	Euro
FAS	Full analysis set
FDA	Food and Drug Administration
GalNAc	N-Acetylgalactosamine
GBP	British pound sterling
GEE	Generalised estimating equations
GO	Glycolate oxidase
HCRU	Healthcare resource utilisation
HD	Haemodialysis
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
iMTA	Institute for Medical Technology Assessment
Inc.	Incremental
INR	International normalised ratio
IPNA	International Pediatric Nephrology Association
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISN	International Society of Nephrology
ISPOR	Professional Society for Health Economics and Outcomes Research
ITT	Intention-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL-36	Kidney Disease Quality of Life-36 items
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LFT	Liver function test
LLOQ	Lower limit of quantitation
LSM	Least square mean
LY	Life year
LYG	Life years gained
M	Missense
M	Month
MAIC	Matched-adjusted indirect comparison
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimally important difference
MIMS	Monthly Index of Medical Specialities
MMRM	Mixed-effect model repeated measures
Mo	Month
N	Nonsense
N/A	Not applicable
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	The Netherlands
N/R	Not reported
OLE	Open-label extension
OER	OxalEurope Registry
OS	Overall survival
OWSA	One-way sensitivity analysis
Ox_c	Controlled oxalate levels
Ox_u	Uncontrolled oxalate levels
PAS	Patient Access Scheme
PD	Peritoneal dialysis

PD	Pharmacodynamics
PedsQL	Pediatric Quality of Life Inventory
PH1	Primary hyperoxaluria type 1
PK	Pharmacokinetics
POx	Plasma oxalate levels
PPP	Purchasing power parities
PR	Pyridoxine responsive
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3M	Once every three months
QALY	Quality-adjusted life year
QM	Once monthly
RaDaR	Registry of Rare Kidney Diseases
RCT	Randomised controlled trial
RKSC	Rare Kidney Stone Consortium
RNAi	Ribonucleic acid interference
RoB	Risk of bias
RSE	Renal stage event
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
ScHARR HUD	University of Sheffield Health Utilities Database
SD	Standard deviation
SEE	Structured expert exercise
SEM	Standard error of the mean
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SMQ	Standardised MedDRA query
SO	Systemic oxalosis
SWL	Shockwave lithotripsy
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
ToT	Time-on-treatment
TSD	Technical support document
TTO	Time trade off
UK	United Kingdom
ULN	Upper limit of normal
UOx	Urinary oxalate
URTI	Upper respiratory tract infection
US	United States (of America)
USA	United States of America
VAS	Visual analogue scale
W	Week
WCN	World Congress of Nephrology
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

1.1 Background

Primary hyperoxaluria type 1 (PH1) is a rare, inherited disorder, which leads to potentially fatal effects including recurrent kidney stones, chronic deposition of calcium salts in the kidney (nephrocalcinosis), progressive renal failure, and, in more advanced cases, multiorgan damage.

PH1 is caused by a deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). This leads to hepatic overproduction of oxalate, which is subsequently excreted by the kidneys. In passing through the kidneys, oxalate binds to calcium to form toxic calcium oxalate crystals, triggering an inflammatory response implicated in tissue damage. Nephrocalcinosis leads to progressive loss of renal function and may also result in acute kidney injury. Oxalate can also cause acute kidney injury via aggregation into stones and resultant obstruction of urinary outflow. In the natural history of PH1, oxalate accumulation drives inevitable progression to end-stage kidney disease (ESKD) due to chronic/acute loss of renal function. PH1 has particularly devastating consequences for patients with infantile onset of PH1, with rapid progression to ESKD and significantly reduced survival in those with earlier clinical onset of disease relative to those with later clinical onset of disease.

Living with PH1 presents many challenges to caregivers and families of patients with PH1. Although disease progression and severity are variable, caring for a child or an adult with PH can add substantial strain to the family due to intense medical requirements and associated financial hardship.

Current treatment includes liver transplant (with or without kidney transplant) which can eliminate PH1. However, this strategy tends to be reserved for the later stages of the disease, due to the risk of serious adverse effects of transplantation. Established clinical management (ECM) in earlier stages of the disease focuses on supportive measures, such as low-oxalate diet, increased fluid intake (hyperhydration), crystallisation inhibitor use, and pyridoxine (vitamin B6) supplementation. In more advanced stages of renal decline, haemodialysis may be initiated to slow the build-up of systemic oxalate and/or replace lost renal function.

It is estimated there are 90 people with PH1 in the United Kingdom (UK), based on National Registry of Rare Kidney Diseases (RaDaR) estimates of the overall hyperoxaluria population (~N=120) and published diagnosis rates. Expert clinical opinion suggests that [redacted] of these patients have not already received a liver transplant or combined liver–kidney transplant (cLKT). Considering that lumasiran would only be used in patients who have not already undergone these transplantation procedures, an estimated [redacted] prevalent patients with PH1 would currently be eligible for lumasiran treatment. In addition to these prevalent patients, according to expert opinion, it is assumed that there will be approximately [redacted] new (i.e. incident) patients with PH1 eligible for lumasiran each year in England and Wales. As detailed in Section 2.2.3, the ERG considers that these values may underestimate the true number of patients eligible for treatment with lumasiran in the UK.

Lumasiran has received marketing authorisation from the European Medicine Agency (EMA) for the treatment of PH1. This was automatically converted to a UK marketing authorisation (effective in Great Britain only).

1.2 Critique of the decision problem in the company's submission

Some components of the decision problem (DP) addressed by the company were in line with the National Institute for Health and Care Excellence (NICE) scope (population and intervention) whilst the ERG noted discrepancies with others (comparators, outcomes and subgroups).

- Population: people with PH1.
- Intervention: lumasiran (OXLUMO™) administered as a subcutaneous injection with dosing schedule based on body weight. Of note, the intervention in the economic model was described as Lumasiran plus ECM, which *"…may include an oxalate-controlled diet, hyperhydration, pyridoxine, and oral citrate…"*, although it appears that only pyridoxine was explicitly costed.
- Comparators: ECM without lumasiran including pyridoxine, oxalate-controlled diet, hyperhydration, haemodialysis and liver transplant with a combined or sequential kidney transplant were listed by both the NICE scope and the company's DP statement. The NICE scope additionally described isolated liver transplant (i.e. without a kidney transplant) as a comparator.
- Outcomes: oxalate levels in urine and plasma, change in estimated glomerular filtration rate (eGFR), mortality, adverse effects of treatment and health-related quality of life (HRQoL) were common to both the NICE scope and the company's DP statement. The NICE scope also listed the need for liver transplant with or without a kidney transplant whereas the company's DP statement mentioned only the need for liver transplant with a kidney transplant. The company's DP statement listed two additional outcomes that did not appear in the NICE scope: renal stone events and systemic oxalosis.
- Subgroups: the NICE scope mentioned a subgroup of infants with rapid and progressive disease. The company undertook cost effectiveness analyses (CEAs) for this group although defined it slightly differently (*"Infants with infantile onset of PH1"*). As infantile onset of PH1 is associated with rapid and progressive disease, the ERG considered that this group matched the one described in the NICE scope. The company also performed CEAs for patients of all ages with infantile onset of PH1 (this was not featured in the NICE scope). CEAs were not performed for two further subgroups listed in the NICE scope because of lack of data, namely children with a family history confirmed by cord blood testing and children and adults presenting with kidney stones.

1.3 Summary of clinical effectiveness evidence submitted by the company

The company presented clinical efficacy results from four studies, two of which were placebo-controlled randomised controlled trials (RCTs) and two were non-comparative. Both RCTs included a double-blind comparative period followed by an open-label extension during which all patients received the active intervention.

The ILLUMINATE-A RCT (ALN-GOI-003) recruited adults and children (age range six to 60 years) with a diagnosis of PH1 and relatively preserved renal function (n=39 patients recruited from 16 study centres in France, Germany, Israel, the Netherlands, Switzerland, the United Arab Emirates, the UK and the United States of America (USA)). [redacted] patients were from the UK. The initial double-blind period entailed a randomisation ratio of lumasiran:placebo 2:1 and was of 6 months duration; the extension (involving the same participants) lasted up to 54 months.

The second RCT (ALN-GOI-001) recruited adults and children aged six to 64 years with a diagnosis of PH1 and eGFR >45 ml/min/1.73 m^2 (n=20 patients recruited in France, Germany, Israel, the Netherlands and the UK). The number of study centres and the number of patients per country was not

reported. Separate cohorts were recruited for the comparative and extensive phases. Participants were randomised in a 3:1 (lumasiran:placebo) ratio during the 3-month double-blind phase; this involved three different dosing schedules of lumasiran according to body weight. The duration of the extension was a further 3-months.

One of the single-arm studies (ALN-GOI-002) recruited the 20 participants who had participated in the second RCT described above and allocated them to three different dosing schedules of lumasiran as used in the RCT.

The second single-arm study (ILLUMINATE-B, ALN-GOI-004) recruited 18 children younger than six years of age from nine study centres in France, Germany, Israel, the UK and the USA (n = [redacted] UK patients) with a diagnosis of PH1 and relatively preserved renal function and administered lumasiran loading and maintenance doses based on body weight.

Below, there is a summary of results with a focus on the double-blind phase of the ILLUMINATE-A RCT (ALN-GOI-003). The results of all phases of all four studies are presented in detail in Section 4.2.

- Use of lumasiran was associated with relative and absolute reductions in 24-hour urinary oxalate excretion between baseline and 6 months versus placebo, with the respective estimates of treatment effect being: -53.5% (95% confidence interval (CI) -62.3 to -44.8) and -0.98 mmol/24-hourss/1.73 m^2 (95% CI -1.18 to -0.77).
- The results for change in 24-hour plasma oxalate between baseline and 6 months also suggested an effect in favour of lumasiran compared with placebo. The respective relative and absolute estimates of treatment effect were: -39.5% (95% CI -50.1 to -28.9) and -8.7 mmol/24 hours/1.73 m^2 (95% CI -11.5 to -6.0).
- The level of eGFR appeared to remain stable for both treatment groups during the 6-month follow-up period, however, estimates of treatment effect were not provided.
- In the group receiving lumasiran, the rate of renal stone events (per person year) was 3.19 (95% CI 2.57 to 3.96) in the 12 months prior to the trial and 1.09 (95% CI 0.63 to 1.87) during the 6-month double-blind period. The respective values in the placebo group were 0.54 (95% CI 0.26 to 1.13) and 0.66 (95% CI 0.25 to 1.76), i.e. groups were not comparable at baseline. A between-group estimate of effect was not provided.
- The number of patients needing a liver transplant without or without a kidney transplant was not reported.
- The mean ± standard deviation (SD) change from baseline to month 6 in the EuroQoL 5-dimension (EQ-5D) visual analogue scale (VAS) was [redacted] for the lumasiran group and [redacted] for the placebo group, with higher scores indicating better health status. However, comparability of baseline could not be assessed by the ERG, as relevant details were not provided.

Adverse event (AE) data were available from the ILLUMINATE-A RCT, ILLUMINATE-B and an additional single-group study (ILLUMINATE-C). During the double-blind phase of ILLUMINATE-A, 85% of patients receiving lumasiran and 69% on placebo reported any type of AE. Injection site reactions were higher among patients in the lumasiran group compared with placebo (23% versus 0%). No serious AEs (SAEs) or severe AEs were recorded in either group. All patients experienced at least one AE in the ILLUMINATE-B study whilst one SAE and no severe AEs were reported. In the ILLUMINATE-C study, 81% of patients experienced any type of AE, 29% experienced at least one SAE and 14% experienced at least one severe AE. No deaths were recorded in any study.

No pairwise meta-analyses, indirect treatment comparisons or multiple treatment comparisons were conducted.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted by the company

The detailed ERG summary and critique of the clinical effectiveness evidence submitted by the company can be found in Section 4 of this report. The key issues highlighted in the ERG's critique are summarised in Tables 1.1 to 1.3.

Information provided within the company submission (CS) and response to the request for clarification provided sufficient details for the ERG to appraise the literature searches and conclude that they had been generally well conducted. The approach used for data extraction was not in line with best practice. The Cochrane Handbook states that whilst it is acceptable for study details and baseline data to be extracted by one reviewer and independently checked by a second reviewer, two independent reviewers should extract outcome data and agree a pre-specified approach for resolving disagreements. For this appraisal, all data were extracted by one reviewer and checked by a second, independent reviewer. Therefore, the risk of inaccuracies within the dataset cannot be discounted.

Most data in the appraisal are derived from the ILLUMINATE-A RCT (ALN-GOI-003) which recruited 39 participants across eight countries. [redacted] participants ([redacted]) were from the UK which may limit the generalisability of the overall trial results to the UK population.

Table 1.1: Key issue 1: Low volume of robust clinical effectiveness evidence

Report Section	**4.2**
Description of issue and why the ERG has identified it as important	The evidence base consists of two small RCTs, both with maximum follow-up period of 6-months for the double-blind phase. Both RCTs have non-comparative extension phases and two additional single-arm studies were identified. The ERG identified examples where groups were not comparable at baseline which makes conclusions for these outcomes unreliable.
What alternative approach has the ERG suggested?	Larger RCTs comparing lumasiran with relevant comparators would decrease uncertainty.
What is the expected effect on the cost effectiveness estimates?	It is likely to increase uncertainty.
What additional evidence or analyses might help to resolve this key issue?	Larger RCTs comparing lumasiran with relevant comparators would decrease uncertainty. However, due to the rare nature of the disease, these trials are not available.
ERG = Evidence Review Group; RCTs = randomised controlled trials	

Table 1.2: Key issue 2: Proportion of patients with PH1 may be higher than stated

Report Section	**2.2.3**
Description of issue and why the ERG has identified it as important	The total eligible population in the UK may be larger than stated in the CS. The CS mentions an assumed number of new (incident) cases per year but the cited literature does not substantiate the proposed figure. This may result in a higher proportion of patients with PH1 being eligible for treatment with lumasiran.
What alternative approach has the ERG suggested?	None, as no data are available to quantify the underestimation.

Report Section	2.2.3
What is the expected effect on the cost effectiveness estimates?	An increase in the number of eligible patients will lead to a higher budget impact, however, as the disease is rare, the impact on the current estimation of the budget impact is likely to be small.
What additional evidence or analyses might help to resolve this key issue?	Further data to provide a more accurate estimate of the eligible target patient population relevant for this submission.
CS = company submission; ERG = Evidence Review Group; PH1 = primary hyperoxaluria type 1	

Table 1.3: Key issue 3: The intermediate outcomes used may not link directly to relevant clinical endpoints

Report Section	4.1.2
Description of issue and why the ERG has identified it as important	Change in urinary or plasma oxalate levels is an intermediate, i.e. surrogate, outcome with unknown prediction of clinical endpoints such as renal stone events, renal failure, need for liver transplant with or without kidney transplant and survival. The maximum follow-up duration in the existing double-blind RCTs is 6 months which may not be long enough to detect the above clinical endpoints. Related to this, the existing RCTs are likely to be statistically underpowered to detect clinical endpoints.
What alternative approach has the ERG suggested?	Include longer follow-up periods for double-blind phases of relevant RCTs.
What is the expected effect on the cost effectiveness estimates?	Reliance on intermediate outcomes may hinder interpretation and result in uncertainty of cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up periods for double-blind phases of relevant RCTs.
ERG = Evidence Review Group; RCTs = randomised controlled trials	

1.5 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

In patients with PH1, there is a hepatic overproduction of oxalate that leads to toxic crystal deposits in the kidneys. This causes a progressive loss of renal function, kidney damage, increase in the occurrence of renal stones and systemic oxalosis complications. The subsequent loss of renal clearance of oxalate creates a feedback loop resulting in an acceleration of further kidney damage and oxalate accumulation. Through targeting a liver-specific enzyme to prevent the formation of a key substrate for oxalate synthesis, lumarisan reduces hepatic oxalate production and is therefore expected to halt the disease.

The key aspects of the CEA model pivot around the progressive nature of PH1 in absence of effective treatment, with patients transitioning over time to increasingly more severe health states defined as stages of chronic kidney disease (CKD), and lumasiran being able to halt disease progression so that patients no longer transition to more severe health states.

An appropriate measure of kidney function is the eGFR, but to detect changes in eGFR that are representative of a clinical effect it would require an RCT with a relatively large sample size (approx. [redacted]) and [redacted] follow-up. Such a sample size is not feasible for an orphan disease; therefore, an appropriate surrogate outcome is required. For this, plasma oxalate levels were used.

An important shortcoming of the company's approach in using plasma oxalate levels as a surrogate outcome for kidney function in PH1 is that it assumes that disease progression (in term of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on increased plasma oxalate levels that are steady yet sustained over time. The ERG considers it likely that disease progression also occurs in patients who sustain a steady, but increased, plasma oxalate level over time.

The progressive nature of the disease was modelled based on the changes in plasma oxalate levels as observed in patients receiving ECM in ILLUMINATE-A over 6 months of follow-up in combination with the relationship between plasma oxalate and eGFR. This allowed the observed increase in plasma oxalate to be translated into an estimated reduction in eGFR per 6-months model cycle. From this it was calculated how many cycles would be needed to transition between CKD health states, the inverse of which provided the transition probabilities.

Since no increases, but rather decreases, in plasma oxalate were observed in patients who received lumasiran in ILLUMINATE-A and ILLUMINATE-B, also no decreases in eGFR were modelled for patients receiving lumasiran. As such, lumasiran is effectively modelled to halt disease progression. When patients discontinue treatment with lumasiran, they switch to the transition probabilities used for ECM. The model did not allow for increases in eGFR, which can be considered as conservative given observed reductions in plasma oxalate in patients receiving lumasiran in ILLUMINATE and the relationship between eGFR and plasma oxalate.

For patients receiving ECM, who have uncontrolled oxalate levels, the transition from CKD 4 to ESKD was modelled using ESKD-free Kaplan-Meier survival curves. As described above, patients receiving lumasiran, who have controlled oxalate levels, were assumed not to transition to ESKD.

Patients receiving lumasiran could not transition to more severe CKD health states. Patients starting treatment in late-stage disease (i.e. CKD 4 or ESKD) health states with plasma oxalate levels above 50 µmol/l (labelled uncontrolled oxalate) could transition to health states based on the same CKD stage but with plasma oxalate levels below 50 µmol/l (labelled uncontrolled oxalate). This transition probability was estimated using data from ILLUMINATE-C. This allowed an estimation of the number of cycles needed to transition that was converted into a transition probability. The ERG noted that an error appears to have been made in this calculation and corrected it. This resulted in a higher transition probability, favouring the intervention.

Patients in CKD 4 and ESKD may receive a cLKT to stop hepatic oxalate overproduction and restore kidney function. The cLKT transplantation rate for patients with controlled oxalate was estimated by combining data on the 3-year rates of liver and kidney transplantations. The company assumed that 100% of patients with controlled oxalate in CKD 4 and ESKD would be placed on a waiting list. For patients in CKD 4 and ESKD with uncontrolled oxalate, the cLKT transplantation rate was estimated based on a study. This yielded a transplantation rate that was about 30 times smaller than for the controlled patients and translated in an average time until transplantation of around 80 years. The ERG found this very unrealistic, and hence choose to use the same approach as for controlled patients, but with the assumption that only 50% of patients would be deemed eligible for transplantation and put on the waiting list. A low probability of re-transplantation was modelled based on data from the aforementioned study.

The model also took the development of renal stones into account in the model, with event rates based on data from the pivotal clinical studies. In contrast, the occurrence of complications related to systemic oxalosis and the frequency and intensity of dialysis in the CKD 4 and ESKD health states were based on interviews with clinical experts.

Mortality was modelled by applying mortality multipliers to the general population mortality. Mortality after cLKT was based on observational data. The company assumed that patients who had well controlled plasma oxalate before the transplantation would have a higher chance of survival than patients who have been uncontrolled. Survival stratified by pre-transplantation condition was reported in the study cited by the company and the survival of the patients in the best two strata were applied to controlled patients in the model, and of the worst two strata to uncontrolled patients. The ERG considers this incorrect, since the whole patient population in the study effectively represents ECM.

For the estimation of utility values for the health states and disutilities for events, complications and for dialysis, the company used various sources, mostly from literature or the three pivotal trials. For the estimation of the utility for CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis, a vignette study was done, where the general public filled out European Quality of Life-5 dimensions (EQ-5D) for each health state (to which the UK tariff was subsequently applied), score the vignette on the visual analogue scale, and performed a time trade-off exercise to arrive at a utility value. For patients in the CKD 4 and ESRD health states a disutility per caregiver of [redacted] was applied for on average [redacted] caregivers per patient. No justification was provided why the caregiver disutility was the same for CKD4 and ESKD, and for high and normal intensity dialysis.

The ERG has doubts regarding the choice of the EQ-5D based valuation of the vignettes instead of the time trade off (TTO) derived utilities. From a methodological point of view, it is not fully clear which option should be preferred, though the ERG would argue that in this instance the TTO valuation should be preferred. When comparing those health states that had both observed utilities through direct application of the EQ-5D and utilities values based on the vignette study, it was clear that the TTO valuations of the vignettes were much better aligned with those measured in the ILLUMINATE A study.

Resource use for the various health states, events and complications were based on expert elicitation. However, for many items it was unclear how the company arrived at the preferred value for the resource use. As lumasiran is administered based on weight and only available in one vial size, the ERG asked the company how much of the drug would be wasted, on average. In response, the company explained that on average [redacted] mg and [redacted] mg of lumasiran is wasted for the paediatric and adult population, with corresponding costs due to wastage of [redacted] and [redacted] per administration, respectively.

The discounted company base-case results using the proposed PAS discount of [redacted]% for lumasiran showed that lumasiran accrues [redacted] incremental QALYs compared to ECM at an additional cost of [redacted]. This corresponds to an ICER of [redacted] per QALY gained.

The undiscounted gain in QALYs with lumasiran was [redacted], indicating a weighting of [redacted] can be used to calculate a weighted threshold (of [redacted]).

In response to the request for clarification, the company submitted a revised model. The ICER has increased from [redacted] per QALY gained to [redacted] per QALY gained. Furthermore, the company explored various scenarios. One with an alternative initial distribution for the paediatric population (10% CKD 4, 90% ESKD) has a very large impact on the ICER, leading to a substantial decrease. Using the TTO values for the valuation of vignettes increased the ICER substantially. Furthermore, eliminating drug wastage would lead to a considerable decrease the ICER. The exploratory analysis with an alternative model structure showed an ICER that was only slightly smaller than the base-case ICER.

1.6 Summary of the ERG's critique of the value for money evidence submitted

The ERG's summary and detailed critique of the value for money evidence submitted by the company can be found in Section 5 of this report. The key issues in the value for money evidence are summarised in Tables 1.4 to 1.8.

Table 1.4: Key issue 4: Modelling of disease progression

Report Section	**5.3.3.4**
Description of issue and why the ERG has identified it as important	The model assumes that disease progression in CKD 1–3b (in terms of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on high plasma oxalate levels that are steady yet sustained over time. The ERG considers it likely that disease progression also occurs in patients who sustain a steady, but very high, plasma oxalate level over time.
What alternative approach has the ERG suggested?	In response to the ERG's clarification question on this issue, the company developed an exploratory version of the model to stratify the risk of progression through CKD stages in the model based on data from the ILLUMINATE studies. This revised exploratory approach partitioned the CKD1–3b cohort into two separate strata: (1) one corresponding to patients with normal or near-normal oxalate levels and (2) the other corresponding to patients with "above-normal" oxalate levels; the transition probabilities between CKD stages were differentiated for each stratum. However, the ERG is not sure this tackles the issue of time spent at same elevated level for a long period in the ECM group.
What is the expected effect on the cost effectiveness estimates?	The results of the company's exploratory analyses with the modified version of the model were quite similar to the company's base case (see Section 6.1.2).
What additional evidence or analyses might help to resolve this key issue?	Instead of using plasma oxalate as a surrogate outcome for kidney function, disease progression could be modelled directly based on changes in eGFR or reaching ESKD. However, to be able to use these outcomes as RCT endpoints it would require larger and longer RCTs. Especially larger RCTs may not be feasible in an orphan disease. Alternatively, it would be relevant to study the relationship between time spent in a uncontrolled oxalate state and the risk of kidney function decline. In addition, expert opinion could be sought to validate the modelled length of time spent in each CKD class for patients starting in CKD 1-2, 3a, 3b (ECM patients).
CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ERG = Evidence Review Group; ESKD = end-stage kidney disease; RCT = randomised controlled trial	

Table 1.5: Key issue 5: Probability of transplantation

Report Section	**5.3.3.5.6**
Description of issue and why the ERG has identified it as important	The company assumed that 100% of patients with controlled oxalate in CKD 4 and ESKD would be placed on a waiting list for cLKT and then have the same chance as non-PH1 patients with ESKD.. For patients in CKD 4 and ESKD with uncontrolled oxalate, the cLKT transplantation rate was estimated based on a study. This yielded a transplantation rate that was about 30 times

Report Section	5.3.3.5.6
	smaller than for the controlled patients and translated in an average time until transplantation of around 80 years.
What alternative approach has the ERG suggested?	The ERG found that the company's assumptions led to a very unrealistic probability of transplantation, and hence chose to use the same approach as for controlled patients, but with the assumption that only 50% of patients would be deemed eligible for transplantation and put on the waiting list.
What is the expected effect on the cost effectiveness estimates?	This change, when applied to the company's revised base-case model in isolation of the other ERG changes (after error correction), changed the ICER from [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Evidence on transplantation rates in UK patients with PH1, for those with controlled and uncontrolled plasma oxalate, for example through a patient record study, could be used to inform the model with inputs that are in line with clinical practice.
CKD = chronic kidney disease; cLKT = combined liver and kidney transplantation; ERG = Evidence Review Group; ESKD = end-stage kidney disease; ICER = incremental cost effectiveness ratio; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life year; UK = United Kingdom	

Table 1.6: Key issue 6: TTO values vignettes

Report Section	5.3.3.7.2
Description of issue and why the ERG has identified it as important	For the estimation of the utility for CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis, a vignette study was done, where the general public filled out the EQ-5D for each health state (to which the UK tariff was subsequently applied), scored the vignette on the visual analogue scale, and performed a time trade-off exercise to arrive at a utility value. The ERG had doubts regarding the choice of the EQ-5D based valuation of the vignettes instead of the TTO derived utilities.
What alternative approach has the ERG suggested?	When comparing those health states that had both observed utilities through direct application of the EQ-5D and utilities values based on the vignette study, it was clear that the TTO valuations of the vignettes were much better aligned with those measured in the ILLUMINATE A study.
What is the expected effect on the cost effectiveness estimates?	Using the TTO valuations of the vignettes, when applied to the company's revised base-case model in isolation of the other ERG changes (after error correction), changed the ICER from [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The most appropriate approach to estimating the utilities would be to apply the EQ-5D from patients with PH1 directly.
EQ-5D = European Quality of Life-5 dimensions; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life year; TTO = time trade off; UK = United Kingdom	

Table 1.7: Key issue 7: High drug wastage costs

Report Section	5.3.3.8.1
Description of issue and why the ERG has identified it as important	The ERG considers the costs due to drug wastage for lumasiran to be high. On average 16.05 mg and 37.43 mg per administration of lumasiran is wasted for the paediatric and adult population, with corresponding costs due to wastage of [redacted] and [redacted] per administration, respectively.
What alternative approach has the ERG suggested?	In response to the request for clarification whether the company has plans to provide lumasiran in vials of smaller quantities to enhance dosing flexibility and reduce wastage, the company indicated that this will not be possible.
What is the expected effect on the cost effectiveness estimates?	If vial sharing (i.e. no drug wastage) is included the company's revised base-case (after clarification, without error correction) ICER amounts to [redacted] per QALY gained, whereas without vial sharing (i.e. including drug wastage) the ICER amounts to [redacted] per QALY gained. As such, [redacted] per QALY gained is solely attributable to drug wastage.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence needed, though this raises the question if treatment administration can be optimised to reduce wastage
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year	

Table 1.8: Key issue 8: Dialysis regimes

Report Section	5.3.3.9.4
Description of issue and why the ERG has identified it as important	The ERG noticed a disconnect between the dialysis schedules suggested by clinical experts and the schedules used for the model. Dialysis is expensive and more intensive schedules lead to a larger decrease of quality of life. No explanation or justification was provided.
What alternative approach has the ERG suggested?	The ERG did a scenario analysis changing the percentage of ECM patients receiving dialysis in CKD stage 4 from 100% to 0%, in line with expert opinion.
What is the expected effect on the cost effectiveness estimates?	In the above scenario, the ICER increased by 15%.
What additional evidence or analyses might help to resolve this key issue?	More insight could be gained through a patient record study, to find dialysis schedules to inform the model with inputs that are in line with clinical practice.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio	

1.7 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

The company have not estimated the proportion of costs outside of the National Health Service (NHS) and Personal Social Services (PSS) that may be saved due to treatment with lumasiran, or of the additional benefits other than health. Only in Section 7.1.4 of the CS some narrative is presented to detail potential benefits outside of the NHS and PSS.

In the CS it is mentioned that, while the impact of lumasiran on cost and cost savings to UK government bodies has not been quantified, lumasiran may be expected to bring cost savings to government bodies

other than the NHS as a result of reduced patient disability especially in the young patients and the patients with late-stage disease. Caregivers are assumed to return to work and thus the company expects expenditures associated with the support for patients with PH1 and unemployed caregivers of PH1 patients may be reduced. Caregiver surveys conducted at the start of ILLUMINATE-A revealed that approximately 38% of caregivers of patients were not fully employed at the start of the study. The proportion of caregivers not fully employed was even greater if the individual was a caregiver of younger patients (ILLUMINATE-B; 72%) or a caregiver of a patient with late-stage disease (ILLUMINATE-C; 69%). Compared with caregivers of patients in ILLUMINATE-A (22%), more caregivers of younger patients with PH1 (54% in ILLUMINATE-B) and caregivers of patients with late-stage disease (39% in ILLUMINATE-C) reported having to reduce work hours to provide care for patients with PH1.

The CS indicated that costs borne by patients not reimbursed by the NHS include transportation to and from the hospital for dialysis treatment, renal stone treatment, and consultation, parking and overnight accommodation, and meals. The company reported costs for transportation for dialysis of £14,000 per year assuming six dialysis sessions per week. Costs may occur when home adaptations and aids are required. It is also indicated that carers often experience a loss of income due to time spent on caring for the patient. However, none of these costs were quantified in the CS.

The CS discussed the findings of caregiver surveys conducted at the start of the ILLUMINATE trials. [redacted].

According to the CS, the evidence base generated by the phase 3 ILLUMINATE trials of lumasiran in PH1 is a major advance considering that PH1 has a limited evidence base to inform clinicians on its management. The ILLUMINATE trials included patients with a range of ages and disease severity for whom lumasiran shows improved outcomes compared to ECM.

Lumasiran therapy will be implemented through the Rare Disease Collaborative Network expert centres at the Birmingham Women's and Children's NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Great Ormond Street Hospital, and the Royal Free Hospital. The treatment should be initiated and supervised by a physician experienced in the management of hyperoxaluria. The company stated that no additional infrastructure will be required to ensure the safe and effective use of the technology and equitable access for all eligible patients.

1.8 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health-related benefits

The CS only included some narrative about costs outside the NHS and PSS, without any quantification. The company reasoned that some of these costs may be saved when patients are treated with lumasiran, given that the treatment may reduce the need for certain time-intensive disease management and thus, frees up time of caregivers. However, there is currently no evidence to indicate to what extent improvements in the patients' condition will also lead to savings in societal, patient, and carer costs.

1.9 Summary of the ERG preferred base case and exploratory sensitivity analyses undertaken by the ERG

The ERG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

1. The probability of transplantation for the uncontrolled patients in CKD4/ESKD was estimated by assuming that 50% of ECM patients in CKD 4/ESKD can be placed on the waiting list, compared to 100% in the lumasiran group.
2. The survival post-transplantation for ECM patients was based on the observed survival for patients in fair and poor condition before transplantation. However, the survival in that study was based on only ECM patients So, for the ERG base case we assume that the overall survival is representative of survival for the ECM group.
3. The vignettes used to elicit utility values for the CKD 4/ESKD health states were valued both by the general public filling out the EQ-5D for the vignette and by a TTO. The ERG is of the opinion that the EQ-5D utilities lack face validity and that the TTO values are more plausible. These are therefore adopted for the ERG base case.

The results from the ERG deterministic base-case are shown in Table 1.9. It is clear that the three changes together have a very large impact on the ICER. In Table 1.10 we can see which of the changes had the largest impact i.e. the probability of transplantations for patients in the ECM group. Changing the valuation of the vignettes from EQ-5D to TTO also has a clear impact, whereas the error correction and the change in post-transplantation survival for ECM patients has little impact.

Table 1.9: ERG discounted base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	20.45	[redacted]				
Lumasiran	[redacted]	23.73	[redacted]	[redacted]	3.28	[redacted]	[redacted]

Based on v11.0 of the Excel model
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 1.10: Isolated impact of the ERGs preferred model assumptions

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company base-case	5.4.1	[redacted]	[redacted]	[redacted]
Company base-case after clarification	6.1.1	[redacted]	[redacted]	[redacted]
Company base-case after clarification and error correction	6.2.1.1	[redacted]	[redacted]	[redacted]
ERG change 1 – Probability of transplantation	5.3.3.5.6	[redacted]	[redacted]	[redacted]
ERG change 2 – Survival post-transplantation	5.3.3.5.12	[redacted]	[redacted]	[redacted]
ERG change 3 - TTO values vignettes	5.3.3.7.2	[redacted]	[redacted]	[redacted]

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
ERG change 4 – Pyridoxine price updated	6.2.1.3	[redacted]	[redacted]	[redacted]
ERG base-case – all 4 changes combined	-	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Ínc. = incremental; QALY = quality-adjusted life year

The ERG scenarios which had the largest impact on results were assessing the cost effectiveness of lumasiran per single CKD class, changing the percentage of ECM patients entering the transplantation waiting list, assuming vial sharing (i.e. no drug wastage), applying differential discount rates, and assuming that no patients receive dialysis in CKD stage 4. The results of the scenarios performed by the ERG are provided in Table 1.11 below.

Table 1.11: ERG scenario analyses results

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£)
ERG base-case	Section 6.3 of this report	[redacted]	[redacted]	[redacted]
Initial distribution isolated CKD classes	CKD 1-2 100%, other 0%	[redacted]	[redacted]	[redacted]
	CKD 3a 100%, other 0%	[redacted]	[redacted]	[redacted]
	CKD 3b 100%, other 0%	[redacted]	[redacted]	[redacted]
	CKD 4 100%, other 0%	[redacted]	[redacted]	[redacted]
	ESKD 100%, other 0%	[redacted]	[redacted]	[redacted]
Percentage ECM patients entering transplantation waiting list	25%	[redacted]	[redacted]	[redacted]
	75%	[redacted]	[redacted]	[redacted]
Vial sharing	Optimal vial sharing	[redacted]	[redacted]	[redacted]
Differential discounting	1.5% outcomes and 3.5% costs	[redacted]	[redacted]	[redacted]
Proportion of patients receiving dialysis in CKD stage 4	0%	[redacted]	[redacted]	[redacted]

Based on electronic model with ERG preferred assumptions
CKD = chronic kidney disease; ECM = established clinical management; ERG = Evidence Review Group; ESKD = end-stage kidney disease; ICER = incremental cost effectiveness ratio; Incr. = incremental QALY = quality-adjusted life year

1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

1.10.1 Strengths of the CS

- The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify studies on lumasiran for primary hyperoxaluria.
- The CS provided comprehensive data concerning several of the outcomes that were in the agreed scope.
- The CS presented the first CEA for patients with PH1. The analysis aligns with the NICE reference case. The model reflects disease progression and its impact on HRQoL and costs.
- Availability of data from controlled studies to estimate model input.

1.10.2 Weaknesses of the CS

- Components of the DP addressed in the CS were in line with the NICE scope (population and intervention) but there are discrepancies with others (comparators, outcomes and subgroups).
- It should be noted that full CSRs were not available to the ERG, see Section 4.2.
- The approach used for data extraction was not in line with best practice.
- Potentially limited generalisability to population in England and Wales.
- The ERG has limited confidence that some of the observed effects in the non-randomised evidence truly reflect the treatment effects of lumasiran.
- The model assumes that disease progression in CKD 1–3b (in term of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on elevated plasma oxalate levels that are steady yet sustained over time.
- A lack of face validity with regards to the mortality after a transplantation and the probability of a transplantation for ECM patients.
- No data on the HRQoL measurements in the ILLUMINATE C was provided.
- No justification was provided why the same caregiver disutilities were applied in CKD 4 and ESKD, and independent of dialysis intensity.

1.10.3 Uncertainties

Three key issues were identified in the clinical effectiveness Section:

- The evidence base consists of two small RCTs, both with maximum follow-up period of 6-months for the double-blind phase. Both RCTs have non-comparative extension phases and two additional single-arm studies were identified, see Section 4.2.
- The total eligible population in the UK may be larger than stated in the CS. The CS mentions an assumed number of new (incident) cases per year but the cited literature does not substantiate the proposed figure. This may result in a higher proportion of patients with PH1 being eligible for treatment with lumasiran, see Section 2.2.3.
- Change in urinary or plasma oxalate levels is an intermediate, i.e. surrogate, outcome with unknown prediction of clinical endpoints such as renal stone events, renal failure, need for liver transplant with or without kidney transplant and survival. The maximum follow-up duration in the existing double-blind RCTs is 6 months which may not be long enough to detect the above clinical endpoints. Related to this, the existing RCTs are likely to be statistically underpowered to detect clinical endpoints, see Section 4.1.2.

A further five key issues were identified in the cost effectiveness Section:

- The model assumes that disease progression in CKD 1–3b (in terms of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on high plasma oxalate levels that are steady yet sustained over time. The ERG considers it likely that disease progression also occurs in patients who sustain a steady, but very high, plasma oxalate level over time, see Section 5.3.3.4.
- The company assumed that 100% of patients with controlled oxalate in CKD 4 and ESKD would be placed on a waiting list for cLKT and then have the same chance as non-PH1 patients with ESKD. For patients in CKD 4 and ESKD with uncontrolled oxalate, the cLKT transplantation rate was estimated based on a study. This yielded a transplantation rate that was about 30 times smaller than for the controlled patients and translated in an average time until transplantation of around 80 years, see Section 5. 3.3.5.6.
- For the estimation of the utility for CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis, a vignette study was done, where the general public filled out the EQ-5D for each health state (to which the UK tariff was subsequently applied), scored the vignette on the visual analogue scale, and performed a time trade-off exercise to arrive at a utility value. The ERG had doubts regarding the choice of the EQ-5D based valuation of the vignettes instead of the TTO derived utilities, both from a methodological point of view as well as based on a lack of face validity, see Section 5.3.3.7.2.
- The ERG considers the costs due to drug wastage for lumasiran high. On average [redacted] mg and [redacted] mg per administration of lumasiran is wasted for the paediatric and adult population, with corresponding costs due to wastage of [redacted] and [redacted] per administration, respectively. This raises the question if treatment administration can be optimised to reduce wastage,see Section 5.3.3.8.1.
- The ERG noticed a disconnect between the dialysis schedules suggested by clinical experts and the schedules used for the model. Dialysis is expensive and more intensive schedules lead to a larger decrease of quality of life. No explanation or justification was provided. See Section 5.3.3.9.4.

2. BACKGROUND

2.1 Introduction

This chapter presents an overview of primary hyperoxaluria type 1 (PH1) and its management. The content of this chapter is based on relevant literature, clinical information obtained by the Evidence Review Group (ERG) and information presented in the background sections of the company submission (CS).[1] For additional information on the aetiology, epidemiology, health impact, prognosis and management of PH1, please see pages 24 to 32 of the CS.[1]

2.2 Description of health problem

2.2.1 Disease overview

PH1 is a rare, inherited disorder, which leads to potentially fatal effects including recurrent kidney stones, chronic deposition of calcium salts in the kidney (nephrocalcinosis), progressive renal failure, and, in more advanced cases, multiorgan damage.[2] It has an incidence of approximately 1 in 100,000 live births, and an estimated prevalence of one to three per million in North America and Europe.[3-5] It is more prevalent in populations where consanguineous marriages are more common.[6-8] It is caused by a deficiency of the liver-specific enzyme alanine-glyoxylate aminotransferase (AGT), which normally catalyses transamination of glyoxylate to glycine.[9] The consequent accumulation of glyoxylate substrate leads to over-production of oxalate, that binds with calcium in the kidneys, forming toxic calcium oxalate crystals. These crystals trigger an inflammatory response which is the chief cause of the clinical effects.[2, 10]

PH1 has more detrimental clinical consequences when it arises in children and has particularly devastating consequences for children with infantile onset (before 1 year of age).[11-14] These include rapid progression to end-stage kidney disease (ESKD), due to early oxalate load and immature renal function, and significantly reduced survival.[3, 12, 13]

ERG comment: No comments on this Section.

2.2.2 Current treatments

Liver transplant (with or without kidney transplant) can eliminate PH1, as the source of the excess oxalate production is eliminated by removal of the patient's liver in the transplant procedure.[15] However, this strategy tends not to be used until later stages of the disease, due to the risk of the serious adverse effects of transplantation. Established clinical management (ECM) in earlier stages of the disease has therefore been focused on supportive measures, such as low-oxalate diet, increased fluid intake (hyperhydration), crystallisation inhibitor use, and pyridoxine (vitamin B6) supplementation.[1] According to the CS, pyridoxine may be useful in about 5% to 10% of patients, but treatment with pyridoxine does not necessarily lead to normalisation of oxalate levels even in this subset of patients.[1, 4, 16-19]

In more advanced stages of renal decline, dialysis may be initiated to slow the build-up of systemic oxalate and/or replace lost renal function.[20, 21]

Lumasiran is a new therapy that is believed to normalise or near-normalise oxalate overproduction, the central driver of morbidity in patients with PH1. Lumasiran has a mechanism of action which involves the inhibition of a liver-specific enzyme glycolate oxidase to prevent formation of a key substrate needed for oxalate synthesis. According to the CS, none of the current approaches, apart from liver–kidney transplantation, is successful at removing the source of the pathogenic metabolite (oxalate) and

preventing/correcting ESKD,[3, 21, 22] which is described as an enormous burden for patients, their families, and society.[23, 24]

ERG comment: Section 2.3 provides greater details on treatments.

It should be noted that Kotb 2019[23] and Engels 2011[24] do not provide any data to substantiate the notion that ESKD is an enormous burden for patients, their families, and society.

2.2.3 Epidemiology

In the United Kingdom (UK), it is estimated there are 90 people with PH1, based on National Registry of Rare Kidney Diseases (RaDaR) estimates of the overall hyperoxaluria population (~N=120) and the 75% diagnosis rate published by Milliner 2020 and Lieske 2005.[25-27] Expert clinician input supports an assumption that [redacted] of these patients have not already received a liver transplant or combined liver–kidney transplant. Considering that lumasiran would only be used in patients who have not already undergone these transplantation procedures, an estimated [redacted] prevalent patients with PH1 would currently be eligible for lumasiran treatment. In addition to these prevalent patients, according to expert opinion, it is assumed that there will be approximately [redacted] new (i.e. incident) patients with PH1 eligible for lumasiran each year, based on the 1/100,000 incidence estimate reported, according to the CS, and the number of live births in England and Wales.[16, 28] Of [redacted] eligible patients, [redacted] would be considered in urgent need of treatment.

ERG comment: It is difficult to see how the overall hyperoxaluria population is estimated at approximately 120, based on the RaDaR number of patient recruits with hyperoxaluria of 118. Given that recruitment to the rare disease groups is voluntary, and that therefore the number of recruits will be a subset of the total number with the disease, the datum suggests a much larger population figure than 120. Meanwhile, Harambat 2010 provides a prevalence figure (one to three per million population in Europe) but not the incidence figure stated by the CS.[16]

2.2.4 Aetiology

PH1 is caused by a deficiency of the liver-specific peroxisomal enzyme AGT, which catalyses transamination of glyoxylate to glycine.[29] This deficiency is caused by pathogenic mutations of the AGXT gene encoding AGT. In PH1, AGT deficiency leads to the accumulation of glyoxylate and subsequent overproduction of oxalate from the accumulated glyoxylate substrate.[9]

ERG comment: No comments on this Section.

2.2.5 Pathogenesis

The core feature of PH1 is hepatic overproduction of oxalate, which is subsequently excreted by the kidneys.[20] In passing through the kidneys, oxalate binds to calcium to form toxic calcium oxalate crystals, which trigger a significant inflammatory response implicated in tissue damage.[10, 20]

Nephrocalcinosis leads to progressive loss of renal function and may also result in acute kidney injury.[10, 20] Oxalate can also cause acute kidney injury via aggregation into stones and resultant obstruction of urinary outflow.[10, 30] As kidney damage from oxalate accumulates, renal clearance of oxalate is impaired and oxalate levels in plasma rise, creating a feedback loop that results in further kidney damage (due to increased oxalate exposure) and further oxalate accumulation (due to worsening kidney damage) along with systemic oxalate deposition that damages organs beyond the kidneys.[2] In the natural history of PH1, oxalate accumulation drives inevitable progression to ESKD due to chronic/acute loss of renal function.[10, 11, 30, 31]

ERG comment: No comments on this Section.

2.2.6 Clinical features

As a genetic condition, PH1 is present from birth, and the clinical manifestations typically first arise in childhood and persist into adulthood.[31] The disease course of PH1 may vary from patient to patient, even within a family, and disease progression can be rapid and unpredictable.[31-33]

2.2.6.1 Renal manifestations

The renal morbidity observed in PH1 has both chronic and acute components. Nephrocalcinosis leads to progressive loss of renal function.[2, 30] Painful and potentially debilitating oxalate renal stones are also observed in PH1 and may cause acute loss of renal function due to obstruction of urinary outflow.[10] The occurrence of chronic and/or acute renal decline in PH1 inevitably leads to ESKD.[31] Consistent with the causative role of oxalate, nephrocalcinosis, urinary oxalate excretion, and plasma oxalate levels are all significantly associated with risk of progression to ESKD in patients with PH1.[30, 34, 35]

PH1 has particularly devastating consequences for patients with infantile onset of PH1, with rapid progression to ESKD (due to early oxalate load and immature renal function) and significantly reduced survival in those with earlier clinical onset of disease relative to those with later clinical onset of disease.[3, 11, 12] Patients with infantile clinical onset of PH1 have a statistically significant 6.0-fold increase in hazard of progression to ESKD versus patients with later clinical onset of PH1.[16] Approximately one in five (19%) of patients with infantile onset of PH1 will progress to ESKD or die by 10 years of age.[16]

ERG comment: No comments on this Section.

2.2.6.2 Systemic oxalosis manifestations

As oxalate-mediated renal impairment progresses and the kidneys can no longer clear the body's daily oxalate load, oxalate levels in the body rise and toxic oxalate crystals may be deposited systemically.[11, 31] Such crystals may deposit in a range of tissues, including bone, heart, skin, joints, and eyes.[CS references 20, 31, 47, 48, 107] Systemic oxalosis causes severe complications that can lead to significant morbidity and disability, e.g. vision loss, pathologic fractures, cardiac insufficiency, skeletal pain, skin ulcers, arrhythmias, and peripheral neuropathy.[CS references 20, 31, 47, 48]

Systemic oxalosis may also be uniquely harmful to children by impairing growth and damaging bones and vital organs during development. Systemic deposition of oxalate may cause failure to thrive, growth retardation, and disability due to bone, joint, and eye damage in children. [CS references 31, 33, 36-38]

ERG comment: No comments on this Section.

2.2.7 Diagnosis

The main challenge in diagnosing PH1 is its association with a low index of suspicion, which is due to the rarity of PH1 and its non-specific symptoms, e.g. renal stones and renal impairment.[36] Evaluation in accordance with published algorithms can facilitate earlier diagnosis.[3] Diagnosis of PH1 depends on diverse diagnostic tools including biochemical urine analysis and genetic studies.[36]

Presentation with symptoms such as nephrocalcinosis, recurrent renal stones in adults, and any renal stones in children may trigger metabolic evaluation of urine, e.g. 24-hour urine test. Test results that show excess oxalate excretion can indicate hyperoxaluria. Subsequent genetic testing can confirm

whether the hyperoxaluria is associated with an underlying genetic defect (i.e. PH) and determine which gene is involved (i.e. AGXT if PH1).[2]

A proportion of patients with PH1 are diagnosed not based on clinical and biochemical manifestations (as described above) but rather based on familial screening, which focuses on siblings of already diagnosed patients. Based on consultation with PH1 experts in the UK, prenatal screening is not routinely performed[1].

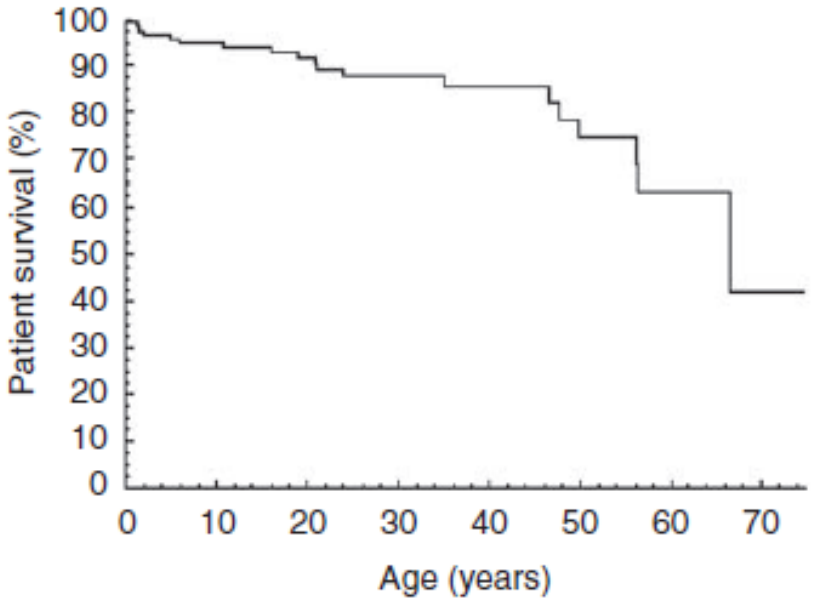
ERG comment: No comments on this Section.

2.2.7 Prognosis

Mortality in PH1 is generally associated with ESKD, dialysis, transplantation, or systemic oxalosis–related complications.[CS references 125, 126] Children with ESKD due to other conditions had a 5-year survival rate after renal replacement therapy of 92%, compared with 76% for PH patients. Altogether, this translates into a three-fold increased risk of death for PH patients on dialysis compared to those on dialysis due to other conditions.[CS references 49, 50]

There are no published data on the average life expectancy of PH1 patients in the UK. Overall survival of PH1 patients depends on the time of clinical disease onset (e.g. infancy versus adolescence or adulthood) and time to ESKD (i.e. renal survival).[CS reference 24] The OxalEurope Registry (OER) has reported cumulative patient survival rates of 95%, 93%, 85%, and 74% at ages five, 10, 30, and 50 years respectively, in a cohort of 526 PH1 patients. Among those who died during registry follow-up, 25% were younger than 2.5 years old, and the median age at death was 15.5 years.[CS reference 24][16] Harambat 2010 has published cumulative overall patient survival in a cohort of 155 PH1 patients, as shown in Figure 2.1. Cumulative patient survival rates were similar to the OER findings described above.[CS reference 24][16] In Harambat 2010, 20 out of the 155 PH1 patients died at median age of 19.9 years.[16]

Figure 2.1: Cumulative patient survival in a cohort of 155 PH1 patients



Based on Harambat 2010[16]

ERG comment: No comments on this Section.

2.2.8 Impact on patients', families' and caregivers' health-related quality of life (HRQoL)

The impact of PH1 on health-related quality of life (HRQoL) is influenced by the degree of PH1 disease progression, which can vary significantly between patients.[CS references 40, 41]

2.2.8.1 Burden of renal impairment

As PH1 advances, HRQoL decreases with progressive renal impairment, and advanced renal impairment can have a profound negative effect on aspects of HRQoL such as physical functioning and physical role limitations.[37, 38] Chronic loss of renal function may be punctuated by acute clinical events, which can further impair patient well-being and hasten kidney damage.[10, 31, 39]

The intensity and burden of dialysis for patients with more advanced stages of renal decline is significant and difficult to sustain, both for the patient and their caregiver(s).[39] It may involve daily travel to hospital for long dialysis sessions, sometimes followed by nocturnal dialysis sessions at home.[39, 40] Furthermore, because conventional dialysis (three sessions per week) is not effective for lowering oxalate levels in PH1, patients with systemic oxalosis may require up to six haemodialysis sessions per week.[41]

ERG comment: Garg 2017 showed that frequent and intensive haemodialysis led to improvements in HRQoL compared to people receiving conventional haemodialysis.[41]

2.2.8.2 Burden of high oxalate levels

Systemic oxalosis (a consequence of advanced renal impairment in PH1) significantly impacts HRQoL through diverse and sometimes severe, debilitating, and life-threatening systemic manifestations.[2] Even before the onset of such manifestations, PH1 patients are burdened with fear of progression to systemic oxalosis with associated anaemia, bone fractures, heart failure, joint damage, neuropathy, skin ulceration, severe weakness, and vision impairment.[39]

PH1 patients are at increased risk of developing painful and potentially debilitating renal stones, which may cause acute loss of renal function due to obstruction of urinary outflow.[39] Eventually, all patients with PH1 are expected to develop renal stones, based on the natural history of the disease.[21] Renal stones negatively impact HRQoL through symptoms including renal or ureteric colic (abdominal pain), blood in the urine, painful urination, the urge to urinate often, blockage of the urinary tract, and repeated urinary tract infections.[42] HRQoL for PH1 patients is further negatively impacted by associated urologic interventions and procedures aimed at managing renal stones.[39]

ERG comment: No comments on this Section.

2.2.8.3 Added burden in childhood

Hyperhydration is particularly burdensome in childhood. Infants and younger children who are unable to comply may require a nasogastric or percutaneous endoscopic gastrostomy tube passed into the stomach through the abdominal wall, to provide a means of delivering continuous hyperhydration.[3]

ERG comment: No comments on this Section.

2.2.8.4 Burden to families and caregivers

Living with PH1 presents many challenges to caregivers and families of patients with PH1. Although disease progression and severity are variable, caring for a child or an adult with PH can add substantial strain to the family due to intense medical requirements and associated financial hardship.[39]

The impact on caregivers, especially of young children, of continuously maintaining hyperhydration regimens over many years can be considerable.[3, 39] Factors such as treatment-related interruptions to school, work and family life, financial strain due to missed work, anxiety associated with potential kidney failure, and the need for frequent dialysis have a significant negative impact on the quality of life of PH1 caregivers and families.[39] In addition, the requirement for almost daily travel to long dialysis sessions following the onset of advanced disease can become all-consuming.[39] The possibility that a child with PH1 will progress to ESKD or die by their second decade of life must also significantly impact the quality of life of caregivers and families.[16]

ERG comment: No comments on this Section.

2.3 Current service provision

Current treatments are used to target one or more manifestations of PH1: reduce calcium oxalate supersaturation in the urine or plasma to minimise oxalate crystallisation; treat calcium oxalate renal stones; promote catalytic activity of the mis localised AGT enzyme; remove oxalate from plasma via dialysis; normalise hepatic oxalate production; and/or restore lost renal function via organ transplantation. According to the CS, each category of treatment options is limited in some way.[1]

2.3.1 Supportive care measurements and pyridoxine

An oxalate-controlled diet, hyperhydration, and citrate supplementation are supportive care measures intended to prevent oxalate crystallisation in the kidneys of patients with preserved renal function. However, these approaches are described by the CS report as not addressing the underlying defect in PH1, as having limited efficacy, and as being ineffective at slowing disease progression.[16, 20, 21, 32, 35]

ERG comment: Cochat 2013[20], Milliner 2017[21], Benshalom 2015[32] and Harambat 2010[16] were cited to demonstrate the ineffectiveness of hyperhydration and citrate supplementation, but these papers do not provide data nor text that strongly substantiates this. In contrast, some of these papers suggest both are useful supportive strategies.[21, 32]

Pyridoxine is one of the few non-invasive options that has been historically available to patients with preserved renal function. The CS report cites evidence that 5% to 10% of the overall PH1 population retain some degree of AGT activity and have the potential to fully respond to pyridoxine.[4, 16, 17] The CS stresses, however, that treatment with pyridoxine does not necessarily lead to normalisation of oxalate levels even in this subset of patients.[4, 16-19]

As an example of this, the CS reports that in a prospective trial, 50% of 12 PH1 patients receiving pyridoxine experienced a pyridoxine response, defined as at least a 30% reduction in urinary oxalate from baseline to week 24.[43] None of the patients, including the G170R homozygotes, experienced complete normalisation of oxalate levels. Only 38% (three of eight) outside of the G170R homozygote subgroup achieved a pyridoxine response of at least a 30% reduction in urinary oxalate from baseline.[43]

The CS concludes that the evidence base for pyridoxine is poor, despite there being considerable discussion on this intervention in the literature.[16, 20, 43, 44]

ERG comment: Benshalom 2015 provides useful data on the effectiveness of pyridoxine [*"Pyridoxine (vitamin B6), a cofactor of AGT, was reported to be beneficial in about a third of patients with PH1, specifically those with p.Gly170Arg or Phe152Ile mutations"*] but this is not referenced in the CS.[32] Likewise, the evidence in support of pyridoxine referred to by Cochat 2013[20] [*Pyridoxine supplementation is helpful in primary hyperoxaluria type 1 (but not in other forms of primary hyperoxaluria)*] is not referenced. One of the references is used in the CS to

substantiate the rate of patients who respond to pyridoxine.[4] This reference states that pyridoxine only works in a minority of patients (~5% of the PH1 population) but this is not based on any cited evidence or data. Lorenz 2014 suggests that pyridoxine does actually lead to a good response which is contrary to the claim made in the CS [*This series suggests that a subgroup of PH1 patients demonstrate sustained response to pyridoxine therapy following KTx*].[17] The CS concludes that the evidence base for pyridoxine is poor, which may be partially true, but this statement should be interpreted in light of the fact that the evidence base for lumasiran is also limited (with the possible exception of the single randomised controlled trial (RCT)).

2.3.2 Dialysis

In more advanced stages of renal decline, dialysis may be initiated to slow the build-up of systemic oxalate. It may also provide some of the key function normally carried out by the kidney in patients with ESKD.[CS references 20, 150, 151] However, the rate of oxalate production in PH1 patients greatly surpasses the ability to remove it since oxalate is sequestered in organs and re-enters the plasma following dialysis. Since conventional dialysis is typically insufficient for lowering oxalate levels in PH1, patients with PH1 require more frequent haemodialysis and peritoneal dialysis sessions (six to seven times per week, as contrasted with three-times-a-week conventional dialysis schedules), and even this intensive schedule is reported by the CS to be inadequate to consistently lower oxalate.[2, 3, 11, 20, 21, 32, 41, 45]

ERG comment: Some of the references used by the CS to support its suggestion that intensive schedules of dialysis are inadequate to lower oxalate do not provide adequate data for this purpose, and indeed sometimes contradict it. For example, Cochat 2013[20] and Milliner 2017[21] cite evidence that intense daily high flux dialysis will maintain plasma oxalate below 30-45 micromol/litre. Furthermore, Garg 2017 showed that frequent and intensive dialysis led to improvements in HRQoL.[41]

2.3.3 Transplantation

In the absence of effective treatment, excessive production of endogenous oxalate will continue for as long as the native liver is present in PH1 patients. For patients with PH1 who have progressed to later-stage kidney disease, European PH1 clinical guidelines recommend combined/sequential liver–kidney transplant to resolve the underlying metabolic defect and restore renal function.[3] A dual transplant is required because transplantation of each organ serves different therapeutic goals. Transplantation of the liver resolves the endogenous overproduction of oxalate in the liver, which is the central driver of the pathology. Transplantation of the kidney is required to restore the renal function previously lost to oxalate nephropathy and thus eliminate the need for continued dialysis.[3, 20]. However, this intervention is associated with morbidity and mortality.[CS references 5 to 53, 59 to 61]

There is no literature beyond individual case reports and case series reporting isolated liver transplantation (i.e. liver transplant without a kidney transplant) as part of ECM for PH1 or regarding appropriate circumstances for use of this approach. Although isolated liver transplantation is a potentially useful procedure that can correct the underlying metabolic defect, it cannot restore lost renal function to the patient and therefore is generally considered to be a standard option for patients in later stages of renal impairment due to PH1.[21]

ERG comment: No comments on this Section.

2.3.3. Other surgical procedures

Aside from the chronic, progressive manifestations of PH1, renal stones may occur frequently throughout the course of PH1, with painful and potentially debilitating effects, and may require surgical remediation or other medical interventions.[21] Shockwave lithotripsy (SWL) is a viable first option but has a low success rate, and subsequent endoscopic surgery is often needed. Calcium oxalate stones are among the hardest renal stones and thus more resistant to SWL.[CS reference 152]

ERG comment: No comments on this Section.

2.3.4 Surveillance

Regular assessment of oxalate levels and serum creatinine (as an indicator of renal function) is recommended as part of monitoring for patients with PH1. Renal ultrasound examination or other kidney imaging, urinalysis, and periodic fundoscopic eye examinations are also recommended to track deposition of oxalate and other manifestations of PH1 disease progression. In patients with severe kidney damage, several additional tests are recommended to ascertain systemic disease manifestations: regular X-ray examination of the long bones, electrocardiogram for detection of conduction abnormalities, echocardiogram for detection of oxalate cardiomyopathy, haemoglobin levels, thyroid function testing, and frequent clinical evaluation for additional complications of systemic oxalosis.[CS references 20, 34, 62]

ERG comment: No comments on this Section.

2.3.5 Avoidance of exacerbating agents

Dehydration can lead to irreversible kidney failure and should be strictly avoided. Intake of vitamin C exceeding the recommended daily allowance, loop diuretics, high doses of nonsteroidal anti-inflammatory medications, or other medications that can compromise renal function should also be avoided. PH1 patients should also avoid consumption of large quantities of foods and beverages with high oxalate content, e.g. beetroot, chocolate, rhubarb, spinach, starfruit, tea.[CS references 20, 34, 62, 154]

ERG comment: No comments on this Section.

2.3.6 Evaluation of relatives at risk

Early diagnosis of at-risk relatives enables early institution of treatment and preventive measures.[21] Based on consultation with PH1 experts in the UK, prenatal screening is not routinely performed except in families with a child who has been diagnosed with PH1.

ERG comment: No comments on this Section.

2.3.7 Issues with current clinical practice

As described in the previous Sections, ECM measures (i.e. oxalate-controlled diet, hyperhydration, citrate supplementation, and pyridoxine) used in patients with PH1 with preserved renal function do not address the underlying cause of disease, have not shown evidence of the ability to halt disease progression, and/or have limited efficacy in a narrow subpopulation (pyridoxine). For patients in more advanced stages of renal decline, even intensive haemodialysis and peritoneal dialysis schedules may not be inadequate to consistently lower oxalate. Combined/sequential liver–kidney transplantation is the only treatment strategy available to resolve the underlying metabolic defect and restore lost renal function among patients with advanced renal disease, although the procedure is associated with

morbidity and mortality. A key consideration for optimising post-transplant outcomes is the patient's clinical status prior to transplantation, which is driven by their oxalate levels.

ERG comment: No comments on this Section.

2.4 Description of treatment under assessment

Lumasiran is an siRNA therapeutic that treats the underlying cause of PH1 manifestations by substantially reducing endogenous oxalate levels, typically to normal or near-normal levels in PH1 patients.

Lumasiran is designed for people who have PH1, who have not had a transplant. People who have undergone liver transplant (with or without kidney transplant) would not require treatment with lumasiran, as the source of the excess oxalate production is eliminated by removal of the patient's liver in the transplant procedure.[15] The CS states that eligible patients appear to cover a wide age-span, reporting that patients in the ILLUMINATE studies ranged in age from infants as young as 3 months old to adults as old as 60 years.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
Population	People with PH1	People with PH1	N/A – in line with the NICE final scope.	The population is in line with the NICE scope. In light of other, contextual information, the ERG asked for more specific details about population eligibility and these are outlined in Section 3.1 below.
Intervention	Lumasiran (OXLUMO™)	Lumasiran (OXLUMO™)	N/A – in line with the NICE final scope.	The intervention is in line with the NICE scope. In the included studies, lumasiran was administered in combination with ECM. The intervention in the economic model was described as Lumasiran plus ECM, which *"…may include an oxalate-controlled diet, hyperhydration, pyridoxine, and oral citrate…",* although it appears that only pyridoxine was explicitly costed.
Comparator(s)	• ECM without lumasiran (including vitamin B6 and an oxalate-controlled diet) • Liver transplant with or	The economic model considered ECM without lumasiran to include: • Pyridoxine • Oxalate-controlled diet	Although isolated liver transplantation is a potentially useful procedure to correct the underlying metabolic defect in patients with PH1, it cannot restore	The company mentions: *'Liver transplant with a combined or sequential kidney transplant in patients with advanced PH1'* whereas the NICE scope does

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
	without a combined or sequential kidney transplant • Haemodialysis • Hyperhydration	• Liver transplant with a combined or sequential kidney transplant in patients with advanced PH1 • Haemodialysis • Hyperhydration Isolated liver transplantation (i.e. liver transplant without a kidney transplant) has not been included in the economic model.	lost renal function to the patient.[21] European PH1 treatment guidelines do not recommend pre-emptive isolated liver transplantation, except in highly selected patients.[3] The procedure is not considered standard practice and may be associated with poorer outcomes than those achieved with combined/sequential liver–kidney transplantation.	not specify patients with advanced PH1. The justification of excluding isolated liver transplantation is uncertain and there are no supporting references for the statement: *'The procedure is not considered standard practice and may be associated with poorer outcomes than those achieved with combined/ sequential liver–kidney transplantation.'*
Outcomes	The outcome measures to be considered include: • Oxalate levels in urine • Oxalate levels in plasma • Change in eGFR • Need for liver transplant with or without a kidney transplant • Mortality • AEs of treatment • HRQoL	The following measures were considered in the economic model: • Oxalate levels • Change in eGFR • Need for liver transplant with a kidney transplant • Mortality • AEs of treatment • HRQoL • Renal stone events • Systemic oxalosis	Excess oxalate production by the liver, regardless of how it is measured, is the driver of PH1 morbidity and mortality.[20] As described above, isolated liver transplantation is not considered standard practice. Renal stone events and systemic oxalosis impact quality of life and can be key drivers of disease progression in PH1.[10, 11, 30, 31]	The company's consideration allows for measurement of urinary or plasma oxalate levels as per the NICE scope. The justification of excluding isolated liver transplantation is uncertain (see ERG comment above). The company has suggested two outcomes not listed in the NICE scope: renal stone events; and systemic oxalosis.
Nature of the condition	• Disease morbidity and patient clinical disability with current	• Disease morbidity and patient clinical disability with current	N/A – in line with the NICE final scope.	These aspects are covered in some detail in Section B of the

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
	standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options		CS as well as in Section 2 of this report.
Clinical effectiveness	• Overall magnitude of health benefits to patients and, when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	Not addressed in the company's statement of the DP	No information provided as part of the company's statement of the DP.	The company's views on health benefits to patients and benefits to carers are summarised in Section 9.9.3 of the CS. The company's views on the heterogeneity of health benefits within the population are summarised in Sections 9.9.3 and 9.9.4 of the CS. In Section 12.8.4 of the CS, the company outlines future analyses that might *'enhance the robustness/completeness of the results'*. This relates to the ongoing extension periods for the ILLUMINATE-A and ILLUMINATE-B trials and the anticipation of being able to detect longer-term events such as renal stone events, nephrocalcinosis and development of ESKD. Section 10.1.16 of the CS outlines treatment discontinuation rules in relation

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
				to patients who are pregnant or breast-feeding and does not mention the overall population with PH1.
Value for money (including cost to the NHS and PSS)	• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	N/A – in line with the NICE final scope.	In line with NICE scope
Impact of the technology beyond direct health benefits	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and PSS • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and PSS • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the	N/A – in line with the NICE final scope	All point were considered in a narrative, but potential benefits were not quantified

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
	specialised service • Staffing and infrastructure requirements, including training and planning for expertise	specialised service • Staffing and infrastructure requirements, including training and planning for expertise		
Other considerations (including subgroups and issues related to equality)	If the evidence allows, the following subgroups will be considered: • Infants with rapid and progressive disease • Children with a family history confirmed by cord blood testing • Children and adults presenting with kidney stones Guidance will only be issued in accordance with the marketing authorisation.	The following subgroups were considered in the economic model: • Patients of all ages with initial infantile onset of PH1 • Infants with infantile onset of PH1	PH1 has particularly devastating consequences for children with infantile onset, with rapid progression to ESKD and significant excess mortality.[3, 11, 12, 16, 21, 46-48] The lumasiran treatment effect is the same across patients, but the derived benefits may be quite different for different patient types. The potential years of life gained are greater for younger patients than for adults. There is inadequate evidence to consider subgroup analysis for: • Children with a family history confirmed by cord blood testing, as cord blood testing is not a part of standard clinical practice in PH1	The company has described different subgroups to those listed in the NICE scope. The company's second-listed subgroup *'Infants with infantile onset of PH1'* (and the associated rationale comment) may encompass the first subgroup listed in the NICE scope (as indicated in Section B 6.1.2 of the CS). Regarding the company's second rationale comment (*'The lumasiran treatment effect is the same across patients, but the derived benefits may be quite different for different patient types'*), the distinction between *'treatment effect'* and *'derived benefits'* is not clear. There are no supporting references for the statements *'The potential years of life gained are greater for younger patients than for adults'* and *'Children with a family history*

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
			• Children and adults presenting with kidney stones, as eventually, all patients with PH1 are expected to develop renal stones, based on the natural history of the disease[21]	*confirmed by cord blood testing, as cord blood testing is not a part of standard clinical practice in PH1'.* Different patients may present with kidney stones at different times so the rationale for the final bullet point is uncertain. The company did not mention issues relating to equality within its DP statement but does provide details on this in Section 5 of the CS.
Based on Table A1 and other sections of the CS as referred to in the table above[1] AE = adverse effect; CS = company submission; DP = decision problem; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ERG = Evidence Review Group; ESKD = end-stage kidney disease; HRQoL = health-related quality of life; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PH1 = primary hyperoxaluria type 1; PSS = Personal Social Services; QALY = quality-adjusted life year				

3.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) scope is people with PH1.[49] The population shown in the company's statement of the decision problem (DP; Table A1 of the CS) is in line with that in the NICE scope.[1] The consideration of the population as applied to the systematic literature review (SLR) is summarised in Section 4.1.2.

The ERG noted the following statements in Sections 6.1 and 13.1 of the CS: *"clinical manifestations of PH1 typically first appear in childhood and persist into adulthood"* and *"considering that lumasiran would only be used in patients who have not already undergone [liver transplant or combined liver–kidney transplant]…"*, respectively.[1]

This prompted the ERG to request clarification on

1. Whether lower or upper age limits or any other criteria for determining eligibility should apply for treatment with lumasiran.
2. Whether eligibility should be limited to people with PH1 who have not already undergone a liver transplant or a combined live and kidney transplant.
3. The proportion of patients with advanced PH1 who would be eligible for treatment with lumasiran.[50]

In its response, the company confirmed that the population in the DP should be re-expressed as people with PH1 who have not already undergone a liver transplant or a combined liver-kidney transplant.[51, 52] In terms of age groups, the company stated that all children with PH1 and elevated oxalate levels despite established clinical management (ECM) who have not undergone liver transplant should be eligible for treatment with lumasiran.

The company enlisted the help of a clinical expert to inform their response in relation to adult patients.[51, 52] This resulted in the company suggesting that for adult patients, treatment with lumasiran should be limited to those in later stages of chronic kidney disease (CKD), for example CKD 3, CKD 4 or ESKD. Exceptions could be made for adult patients in early CKD stages showing evidence of progression or severe comorbidities. The clinical expert suggested that progression may be defined as at least a five-point decline per year in estimated glomerular filtration rate (eGFR). In light of the clinical expert's further advice, the company maintained that most adult patients eligible for treatment with lumasiran would have advanced PH1 (defined as eGFR no more than 45 ml/min/1.73 m^2 which corresponds to CKD stages 3b, 4 and 5 and plasma oxalate level (POx) of at least 20 μmol/l). This definition was used in the included ILLUMINATE-C trial.[51, 52]

On 15 October 2020, lumasiran received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), recommending its use for the treatment of PH1.[53] Lumasiran received centrally authorised European Union (EU) marketing authorisation for the treatment of PH1 on 19 November 2020,[53] which was automatically converted to a UK marketing authorisation (effective in Great Britain only). Lumasiran was issued with a UK marketing authorisation number (PLGB 50597/0005) on 1 January 2021. Outside of the UK, lumasiran is approved for use in the EU, United States of America (USA), Brazil and Switzerland.[1]

3.2 Intervention

The intervention, lumasiran (OXLUMO™), as described in the company's statement of the DP (Table A1 of the CS) and the study selection criteria for (Table C1 of the CS)[1] is in line with the NICE scope.[49]

Lumasiran is administered as a subcutaneous injection with dosing based on body weight, as follows:[1]

- Patients <10 kg: 6 mg/kg once monthly for 3 months (loading dose), then 3 mg/kg once monthly (maintenance dose)
- Patients 10 kg to <20 kg: 6 mg/kg once monthly for 3 months (loading dose), then 6 mg/kg every 3 months (maintenance dose)
- Patients ≥20 kg: 3 mg/kg once monthly for 3 months (loading dose), then 3 mg/kg every 3 months (maintenance dose)

Administration of the subcutaneous injection is assumed to take minutes.

It is expected that patients will be treated with lumasiran for the duration of their lives or until combined or sequential liver–kidney transplantation, subject to the clinical judgement of the treating physician.[1]

In the included studies, lumasiran was administered in combination with ECM, as described in Section 3.3. The intervention in the economic model was described as Lumasiran plus ECM, which *"…may include an oxalate-controlled diet, hyperhydration, pyridoxine, and oral citrate…"*, although it appears that only pyridoxine was explicitly costed, see Section 5.3.3.2.

3.3 Comparators

The NICE scope specified the following comparators: ECM without lumasiran (including vitamin B6 and an oxalate-controlled diet); a liver transplant with or without a combined or sequential kidney transplant; haemodialysis; and hyperhydration.[49]

The company's statement of the DP indicated congruence with the NICE scope apart from the exclusion of isolated liver transplant, i.e. a liver transplant without a kidney transplant. The company's rationale for this exclusion was that isolated liver transplant may be associated with poorer outcomes compared with combined or sequential liver-kidney transplants, however no supporting evidence was cited and the impact of applying this criterion to the submission is uncertain. This was also discrepant with the company's study selection criteria for the SLR which stipulated vitamin B6, hyperhydration, calcium oxalate (CaOx) crystallisation inhibitors, haemodialysis, combined or sequential liver-kidney transplant and isolated liver or kidney transplant as comparators (see Table 4.2).[1]

Of the studies included in the company's SLR, the ILLUMINATE-A RCT was placebo controlled and all patients were required to continue their ECM including vitamin B, crystallisation inhibitors and hyperhydration (haemodialysis was not mentioned in the CS or clinical study report (CSR)).[1, 46] The other two ILLUMINATE studies did not include control groups.[54, 55]

Within their consideration of the DP, the company also specified that combined or sequential liver-kidney transplants would be undertaken in patients with advanced PH1.[1] The NICE scope did not specify patients with advanced PH1 in relation to this intervention.

The company were requested to provide clarification as to the precise nature of ECM as implemented in NHS clinical practice to which they responded that they planned to answer this question by 22 February 2022.[50] The company was also asked to compare this to the ILLUMINATE trials to which they responded that across the 78 patients in the ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATEC trials, 44 (56%) were receiving pyridoxine. They also stated that the same number of patients (i.e. 44) were receiving hyperhydration at baseline across ILLUMINATE-A and ILLUMINATE-B. They stated that hyperhydration status was not being available for ILLUMINATE-C, but because fluid control is necessary for patients with advanced kidney disease, it is unlikely that any ILLUMINATE-C patients would be on hyperhydration. Although no details of NHS clinical

practice were provided, they asserted that the clinical trial and economic model results were generalisable.[51, 52]

3.4 Outcomes

The NICE scope listed the following outcome measures:[49]

- Oxalate levels in urine
- Oxalate levels in plasma (POx)
- Change in eGFR
- Need for liver transplant with or without a kidney transplant
- Mortality
- AEs of treatment
- HRQoL

The outcomes listed in the company's DP statement were mainly in line with the NICE scope, with exceptions as follows:

- The company included assessment of oxalate levels regardless of measurement method (i.e. from urine or plasma) as a single outcome. The correspondence between urinary and plasma oxalate measurements is not clear from the information provided.
- Similar to the points above, the need for transplant outcome only referred to combined or sequential liver-kidney transplants, with isolated liver transplants being excluded from consideration.
- The ERG noted that the company added two outcomes that were not listed in the NICE scope, namely, renal stone events and systemic oxalosis.

3.5 Nature of the condition

The ERG's summary and critique of the company's description of the nature of the condition can be found in Section 2.

3.6 Clinical effectiveness

The NICE scope suggested aspects of clinical effectiveness that should be considered in the CS.[49] None of these were considered as part of the company's DP statement. In light of this, the ERG considered whether the points had been addressed elsewhere in the submission. The points from the NICE scope have been listed below in italicised font, followed in each instance by observations from the ERG. These points are discussed further in Section 4 of this report.

- *'Overall magnitude of health benefits to patients and, when relevant, carers'* – the company provides a summary of benefits to patients and carers in Section 7.2.2 of the CS but since this is presented within a context-setting part of the CS, this appears pre-emptive of the results.[1]
- *'Heterogeneity of health benefits within the population'* – it is not clear whether the NICE scope is referring to heterogeneity of health benefits or heterogeneity within the population and resulting differential results across subgroups. As part of Section 7 of the CS (*'Impact of the disease on quality of life'*), the company discusses expectations of the effects of the intervention in patients initiating lumasiran in earlier or later stages of PH1. As for the point above, this seems pre-emptive of the CS results sections.[1]
- *'Robustness of the current evidence and the contribution the guidance might make to strengthen it'* – this statement from the NICE scope is not clear. For example, it is not clear what is meant by *'current evidence'* as this could be the CS or whatever information was available on clinical

management of PH1 before that. The company refers to robustness in Section 12.8.4 but this is slightly misleading as the discussion concerns longer-term outcomes (*'completeness'* which is a term used by the company within the same discussion is a more apt term).[1]
- The treatment discontinuation details in the CS only refer to pregnant or breastfeeding patients and not to the population overall (Section 10.1.6 of the CS).[1]

3.7 Value for money

The NICE scope indicated that the following should be covered:[49]

- Cost effectiveness using incremental cost per quality-adjusted life year (QALY)
- Patient access schemes and other commercial agreements
- The nature and extent of the resources needed to enable the new technology to be used

The CS includes cost effectiveness analyses in which results were presented in the form of incremental costs per quality-adjusted life years (QALYs) over a lifetime time horizon, with the impact of treatment on the HRQoL of patients and caregivers included in the analysis. Costs were calculated according to the National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and QALYs were discounted at 3.5%. In general, the NICE scope and reference case were followed when assessing the costs of lumasiran to the NHS and the value for money it provides.

3.8 Impact of the technology beyond direct health benefits

Information in the NICE scope suggested that the following aspects should be considered within the CS:[49]

- Whether there are significant benefits of the intervention other than health
- Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and PSS
- The potential for long-term benefits to the NHS of research and innovation
- The impact of the technology on the overall delivery of the specialised service
- Staffing and infrastructure requirements including training and planning for expertise

The company's consideration of these aspects was in line with the NICE scope.[1] All point were considered in a narrative, but potential benefits were not quantified.

3.9 Other considerations

The NICE scope specified that the following subgroups should be considered, subject to availability of evidence:[49]

- Infants with rapid and progressive disease
- Children with a family history confirmed by cord blood testing
- Children and adults presenting with kidney stones

In their consideration of the DP, the company described different subgroups to those in the NICE scope, as follows:[1]

- Patients of all ages with initial infantile onset of PH1
- Infants with infantile onset of PH1

Information in Section B 6.1.2 of the CS suggests that the company's second-listed subgroup matches the first-listed subgroup in the NICE scope. Other parts of the company's DP statement are uncertain

because of lack of clarity (i.e. the distinction between 'treatment effect' and 'derived benefits' is unclear) and absence of supporting references (i.e. the statements referring to greater life years gained for younger patients compared with adults; and family history confirmed by cord blood testing not being part of standard clinical practice). The rationale for not analysing the subgroup of patients with kidney stones is also unclear.[1]

Issues of equality were not mentioned within the company's consideration of the DP, but these are outlined in Section 5 of the CS.

4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical and cost effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[56, 57] The ERG has presented only the major limitations of each search strategy in the report.

Appendices A to C of the SLR detail the searches undertaken to identify clinical efficacy and safety data for lumasiran for primary hyperoxaluria and to identify any relevant cost, healthcare resource use, or utilities data in PH1.[58] The searches were conducted in three stages: an initial search in June 2020 and two updates in April 2021 and August 2021, respectively. The same search strategies were used in the original SLR and updates.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the SLR (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE	Ovid	1946-19/6/20 1946-12/4/21 1946-3/8/21	20/06/20 13/04/21 4/08/21
Embase	Embase	Embase.com	1980-Wk 25 2020 1980-Wk 14 2021 1980-Wk 30 2021
CENTRAL CDSR	Wiley	Issue 6/12, June 2020 Issue 4/12, April 2021 Issue 8/12, Aug 2021	20/06/20 12/04/21 4/08/21
PubMed	Internet	To-date	20/06/20 12/04/21 4/08/21
EconLit	EBSCO	1886-Present	20/06/20 12/04/21 4/08/21
NHS EED HTA Database	CRD	To 2015	20/06/20
ScHARR HUD	Internet	To-date	20/06/21 12/04/21 4/08/21

Resource	Host/Source	Date Ranges	Dates searched
International HTA Database	Internet	To-date	12/04/21 4/08/21
CPCI-S	Web of Science	1990-Present	20/06/20 13/04/21 4/08/21
Additional resources			
ClinicalTrials.gov	Internet	To-date	21/06/20 12-15/04/21 4/08/21
EUCTR			
NICE			
IQWiG			
US FDA			
EMA			
Conferences			
ASN Annual Meeting ESPN Annual Meeting IPNA Congress ISN WCN ISPOR	Internet/Handsearch	2018-2021 (where available)	Not stated

ASN = American Society of Nephrology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CPCI-S = Conference Proceedings Citation Index-Science; CRD = Centre for Reviews and Dissemination; EED = Economic Evaluation Database; EMA = European Medicines Agency; ESPN = European Society for Paediatric Nephrology; EUCTR = European Union Clinical Trials Register; FDA = Food and Drug Administration; HTA = health technology assessment; IPNA = International Pediatric Nephrology Association; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; ISN = International Society of Nephrology; ISPOR = Professional Society for Health Economics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; ScHARR HUD = University of Sheffield Health Utilities Database; US = United States; WCN = World Congress of Nephrology

ERG comment:

- A single set of searches was undertaken to identify clinical efficacy and safety data for lumasiran and established clinical management, and to identify any relevant cost, healthcare resource use, or utilities data in primary hyperoxaluria.
- No date or language limits were applied to the majority of the searches. Searches of conference proceedings were limited to 2018-date.
- An extensive range of databases, conference proceedings, clinical trials registers and additional grey literature resources were searched.
- Searches were well structured, transparent, and reproducible.
- The search strategies contained a population facet (primary hyperoxaluria), which in the MEDLINE and Embase searches was then combined with filters for randomised and controlled trials, observational studies, AEs, systematic reviews, economics, and HRQoL. All filters used were named and cited where appropriate.
- Given the relatively small size of the results set retrieved by the search for primary hyperoxaluria, it may have been more beneficial to search MEDLINE and Embase for just the population facet without search filters, as any filter introduces the chances of relevant records

being missed by a search. However, given the range of resources covered by the literature searches, the quality of the filters used, and the fact that for many databases the searches did not include filters, the ERG believes it unlikely that relevant references were missed.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for experimental and observational evidence is presented in Table 4.2.

Table 4.2: Eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	Adult and paediatric patients (any age) with PH1	• Animal studies • In vitro studies • Healthy populations
Interventions	• Lumasiran (ALN-GO1) • BSC (hyperhydration, vitamin B6, calcium oxalate crystallisation inhibitors (citrate, pyrophosphate, magnesium), haemodialysis, and combined/sequential liver–kidney transplantation or isolated kidney/liver transplantation) • Any intervention reporting on HCRU and costs in patients with PH1	Investigational therapies including: • Oxabact® (Oxalobacter formigenes) • Nedosiran • Betaine • Diacomit® (stiripentol) • Reloxaliase
Comparators	• All comparators (placebo, BSC, active treatment) • No comparator	N/A.
Outcomes	**Effectiveness and safety** All effectiveness and efficacy outcomes including: • Change in 24-hour urinary oxalate excretion (percent and absolute) • Change in 24-hour urinary oxalate:creatinine ratio • Change in eGFR • Percentage of patients with 24-hour urinary oxalate level ≤1.5×ULN • Percentage of patients with 24-hour urinary oxalate level ≤ULN • Percentage of time that 24-hour urinary oxalate is ≤1.5×ULN • Percentage of time that spot urinary oxalate:creatinine ratio is ≤1.5×ULN • Change in plasma oxalate (percent and absolute) • Change in pre-dialysis plasma oxalate (percent) • Change in plasma oxalate AUC between dialysis sessions (percent) • Change in nephrocalcinosis	Not listed as outcomes of interest.

	Inclusion criteria	Exclusion criteria
	• Change in frequency of dialysis • Change in mode of dialysis • Change in frequency of renal stone events • Change in measures of systemic oxalosis • Time to death/graft failure, whichever occurs first • Percentage of patients with graft failure, re-transplant, or need for maintenance dialysis following graft failure • 6-month and/or 1-year acute graft rejection • Incidence of graft rejection • Reduced graft function over time (eGFR <60 ml/min/1.73 m^2) • Primary graft non-function **AEs, including:** • Incidence of any AE and proportion of patients experiencing any AEs • Incidence of SAEs and proportion of patients experiencing SAEs • Incidence of TEAEs and proportion of patients experiencing TEAEs • Proportion of patients discontinuing due to AEs **Cost effectiveness** ICERs including: • Costs per QALY, LYG, and DALY HCRU and costs including: • Resource use and monitoring frequency • Direct costs (related to drugs/treatments, AEs, and health states) • Direct medical and pharmacy healthcare costs • Indirect costs for patient and caregiver (i.e. annual loss of income (employment rate), presenteeism/absenteeism, withdrawal from labour force, and work productivity) **HRQoL** Utility values including: • Directly elicited values (time trade-off or standard gamble), generic preference-based utilities (e.g. EQ-5D), and non–preference-based utilities (e.g. SF-36) for relevant health states • Measures mapped to preference-based utility • Utilities and dis-utilities for AEs	

	Inclusion criteria	Exclusion criteria
Study design	**Effectiveness and safety:** • RCTs and open-label extensions • Single-arm trials • Observational (retrospective and prospective) studies (e.g. chart reviews, registries, surveys) • Pharmacodynamic and pharmacokinetic studies • Dose-finding/escalation studies **Economic:** • CEA, CUA, CBA, CMA, and cost-consequence analyses • Any study design for HCRU and cost HRQoL **HRQoL:** • Any study design	• Reviews • Letters • Commentaries • Editorials • Case reports • Adherence studies • Prognostic studies • Epidemiological studies • Studies of treatment prescribing patterns
Language restrictions	Publications in the English language.	Records in languages other than English.
Other limitations	For cost and resource use records: UK data only.	Non-UK cost and resource use data.

Based on Table 1 of the SLR[58]
AE = adverse event; AUC = area-under-the-curve; BSC = best supportive care; CBA = cost-benefit analysis; CEA = cost effectiveness analysis; CMA = cost-minimisation analysis; CS = company submission; CUA = cost-utility analysis; DALY = disability-adjusted life year; eGFR = estimated glomerular filtration rate; EQ-5D = European Quality of Life-5 dimensions; HCRU = healthcare resource utilisation; ICER = incremental cost effectiveness ratio; LYG = life year gained; N/A = not applicable; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life year; RCT = randomised controlled trial; SAE = serious adverse event; SF-36 = 36-Item Short Form Survey; SLR = systematic literature review; TEAE = treatment-emergent adverse event; UK = United Kingdom; ULN = upper limit of normal

ERG comment: The study selection criteria for the SLR described in the CS stipulated that studies recruiting adult and paediatric patients of any age with PH1 were sought (Table C1 of the CS).[1] This was in line with the population specified in the NICE scope.[49] Patients across the three included ILLUMINATE studies ranged in age from 3 months to 60 years. Patients in the ILLUMINATE-A RCT had a minimum age of six years.[1, 51]

There is an overlap between the intervention and comparators, i.e. best supportive care (BSC), leading to confusion. Also, in terms of intervention, there is a discrepancy between including "any intervention" reporting on healthcare resource utilisation; and excluding investigational therapies which may have reported such data.

The list of outcomes in the SLR is broader than the NICE scope.[49] Out-of-scope outcomes in the SLR included:

- Change in nephrocalcinosis
- Change in frequency of dialysis
- Change in mode of dialysis; time to death or graft failure (whichever occurs first)

- Percentage of patients with graft failure
- Re-transplant or need for maintenance dialysis following graft failure
- Incidence of graft rejection
- 6-month and/or 1-year acute graft rejection
- Reduced graft function over time (eGFR <60 ml/min/1.73 m^2)
- Primary graft non-function

In addition to these outcomes, the company listed variants of the outcomes relating to oxalate levels in urine and plasma, for example, change in 24-hour urinary oxalate excretion (percent and absolute) and change in pre-dialysis plasma oxalate (percent).[1]

The ERG notes the inclusion of intermediate (surrogate) outcomes and clinical endpoints in both, the NICE scope and the SLR study eligibility criteria (Table 4.2).[49] In terms of the NICE scope, the intermediate outcomes comprise change in urinary and plasma oxalate levels and change in eGFR level whilst clinical endpoints include mortality and the need for liver transplant with or without a kidney transplant. In addition, adverse effects and a patient-reported outcome measure (HRQoL) are common to both the NICE scope and the SLR study eligibility criteria.[49]

The results of the SLR focus on change in urinary and plasma oxalate levels with limited data provided for clinical endpoints, see Section 4.2.1 for further details. These intermediate outcomes were in turn used to inform the cost effectiveness analysis, see Section 5.3. In light of this, the ERG asked the company to explain to what extent oxalate excretion outcomes predict clinical endpoints (e.g. mortality) and HRQoL.[51, 52]

The company provided a response that outlined their reflections on the relationship between oxalate excretion outcomes and clinical endpoints from causal, correlational and biological perspectives.[51, 52] In terms of causality, the company provided a series of arguments around the effects of pre-emptive liver transplantation in patients with PH1 (describing this intervention as *"the closest clinical analog to Lumasiran treatment in this disease context"*) on outcomes such as mortality and ESKD. The nature of the relationship between pre-emptive liver transplant and clinical endpoints is not explored further in terms of taking the effects of confounding into account and so the strength of the association is uncertain. The company provided several supporting references involving patients with PH1 but scrutiny suggested that they provided weak substantiation of the arguments made because of being individual case reports or small case series,[59-63] a brief account provided in a letter to the journal editor,[64] older literature[65, 66] and duplicate references to the same evaluation.[60, 67] The company also presented supporting references relating to the correlation between oxalate levels and clinical endpoints but again, this does not provide convincing evidence as correlation is not a proxy for causation. The company concludes their response by discussing the biological effects of raised oxalate levels, but some statements are unsubstantiated or focus purely on describing the related pathophysiology.[51, 52]

The ERG argues that the use of surrogate endpoints, i.e. oxalate levels, should be restricted to chronic diseases and especially when collecting data on patient-relevant outcomes requires trials with unattainably long follow-up.[26, 34, 68] However, proposed statistical methods for surrogate endpoint evaluation, namely bivariate network meta-analysis, were not employed by the company hence any prediction of the treatment effect on the final outcome, e.g. mortality or HRQoL cannot be evaluated.[69, 70] Furthermore, results from a recent study of 187 blood samples taken from 41 patients with PH1 who had neither undergone dialysis nor transplantation, suggested that plasma oxalate levels may have limited validity to predict clinical endpoints because of fluctuating values within individuals.[71] Overall,

the ERG remains uncertain about the extent to which urinary or plasma oxalate levels can predict clinical endpoints or HRQoL and note that this is likely to result in persisting uncertainty when attempting to interpret the treatment effect for lumasiran. Therefore, this has been identified as a key issue.

The company was asked to clarify on epidemiological study designs, i.e. cross-sectional surveys, or cohort studies which were listed both as includes and excludes. In response to the request for clarification, the company stated that "*studies that were solely focused on epidemiology, and that did not report on any of the outcomes of interest, were deemed to be epidemiological studies and were excluded".* The company was also asked to clarify on English language restrictions. In response to the request for clarification, the company stated that "*The searches were broad and did not incorporate any language restrictions. Table 1 details the PICOS criteria that were used during the study selection stage. At the study selection stage, studies published in languages other than English were excluded*".[52] The ERG believes there is uncertainty about the rigour and clarity of the SLR process, i.e. potentially relevant references might have been missed.

4.1.3 Critique of data extraction

The CS states that data were extracted by one researcher and verified for accuracy by a second independent researcher.[1] In response to the request for clarification, the company stated that *"parallel extraction is generally considered the gold standard, it is limited by real-world constraints on time and resources and is not globally recommended in systematic review guidance"*.[51, 52]

ERG comment: Data extraction by two reviewers independently of each other with a third reviewer acting as an arbiter to resolve any discrepancies, is recommended to reduce the risk of bias.[72] Therefore, there is greater uncertainty about the accuracy of the extracted data.

4.1.4 Quality assessment

As per Section 2.7 of the SLR, quality assessment of RCTs and observational studies was performed by two independent researchers using a 7-item qualitative tool adapted from the Centre for Reviews and Dissemination (CRD)[73] and a 7-item qualitative tool adapted from the Critical Appraisal Skills Programme (CASP) respectively.[74]

ERG comment: The methodological quality appraisal tools used were appropriate and covered all relevant domains for the included study designs. Whilst appraisal by two independent reviewers is in line with recommended best practice for SLRs,[75] the approach for resolving disagreements was not stated.

4.1.5 Evidence synthesis

The CS stated that the lack of RCTs for the comparators listed by NICE precluded any meta-analyses or indirect comparisons. In response to the request for clarification, the company stated that *"all studies evaluating established clinical management without lumasiran were observational in design"*.[52]

ERG comment: The ERG acknowledges the lack of clinical data for conducing meta-analyses or indirect comparisons. However, the ERG believes that matched-adjusted indirect comparisons (MAIC) would have been feasible for lumasiran against ECM.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in /excluded from the submission

As reported in Section 9.2 of the CS, the SLR identified 34 studies that met the eligibility criteria.[1] No eligible unpublished studies were identified. The study selection decisions are represented in Figure C1 of the CS.[1] Only four of these studies concerned the efficacy and safety of lumasiran, and the CS only elaborates on the findings of these trials in the results section of the CS.[15, 76-78]

The other 30 trials were observational trials related to the efficacy and safety of other current treatments, and although these papers have been utilised in the background Sections of the CS, they have not been used as references in the results Section of the CS. This Section will therefore also focus on the four lumasiran studies and omit discussion of the studies relating to other treatments.[15, 76-78] Table 4.3 summarises the population characteristics of the four lumasiran trials.

Table 4.3: List of included published studies from the SLR

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Garrelfs et al. 2021[15]	ALN-GO1-003 Phase 3 ILLUMINATE-A NCT03681184	39 adults and children aged ≥6 years with diagnosis of PH1 and relatively preserved renal function. Randomised 2:1 in the 6-month double-blind period to: lumasiran 3 mg/kg SC QM×3, then Q3M starting 1 month thereafter (i.e. at study month 3), n=26 Placebo SC QM×3, then Q3M, starting 1 month thereafter (i.e. at study month 3), n=13 Extension period (up to 54 months): Patients originally randomised to lumasiran received lumasiran 3 mg/kg SC Q3M Patients originally randomised to placebo received lumasiran 3 mg/kg SC QM×3, then Q3M starting 1 month thereafter	Lumasiran. All patients continue their PH1 standard of care therapy through month 12 of the study including hyperhydration, vitamin B6, and crystallization inhibitors.	Placebo. All patients continue their PH1 standard of care therapy through month 12 of the study including hyperhydration, vitamin B6, and crystallisation inhibitors.
Frishberg et al. 2021[77]	ALN-GO1-001 Phase 1/2 NCT02706886	20 adults and children aged 6 to 64 years with diagnosis of PH1 and eGFR >45 ml/min/1.73 m^2 (Part B) Randomised 3:1 to one of three doses of lumasiran, or placebo: lumasiran, n=9 1 mg/kg SC QM (n=3) 3 mg/kg SC QM (n=3) 3 mg/kg SC Q3M (n=3) Placebo, n=3 (there was one patient for each lumasiran arm) Open-label expansion cohorts:	Lumasiran. All patients continue their PH1 standard of care therapy through month 12 of the study including hyperhydration, vitamin B6, and crystallisation inhibitors.	Placebo. All patients continue their PH1 standard of care therapy through month 12 of the study including hyperhydration, vitamin B6, and crystallisation inhibitors.

Primary study reference	Study name NCT number	Population	Intervention	Comparator
		lumasiran 1 mg/kg SC QM (n=4) lumasiran 3 mg/kg SC Q (n=4)		
Frishberg et al. 2020[76]	ALN-GO1-002 Phase 2 OLE NCT03350451	20 adults and children aged 6 to 64 years with diagnosis of PH1 who participated in the ALN-GO1-001 phase 2 multi-dose study of lumasiran (NCT02706886): 1 mg/kg SC QM (n=3) 3 mg/kg SC QM (n=7) 3 mg/kg SC Q3M (n=10)	Lumasiran. All patients continue their PH1 standard of care therapy through month 12 of the study including hyperhydration, vitamin B6, and crystallisation inhibitors.	None.
Michael et al. 2020[78]	ALN-GO1-004 ILLUMINATE-B Phase 3 NCT03905694	18 children aged under 6 years with diagnosis of PH1 and relatively preserved renal function lumasiran loading and maintenance dose based on patient weight category (up to 60 months): <10 kg: 6 mg/kg QM×3, then 3 mg/kg QM ≥10 mg to <20 kg: 6 mg/kg QM×3, then 6 mg/kg Q3M starting 1 month thereafter (i.e. at study month 3) ≥20 kg: 3 mg/kg QM×3, then 3 mg/kg Q3M starting 1 month thereafter (i.e. at study month 3)	Lumasiran. All patients continue their PH1 standard of care therapy through month 12 of the study including hyperhydration, vitamin B6, and crystallisation inhibitors.	None.

Based on Table C2 of the CS[1]

CS = company submission; eGFR = estimated glomerular filtration rate; PH1 = primary hyperoxaluria type 1; Q3M = once every three months; QM = once monthly; SC = subcutaneous; SLR = systematic literature review

As discussed in Section 3.4, the outcome measures in the NICE scope to be considered include:[49]

- Oxalate levels in urine
- Oxalate levels in plasma
- Change in eGFR
- Need for liver transplant with or without a kidney transplant
- Mortality
- Adverse effects of treatment
- HRQoL

Below, the results of each of the four trials will now be described in turn in relation to these required outcomes. In addition, additional unpublished data for an additional trial highlighted by the CS (but not included in the SLR in the CS) will be discussed.

The following will therefore be discussed in turn:

1. ILLUMINATE-A
2. ILLUMINATE-B
3. ILLUMINATE-C (unpublished data not in CS SLR)
4. ALN-GO1-001
5. ALN-GO1-002

ERG comment: The four trials were not meta-analysed in the CS, because the PICOs of each trial were very different, and only the 6-month part of the ILLUMINATE-A study could be regarded as a 'full RCT'.[1] The other RCT in ALN-GO1-001 only had one participant randomly allocated to the placebo group in each of the three dose strata. Although strictly 'randomised', and thus affording some protection against systematic selection bias, such a design would not have allowed any random mixing of characteristics across intervention and placebo groups, and so would not have gained any reductions in selection bias due to random effects. This study was therefore not recognised by the ERG as a 'full RCT'. As noted in Section 4.3, no indirect comparison analyses were carried out.

In response to the request for clarification, the company provided an overview of the outcomes listed in the NICE scope which included cross-references to the relevant Sections in the CS, please see Table 4.4.[51, 52] These are covered in Sections 4.2.1 and 4.2.2, respectively.

Table 4.4: Outcomes listed in the NICE scope and addressed in the CS

Outcome per NICE scope	Cross-reference	Specific page numbers
Oxalate levels in urine	Section 9.6.1 of the CS	ILLUMINATE-A: pg 69-77
		ILLUMINATE-B: pg 81-84
		ILLUMINATE-C: pg 86, 88, 89
Oxalate levels in plasma	Section 9.6.1 of the CS	ILLUMINATE-A: pg 69, 72, 77, 78
		ILLUMINATE-B: pg 81, 83, 85
		ILLUMINATE-C: pg 86-88
Change in eGFR	Section 9.6.1 of the CS	ILLUMINATE-A: pg 73, 74, 78, 79

Outcome per NICE scope	Cross-reference	Specific page numbers
		ILLUMINATE-B: pg 81, 83, 85
Need for liver transplant with or without a kidney transplant	Section 9.4.6 of the CS	ILLUMINATE-C: pg 67, 92
Mortality	Section 9.7.2 of the CS	ILLUMINATE-A: pg 90
		ILLUMINATE-B: pg 91-92
		ILLUMINATE-C: pg 92
		Phase 2 OLE: pg 93
Adverse effects of treatment	Section 9.7.2 of the CS	ILLUMINATE-A: pg 89-91
		ILLUMINATE-B: pg 91-92
		ILLUMINATE-C: pg 92
		Phase 2 OLE: pg 92-93
Health-related quality of life	Section 10.1.3 of the CS	ILLUMINATE-A: pg 99

Based on Table provided in response to question A5.b of the response to request for clarification[51, 52]
CS = company submission; eGFR = estimated glomerular filtration rate; NICE = National Institute for Health and Care Excellence; OLE = open-label extension

4.2.1.1 ILLUMINATE-A: 6-month RCT

ILLUMINATE-A (ALN-GO1-003) project comprised two parts:[15]

- The first part was a double blinded 6-month randomised trial, where it was possible to make valid inferences about treatment effects.
- The second part, which was a continuation of the first part, involving the same participants, was an open label extension period where all participants had the study drug and there was no comparator.

Because the possible level of inference about treatment effects will be very different from these two Sections the two parts will be dealt with separately. The information below is taken from the information in the CS, and the ERG inferred or took information from the included papers.[1]

4.2.1.1.1 Study characteristics

Table 4.5 summarises the main characteristics of Garrelfs 2021.[15]

Table 4.5: Study characteristics for ILLUMINATE-A 6 month double blind RCT

Study	**Garrelfs 2021[15]**
Study type	RCT; international, multicentre, phase 3 study: double-blind period: randomised, 6-month, placebo-controlled, double-blind treatment period
Number of participants randomised	39 (26 lumasiran, 13 placebo)
Study sites	Sixteen study centres across eight countries (UK (three sites), France (three), Germany (one), Israel (three), the Netherlands (one), Switzerland (one), United Arab Emirates (one), and USA (three)) The three UK sites were: • Birmingham Women's and Children's Hospital, Birmingham • Great Ormond Street Hospital, London • Royal Free Hospital, London [redacted]
Inclusion	• Age ≥6 years with documented or confirmed PH1 as determined by genetic analysis • Mean 24-hour urinary oxalate excretion ≥0.70 mmol/24 hours/1.73 m^2 (from first two valid 24-hour urine collections) • Pyridoxine: allowed if patient was on a stable regimen for >90 days before randomisation and willing to remain on this stable regimen for 12 months from first study drug administration • Willing to comply with study requirements; written informed consent from patient or legal guardian(s) Note that all patients were required to continue their PH1 established clinical management (including hyperhydration, crystallisation inhibitors, and pyridoxine) through month 12 of the study.

Study	Garrelfs 2021[15]
	All patients were to continue the PH1 standard-of-care regimen that had been in place at the time of enrolment in the trial, including hyperhydration, crystallization inhibitors, pyridoxine therapy, or a combination of these treatments, through month 12 of the trial.
Exclusion	• Clinical evidence of extrarenal systemic oxalosis • ALT or AST >2×ULN • Total bilirubin >1.5×ULN (patients with elevated total bilirubin that was secondary to documented Gilbert's syndrome were eligible if the total bilirubin was <2×ULN) • INR >1.5 (patients on oral anticoagulant (e.g. warfarin) with an INR <3.5 were allowed) • Known active human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection • eGFR <30 ml/min/1.73 m^2 at screening (calculated using the MDRD formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age) • Investigational agent within the last 30 days or five half-lives, whichever was longer, or are in follow-up of another clinical study prior to randomisation • History of renal or liver transplant • Other medical conditions or comorbidities, which in the opinion of the Investigator, would interfere with study compliance or data interpretation • History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc • History of intolerance to SC injection(s) • Unwilling to comply with the contraceptive requirements during the study period • Pregnant, planning a pregnancy, or breast-feeding • Unwilling or unable to limit alcohol consumption; alcohol intake of >two units per day was excluded during the study (unit: one glass of wine (125 ml) = one measure of spirits (one fluid ounce) = ½ pint of beer (284 ml)) • History of alcohol abuse within the last 12 months before screening
Baseline differences	• ≥10% difference in distribution of ethnicity between groups • Ethnicity, lumasiran/placebo, n (%) • Asian: 3 (12)/3 (23) • White: 21 (81)/9 (69) • ≥10% difference in distribution of region between groups

Study	Garrelfs 2021[15]		
	• Region, lumasiran/placebo, n (%) • Europe: 10 (38)/8 (62) • North America: 11 (42)/2 (15)		
Randomisation	Randomised with stratification for mean baseline urinary oxalate level (>1.70 versus ≤1.70 mmol/24 hours/1.73 m^2); used poorly described form of allocation concealment (merely stated that there was an interactive response system). However, trends for systematic differences between groups at baseline, with a tendency for the lumasiran group to be older, have less pyridoxine use and a higher eGFR.		
Intervention	Lumasiran (3 mg per kilogram of body weight) was administered once monthly for three doses, followed by maintenance doses given once every 3 months beginning 1 month after the last loading dose.		
Comparator	Placebo was administered once monthly for three doses, followed by maintenance doses given once every 3 months beginning 1 month after the last loading dose.		
Baseline demographics		**Lumasiran, n=26**	**Placebo, n=13**
	Age, median (range), years	16.5 (6–47)	11.0 (6–60)
	Age at diagnosis, median (range), years	3 (−1 to 59)	8 (0–36)
	Female, n (%)	8 (31)	5 (38)
	Asian	3 (12)	3 (23)
	White	21 (81)	9 (69)
	Other	2 (8)	1 (8)
	Europe	10 (38)	8 (62)
	Middle East	5 (19)	3 (23)
	North America	11 (42)	2 (15)
	24-hour urinary oxalate excretion (corrected for BSA), mean (SD), mmol/24 hours/1.73 m^2	1.84 (0.60)	1.79 (0.68)
	24-hour urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	0.209 (0.101)	0.237 (0.110)
	Spot urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	0.225 (0.110)	0.236 (0.140)
	Plasma oxalate, mean (SD), mmol/l	14.8 (7.6)	15.5 (7.3)

Study	Garrelfs 2021[15]		
	eGFR, mean (SD), ml/min/1.73 m^2	83.0 (25.5)	78.9 (26.8)
	CKD stage by eGFR, n (%), ml/min/1.73 m^2 ≥90	9 (35)	4 (31)
	CKD stage by eGFR, n (%), ml/min/1.73 m 260 to <90	13 (50)	6 (46)
	CKD stage by eGFR, n (%), ml/min/1.73 m 230 to <60	4 (15)	3 (23)
	Renal stone events	23 (89)	10 (77)
	Lithotripsy/stone removal procedures in the 12 months prior to consent	4 (15.4)	3 (23.1)
	Pyridoxine use at baseline	13 (50)	9 (69)
	Pyelonephritis	5 (19)	5 (39)
	Urinary tract infections	11 (42)	5 (39)
	Nephrocalcinosis	12 (46)	9 (69)
	Symptomatic renal stone events in the 12 months prior to consent, n (%):1 to 5	8 (31)	4 (31)
	Symptomatic renal stone events in the 12 months prior to consent, n (%):6 to 10	2 (8)	0
	Symptomatic renal stone events in the 12 months prior to consent, n (%):>10	1 (4)	0
	Presenting symptoms - asymptomatic (familial screening)	2 (8)	3 (23)
	Presenting symptoms – renal stone	21 (81)	7 (54)
	Presenting symptoms - ESKD	N/A	N/A
	Presenting symptoms - nephrocalcinosis	10 (39)	7 (54)
	Presenting symptoms - other	4 (15)	3 (23)
	Genotype – PR/any genotype of PR, M or N	11 (42)	6 (46)
	Genotype – M/M or M/N	6 (23)	4 (31)
	Genotype – N/N	9 (35)	3 (23)

Study	Garrelfs 2021[15]
Based on Tables C3, C6, and C7 in the CS[1] as well as the primary source.[15] ALT =alanine transaminase; AST =aspartate transaminase; BSA = body surface area; CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; GalNAc = N-Acetylgalactosamine; INR = international normalised ratio; M = missense; MDRD = Modification of Diet in Renal Disease; N=nonsense; PH1 = primary hyperoxaluria type 1; PR = pyridoxine responsive; RCT = randomised controlled trial; SC = subcutaneous; SD = standard deviation UK = United Kingdom; ULN=upper limit of normal; USA = United States of America	

The 6-month double-blind study duration was chosen by the trialists was based on the sustained reduction of urinary oxalate levels in PH1 patients in the phase 2 multi-dose study, together with advice received from health authorities (European Medicines Agency, EMA; US Food and Drug Administration, FDA) at the end of phase 2.[46]

Both groups received ECM in addition to their allocated interventions.

Change in oxalate was regarded by the developers as a clinically relevant primary endpoint that maximised the power of this clinical study in a disease state in which trial population size is fundamentally limited by the extreme rarity of the condition.[46]

ERG comment: It is acknowledged that the small population size will place an absolute limit on the statistical power of any analyses, and that therefore outcomes with intrinsically low variance (which may include plasma and urinary oxalate levels) will be useful even if lacking full clinical relevance. However, it is unclear why the more patient-relevant measure of HRQoL was not given more prominence in the report than these surrogate outcomes (please see comments on quality of life in Section 4.2.1.1.3).

4.2.1.1.2 Subgroup and sensitivity analyses (ILLUMINATE-A 6 month double blind RCT)

Prespecified subgroup analyses were performed for the primary endpoint using the full analysis set (FAS) population in the following subgroups:[46]

- Age at screening (six to <12, versus 12 to <18, versus ≥18 years)
- Gender (male or female)
- Race (white or non-white)
- Baseline 24-hour urinary oxalate corrected for BSA (≤1.70 versus >1.70 mmol/24 hours/1.73m^2)
- Baseline eGFR (<60 versus ≥60 ml/min/1.73m^2)
- History of renal stones (yes or no)
- Baseline vitamin B6 use (yes or no)
- Region 1: North America (including US and Canada) versus Other (outside North America)
- Region 2: Europe versus Other (outside Europe)

Two pre-specified sensitivity analyses were performed to evaluate the estimated treatment effect on the primary endpoint of percent change in 24 hour urinary oxalate (corrected for body surface area; BSA) from baseline to month 6.[15] The primary analysis assumed that the treatment effect reached steady state at month 3 and was maintained through month 6.[46] Both sensitivity analyses estimated the treatment effect of the primary endpoint without assuming equal treatment effect from month 3 through month 6.

1. Sensitivity analysis 1 added the interaction of visit and treatment to the primary mixed-effect model repeated measures (MMRM) model, when month 3 through month 6 data were used.
2. In contrast, sensitivity analysis 2 included all post-baseline data (including percent change from baseline at months 1 and 2).[46]

4.2.1.1.3 Efficacy

Table 4.6 summarises the clinical efficacy outcomes considered in the CS that were within the NICE scope.

Table 4.6: Clinical efficacy outcomes

Study name	**ILLUMINATE-A, NCT03681184, EudraCT 2018-001981-40**						
Size of study groups	Lumasiran (n=26) Placebo (n=13)						
Study duration	60 months						
Outcome Name (unit)	**Treatment effect (95% CI)**		**Effect Size**		**Statistical test**		**Comments**
	Lumasiran	**Placebo**	**Value**	**95% CI**	**Type**	**P value**	
Percent change in 24-hour urinary oxalate excretion from baseline to month 6, %, LSM[*†]	−65.4 (−71.3 to −59.5)	−11.8 (−19.5 to −4.1)	−53.5	(−62.3 to −44.8)	MMRM	1.685×10^{-14}	Primary endpoint; FAS; using two sensitivity analyses, a clinically meaningful and statistically significant change was demonstrated with lumasiran compared to placebo
Absolute change in 24-hour urinary oxalate from baseline to month 6, mmol/24 hours/1.73 m2, LSM[*†]	−1.24 (−1.37 to −1.12)	−0.27 (−0.44 to −0.10)	−0.98	(−1.18 to −0.77)	MMRM	1.225×10^{-11}	Secondary endpoint; FAS
Percent change in plasma oxalate from baseline to month 6, %, LSM[†‡]	−39.8 (−45.8 to −33.8)	−0.3 (−9.1 to 8.5)	−39.5	(−50.1 to −28.9)	MMRM	2.862×10^{-8}	Secondary endpoint; plasma oxalate analysis set
Proportion of patients with 24-hour urinary oxalate ≤1.5×ULN at month 6, %[*§]	84	0	84	(55 to 94)	CMH	8.341×10^{-7}	Secondary endpoint; FAS
Proportion of patients with 24-hour urinary oxalate ≤ULN at month 6, %[*§]	52	0	52	(23 to 70)	CMH	0.0010	Secondary endpoint; FAS
Absolute change in plasma oxalate from baseline to month 6, µmol/l, LSM[†‡]	−7.5 (−9.0 to −5.9)	1.3 (−1.0 to 3.5)	−8.7	(−11.5 to −6.0)	MMRM	3.893×10^{-7}	Secondary endpoint; plasma oxalate analysis set

Study name	**ILLUMINATE-A, NCT03681184, EudraCT 2018-001981-40**

Based on Table C10 of the CS.[1]

*Corrected for BSA; †Calculated as the mean change or mean percent change during months 3 to 6; ‡Plasma oxalate analysis set included 23 patients in the lumasiran group and 10 patients in the placebo group; § Data were available for 25 patients in the lumasiran group and 13 patients in the placebo group. ULN was 0.514 mmol/24 hours/1.73 m^2.

BSA = body surface area; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CS = company submission; FAS = full analysis set; LSM = least squares mean; MMRM = mixed-effect model repeated measures; SEM = standard error of the mean; ULN = upper limit of normal

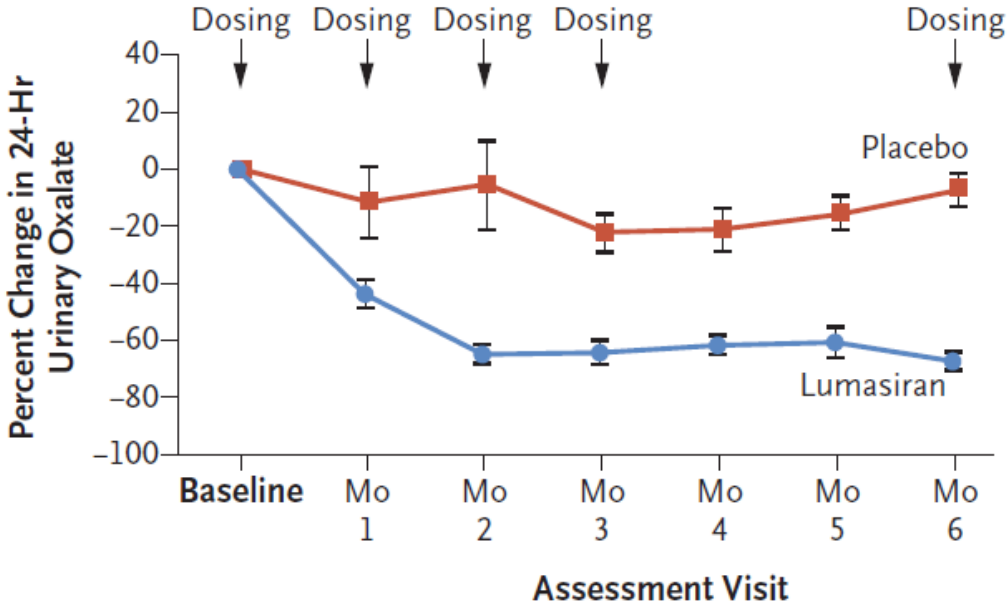
ERG comment: Data presented in the CS tally with that in referenced studies. The outcomes did not include need for liver/kidney transplant. They included oxalate:creatinine ratio, which was not in the scope and is a surrogate outcome.

The outcomes relevant to the NICE scope and the details of results for each are given below.

Oxalate levels in urine

Lumasiran met the primary endpoint in ILLUMINATE-A: the reduction from baseline in 24-hour urinary oxalate (average of months 3 to 6 and corrected for BSA) was significantly greater in the lumasiran group than in the placebo group. At 6 months, the least square mean (LSM); 95% confidence interval (CI) change in 24-hour urinary oxalate from baseline was −65.4% (−71.3% to −59.5%) in the lumasiran group and −11.8% (−19.5% to −4.1%) in the placebo group (LSM (95% CI) difference: −53.5% (−62.3% to −44.8%); $P=1.685\times10^{-14}$), see Figure 4.1.

Figure 4.1: ILLUMINATE-A primary analysis: percent change from baseline in 24-h urinary oxalate (corrected for BSA) to month 6

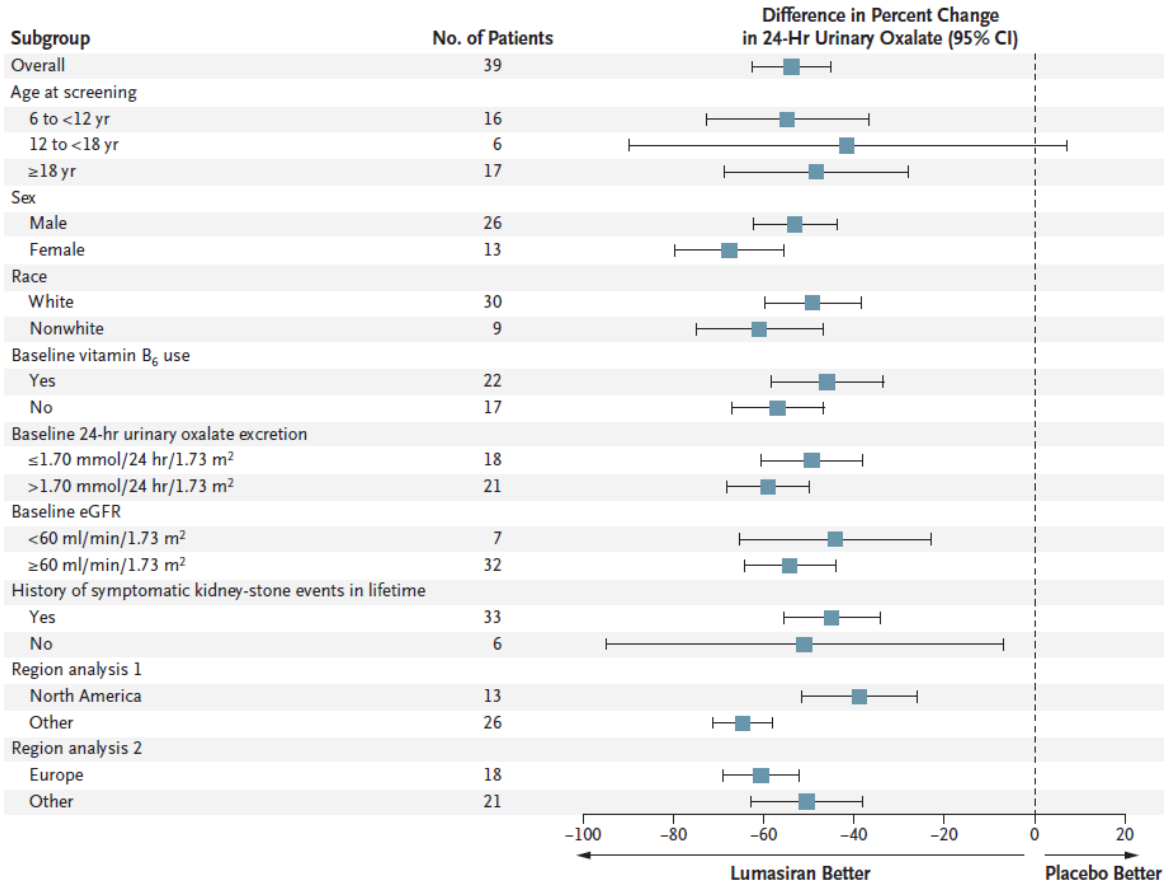


No. of Patients							
Placebo	13	13	12	13	13	13	13
Lumasiran	26	24	26	24	23	25	25

Based on CS[1] with primary source: Garrelfs et al. 2021[15]
BSA = body surface area; CS = company submission

Additional prespecified sensitivity analyses (involving the use of varied assumptions in the MMRM model) on the primary endpoint resulted in a consistent estimate of the treatment effect of lumasiran compared to placebo on percent change in 24-hour urinary oxalate, confirming the robustness of the primary analysis. The robust improvement from baseline in 24-hour urinary oxalate with lumasiran was present across subgroups, including subgroups defined by baseline urinary oxalate levels (24-hour urinary oxalate (corrected for BSA) of ≤1.70 versus >1.70 mmol/24 hours/1.73 m^2), baseline pyridoxine use, and baseline renal function categories (Figure 4.2).

Figure 4.2: ILLUMINATE-A primary analysis: percent change from baseline in 24-h urinary oxalate in patient subgroups

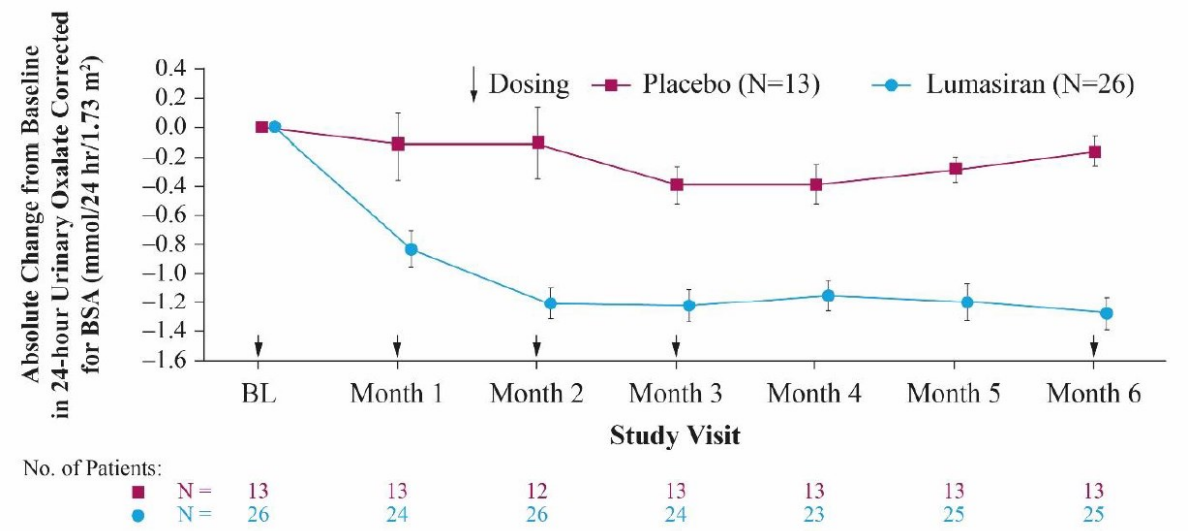


Based on CS[1] with primary source: Garrelfs et al. 2021[15]
CI = confidence interval; CS = company submission; eGFR = estimated glomerular filtration rate

The secondary endpoint of change in absolute 24-hour urinary oxalate (corrected for BSA) from baseline to month 6 was analysed using the same MMRM model as specified for the primary endpoint.

A reduction in 24-hour urinary oxalate was demonstrated with lumasiran compared to placebo from baseline to month 6 (average of months 3 to 6). The LSM (95% CI) absolute change from baseline was −1.24 mmol/24 hours/1.73 m^2 (−1.37 to −1.12) in the lumasiran group and −0.27 mmol/24 hours/1.73 m^2 (−0.44 to −0.10) in the placebo group (LSM (95% CI) difference: −0.98 mmol/24 hours/1.73 m^2 (−1.18, −0.77); $P=1.225\times10^{-11}$). Patients treated with lumasiran had a sustained decrease in absolute 24-hour urinary oxalate corrected for BSA (Figure 4.3).

Figure 4.3: ILLUMINATE-A primary analysis: absolute change from baseline in 24-h urinary oxalate (corrected for BSA) to month 6



Based on CS[1] with primary source: Garrelfs et al. 2021[15]
BL = baseline; BSA = body surface area; CS = company submission

A higher proportion of lumasiran-treated patients achieved normalisation or near-normalisation (≤1.5×ULN) at month 6 in 24-hour urinary oxalate levels versus placebo-treated patients, which was considered clinically meaningful and statistically significant ($P=8.341\times10^{-7}$). Specifically, 21 of 25 patients (84%) in the lumasiran group achieved normalisation or near-normalisation versus no patients (0%) in the placebo group. Furthermore, in the lumasiran group, this goal was achieved by 100% and 71.4% of patients with lower and higher baseline urinary oxalate levels (≤1.70 and >1.70 mmol/24 hours/1.73 m^2), respectively.

Similarly, a higher proportion of lumasiran-treated patients achieved normalisation (≤ ULN) at month 6 in 24-hour urinary oxalate levels versus placebo-treated patients, which was considered clinically meaningful and statistically significant (P=0.001). Specifically, 13 of 25 patients (52%) in the lumasiran group achieved normalisation versus no patients (0%) in the placebo group. Furthermore, in the lumasiran group, this goal was achieved by 72.7% and 35.7% of patients with lower and higher baseline urinary oxalate levels (≤1.70 and >1.70 mmol/24 hours/1.73 m^2), respectively.

ERG comment: In the request for clarification, it was asked if the use of pyridoxine by 56.4% of patients at study entry was adjusted for in the analyses.[50] The response was that there was no effect of pyridoxine, and therefore no need for any adjustment.[51, 52] This was based on the fact that the 95% CIs overlapped in the sub-group analysis results of the *difference in % change in 24-hour urinary oxalate* between those taking pyridoxine and those not taking pyridoxine.

However, this argument demonstrates an incorrect interpretation of confidence intervals. For evaluating whether differences are statistically important, we should estimate the probability that the non-extreme parts of the sampling distribution around the point estimate of the mean difference between the pyridoxine groups (the spread of this distribution being informed by the variance of the measure and the sample sizes) – which are represented by the 95% CI - includes the null value. Importantly, the 'overlap' method used by the developers does not do this; instead, the 'overlap method' might incorrectly conclude no difference when in fact one exists. Although the method of 'overlapping confidence intervals' can show a definite difference when there is no overlap it *cannot* directly confirm

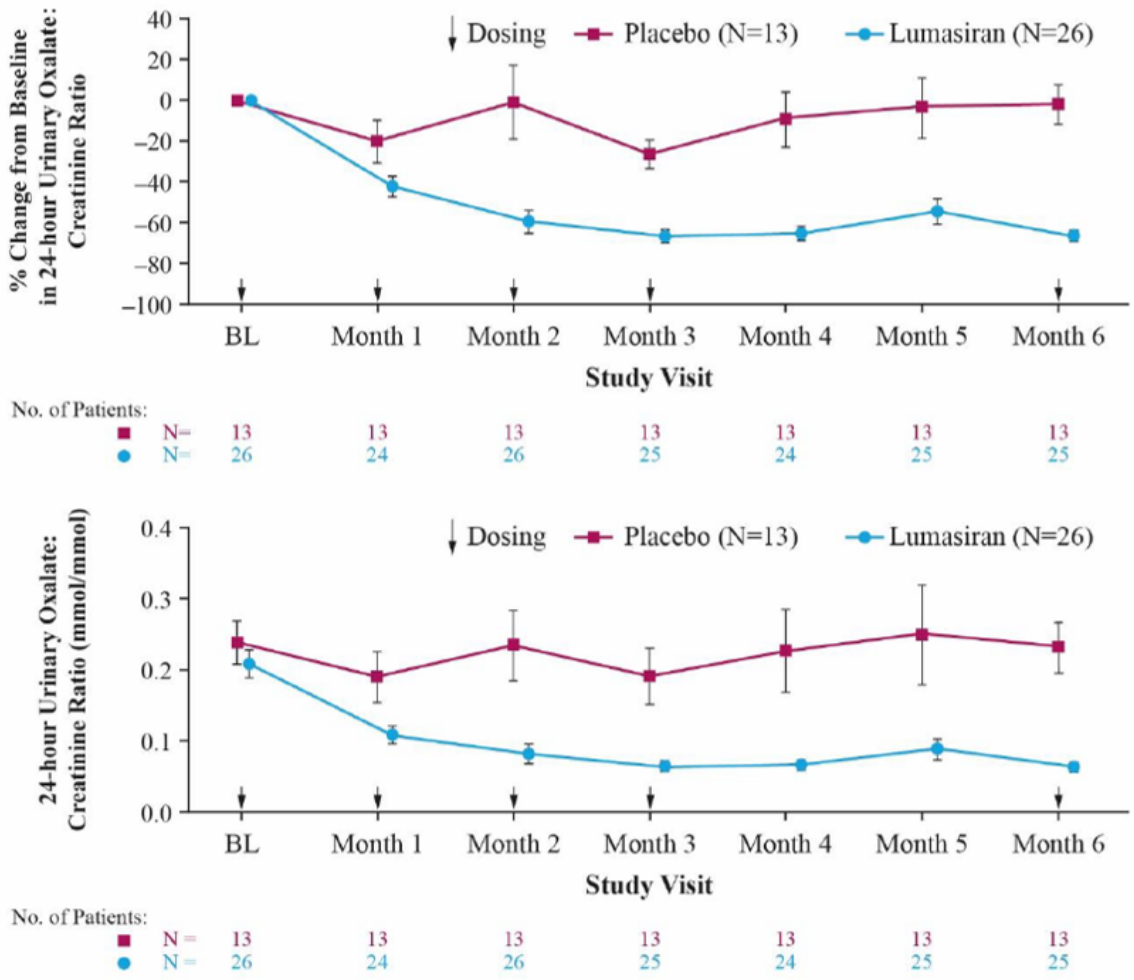
no difference when there *is* an overlap.[79] Therefore, the issue of whether pyridoxine use has been adjusted for has not been fully answered.

As with all analyses in the CS there has been a tendency to 'over-analyse' the data; in this case, to analyse the same outcome in subtly different ways. For example, oxalate was evaluated in terms of the absolute and the percentage change. This will increase the risk of type I errors. For this outcome, there is sufficiently strong evidence that lumasiran reduces oxalate in urine for the risk of type I errors to not be a problem. However, this outcome is not a patient-reported measure and so has less relevance to the DP than more patient-related outcomes like quality of life.

Oxalate levels in plasma

Plasma oxalate endpoints were evaluated using the prespecified plasma oxalate analysis set, which included patients who received study drug and had a baseline plasma oxalate level ≥1.5×LLOQ (lower limit of quantitation). This ensured that meaningful reductions in plasma oxalate could be evaluated for the study population without confounding from a floor effect due to the sensitivity of the plasma oxalate assay .

Figure 4.4: ILLUMINATE-A primary analysis: percent and absolute change from baseline in 24-h urinary oxalate:creatinine ratio (mmol/mmol) to month 6

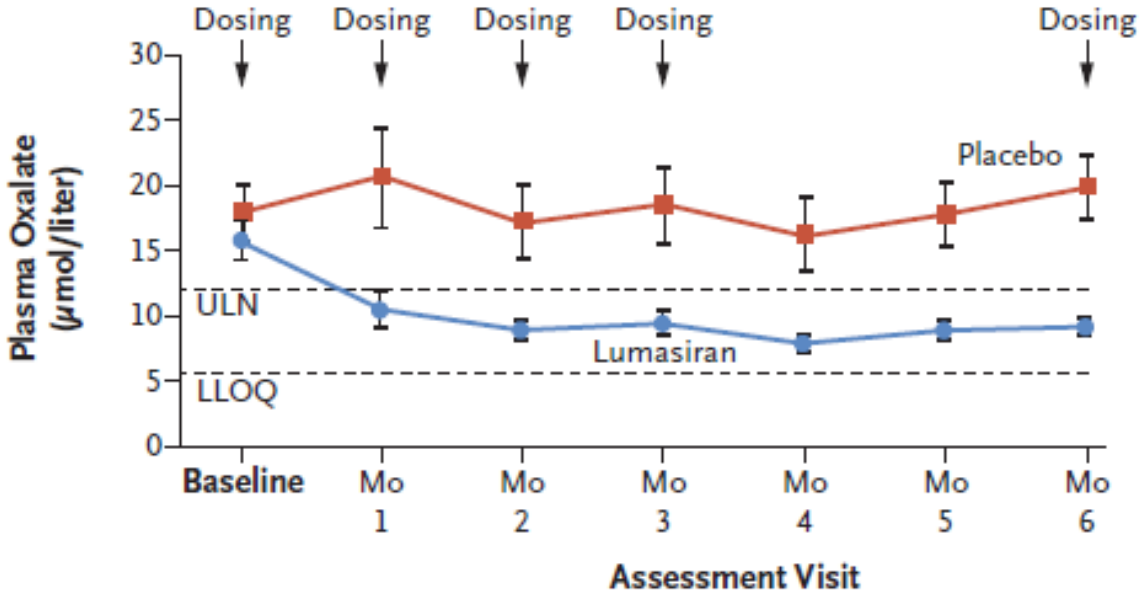


Based on CS[1] with primary source: Garrelfs et al. 2021[15]
BL = baseline; CS = company submission

As per Figure 4.4, patients in the plasma oxalate analysis set treated with lumasiran demonstrated a statistically significant percent reduction from baseline to month 6 (average of months 3 to 6) in plasma oxalate compared to placebo. The LSM (95% CI) percent change averaged across months 3 to 6 was −39.8% (−45.8% to −33.8%) in the lumasiran group and −0.3% (−9.1% to 8.5%) in the placebo group. The LSM (95% CI) difference in percent change was −39.5% (−50.1% to −28.9%; P=2.862×10^{-8}).

Patients treated with lumasiran demonstrated a statistically significant reduction from baseline to month 6 in absolute plasma oxalate compared to placebo. The LSM (95% CI) absolute change in plasma oxalate averaged across months 3 to 6 was −7.5 µmol/l (−9.0, −5.9) in the lumasiran group and 1.3 µmol/l (−1.0, 3.5) in the placebo group. The LSM (95% CI) difference in absolute change was −8.7 µmol/l (−11.5, −6.0; P=3.893×10^{-7}). Steady state was achieved at the end of the loading-dose phase in patients treated with lumasiran. The true treatment effect may be underestimated because 14 of 23 (60.9%) lumasiran-treated patients had at least one value that was below LLOQ (and was thus imputed to be equal to LLOQ) at months 3 through 6. In contrast, none of the placebo-treated patients had a value below LLOQ at months 3 through 6 (Figure 4.5).

Figure 4.5: ILLUMINATE-A primary analysis: absolute change from baseline in plasma oxalate (µmol/l) to month 6



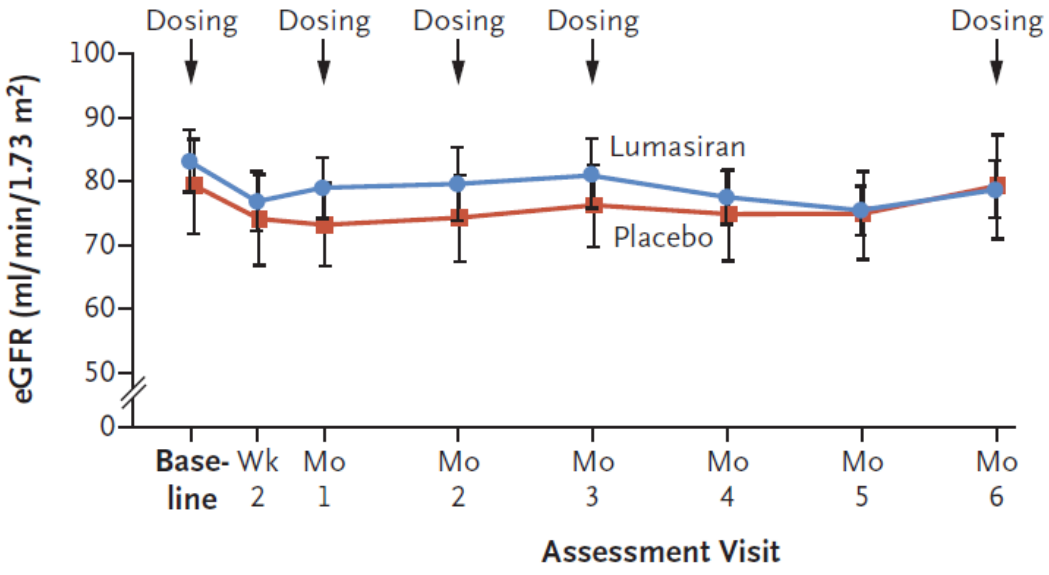
Based on CS[1] with primary source: Garrelfs et al. 2021[15]
The plasma oxalate analysis set was defined as patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ was 5.55 µmol/l. ULN was 12.11 µmol/l.
CS = company submission; LLOQ = lower limit of quantification; Mo = month; ULN = upper limit of normal

ERG comment: Again, the same outcome has been analysed in subtly different ways (for example, absolute and percentage change). This will increase the risk of type I errors.

Change in eGFR

As expected, based on the natural course of the disease, eGFR remained relatively stable for both treatment groups during the 6-month double-blind treatment period. eGFR was not included in the hierarchical testing of secondary endpoints at month 6 because of this expectation (Figure 4.6).

Figure 4.6: ILLUMINATE-A primary analysis: observed values for eGFR (ml/min/1.73 m^2) from baseline to month 6



No. of Patients								
Placebo	13	13	12	13	13	12	13	13
Lumasiran	26	24	25	25	25	25	25	25

Based on CS[1] with primary source: Garrelfs et al. 2021[15]
CS = company submission; eGFR = estimated glomerular filtration rate; Mo = month

Need for liver transplant with or without a kidney transplant

This outcome was not covered.

ERG comment: No explanation was given for the lack of this outcome. Although it is likely that the sample characteristics and short follow-up period would make events unlikely, there seems to be no good reason why this highly relevant outcome was not surveyed.

Mortality

No deaths were recorded, see Section 4.2.2.1.

Health-related quality of life

The mean (SD) change from baseline to month 6 in the EQ-5D VAS was [redacted] for the lumasiran group and −2.0 (8.93) for the placebo group, with higher scores indicating better health status.[46]

ERG comment: No details of the data were provided, i.e. Table 14.2.5.1 of the CSR was missing, so it was not possible to compare the baseline characteristics.

Assuming baseline characteristics would be comparable, this result would that lumasiran improves quality of life but using the default minimally important difference (MID) of 0.5 x the standard

deviation of the control group, this is not a clinically significant difference. This result is described briefly in the CS report and is not discussed.[1]

The ILLUMINATE-A clinical study report provides the same result and also directs the reader to data on the KDQoL, PedsQOL and EQ5D in Tables 14.2.5.2 to 14.2.5.6, but these tables were not found in the document.[46] If quality of life is not appreciably affected by a treatment, then it is arguable that the treatment has made little difference to the patient.

Outcomes out of scope

The company also reported 24-hour urinary oxalate:creatinine ratio, rate of renal stone events, nephrocalcinosis, levels of plasma glycolate and 24-hour urinary glycolate:creatinine ratios (see pages 74-75 of the CS).[15]

These outcomes are outside the NICE final scope and therefore most have not been included in the ERG report. However, the ERG decided to include the rate of renal stone events in the ERG report, because, unlike many of the other outcomes considered, it is not a surrogate outcome and is directly related to the experience of the patient.

Rate of renal stone events

In the lumasiran group, the rate of renal stone events decreased from a calculated rate of 3.19 per person-year (95% CI: 2.57 to 3.96) in the 12 months prior to the trial to an observed rate of 1.09 per person-year (95% CI: 0.63 to 1.87) during the 6-month double-blind period. In the placebo group, the rates of renal stone events were 0.54 per person-year (95% CI: 0.26, 1.13) in the 12 months prior to the trial and 0.66 per person-year (95% CI: 0.25, 1.76) over the 6-month treatment period.[15]

ERG comment: The considerable difference in renal stone event rates between groups before treatment reflects the difficulty in gaining adequate random mixing in such small, randomised trials. Although this specific analysis partially allows for the baseline difference by looking at the magnitude of change (suggesting that the lumasiran group had a greater benefit), this lack of baseline comparability suggests that other group differences may exist in other variables that could confound findings more generally.

4.2.1.1.4 Critical appraisal

The CS critically appraised the project, as shown below in Table 4.7. Both the published paper[15] and the study report[46] were used to complete the task.

Table 4.7: Critical appraisal of randomised control trials – ILLUMINATE-A

Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Randomised 2:1 to lumasiran or placebo, stratified by mean baseline urinary oxalate level.
Was the concealment of treatment allocation adequate?	Yes	By Interactive Response System.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Not clear	Study reports groups were similar, however, some differences in median and ranges of age, proportion female and proportions in the categories of race.

Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes (first 6-month period) Not clear (extension period)	Participants and study personnel were blinded until primary analysis (month 6) and then for the first 3 months of the extension. Some unblinding was permitted in the protocol but not reported that this occurred. The method of masking was not reported. Main outcome measures were objective Some concerns regarding detection and performance bias.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	No imbalance in dropouts.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	Exploratory outcomes were not listed in the published protocol to check, HRQoL and Patient and Carer Impact questionnaires were stated in the protocol but not specifically stated to be outcomes.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Analysis was a modified ITT analysis (all those undergoing randomisation and received at least one dose of treatment).
Based on Table C8 of the CS[1] Adapted from CRD guidance[73] CRD = Centre for Reviews and Dissemination; CS = company submission; HRQoL = health-related quality of life; ITT = intention-to-treat		

ERG comment: The CS appraisal of risk of bias was broadly in line with our independent assessment, which is summarised below. The Risk of Bias 2 (RoB2) evaluation was used as detailed in Table 4.8.

.

Table 4.8: Risk of Bias 2 (RoB2) evaluation of ILLUMINATE-A

Risk of Bias 2 domain	Evaluation
Risk of bias arising from the randomisation process (selection bias)	Participants were randomised with stratification for mean baseline urinary oxalate level (>1.70 versus ≤1.70 mmol/24 hours/1.73 m^2). A poorly described form of allocation concealment was used: it is merely stated that there was an 'interactive response system' which infers (by convention) but does not confirm that recruiters were unaware of the next allocation in the random sequence when deciding whether to recruit the next patient. There were trends for systematic differences between groups at baseline, with a tendency for the lumasiran group to be older, have less pyridoxine use, a higher renal stone event rate and a higher eGFR. As explained previously, these effects are likely to be due to poor random mixing secondary to small numbers, though in the absence of adequate reporting of methods they could be related to poor allocation concealment. The tendency for the lumasiran group to be 'less well' may indicate a poorer prognosis for the lumasiran group, and thus suggest that the direction of any bias favours the placebo group. However, this tendency could also contribute to a 'regression to the mean' extraneous effect, whereby greater improvements would tend to be observed in the lumasiran group.
Risk of bias due to deviations in the intended interventions (performance bias)	Patients (including their families or caregivers) and health care professionals were reported to be blinded.
Missing outcome data (attrition bias)	One participant withdrew from the lumasiran group, but this participant appears to have been followed up in a modified ITT analysis; therefore, no attrition bias is likely. The reasons for discontinuation during the 6-month blinded RCT period was unclear. It was either due to AEs (n=1; fatigue and disturbance in attention, considered unrelated to the study drug) or withdrawal of parent/caregiver consent (n=1). The CS reported the reasons for two withdrawals made during both parts of the project (initial 6 months and extended open label period) but did not specify which was which. None of the 13 placebo-treated patients withdrew from the study during the primary analysis period.
Risk of bias in measurement of the outcome (detection bias)	There was no specific mention of assessor blinding, but it was stated that 'study personnel were blinded to study drug treatment assignment', which almost certainly includes assessors.
Risk of bias in selection of the reported result (outcome reporting bias)	All of the important pre-hoc variables were measured.
Overall risk of bias	Some concerns of risk of bias, largely due to potential selection bias. Direction of bias is unclear.
Risk of bias 2 tool details from: https://methods.cochrane.org/risk-bias-2 AE = adverse event; CS = company submission; eGFR = estimated glomerular filtration rate; ITT = intention-to-treat; RCT = randomised controlled trial	

4.2.1.2 ILLUMINATE-A: 54-month extension period

4.2.1.2.1 Study characteristics

Because all participants from the 6-month ILLUMINATE-A trail were due to go on to the extension period, the participant characteristics are identical to those of the 6-month RCT (please see previous Table 4.5), apart from details related to the study, study type, number of participants, randomisation, intervention and comparator. Therefore, only data relating to these criteria are listed below in Table 4.9.

Table 4.9: Study characteristics for ILLUMINATE-A 54-month extension

Study	Saland et al. 2020, Sas, 2021[46, 80-82]
Study type	54-month extension of the 6-month randomised trial, with both arms receiving the study drug. The study comprised a 3-month blinded treatment extension followed by an open label extension period of up to 51 months. The 3-month blinded treatment extension period enables the transition of patients previously receiving blinded placebo to initiate treatment with lumasiran while investigators and patients remain blinded to the earlier double blind period treatment assignment. For this reason, during the 3-month blinded treatment extension period, patients who had been randomised to lumasiran also receive 2 monthly doses of placebo, so that all patients receive blinded monthly treatment during this period (administered at the month 6, 7, and 8 visits). At the month 9 visit, all patients receive their first open-label maintenance dose of lumasiran, marking the beginning of the OLE period. lumasiran is administered Q3M thereafter.
Number of participants randomised	39 (26 lumasiran, 13 placebo). A total of 24 of 26 patients initially randomised to receive lumasiran in the double-blind period continued to receive lumasiran in the extended-dosing period. All patients initially randomised to receive placebo crossed over to receive lumasiran.
Randomisation	For the extension phase all participants received the study drug.
Intervention	• Q3M (3-month blinded extension that included 2 monthly doses of placebo after the first Q3M lumasiran dose to preserve the blind) • Lumasiran 3 mg/kg Q3M (51-month OLE)
Comparator	• Lumasiran 3 mg/kg QM (3-month blinded extension) • Lumasiran 3 mg/kg Q3M starting one month after the end of QM dosing (51-month OLE)

Based on Table C8 of the CS[1]
CS = company submission; HRQoL = health-related quality of life; ITT = intention-to-treat; OLE = open-label extension; Q3M = once every three months; QM = once monthly

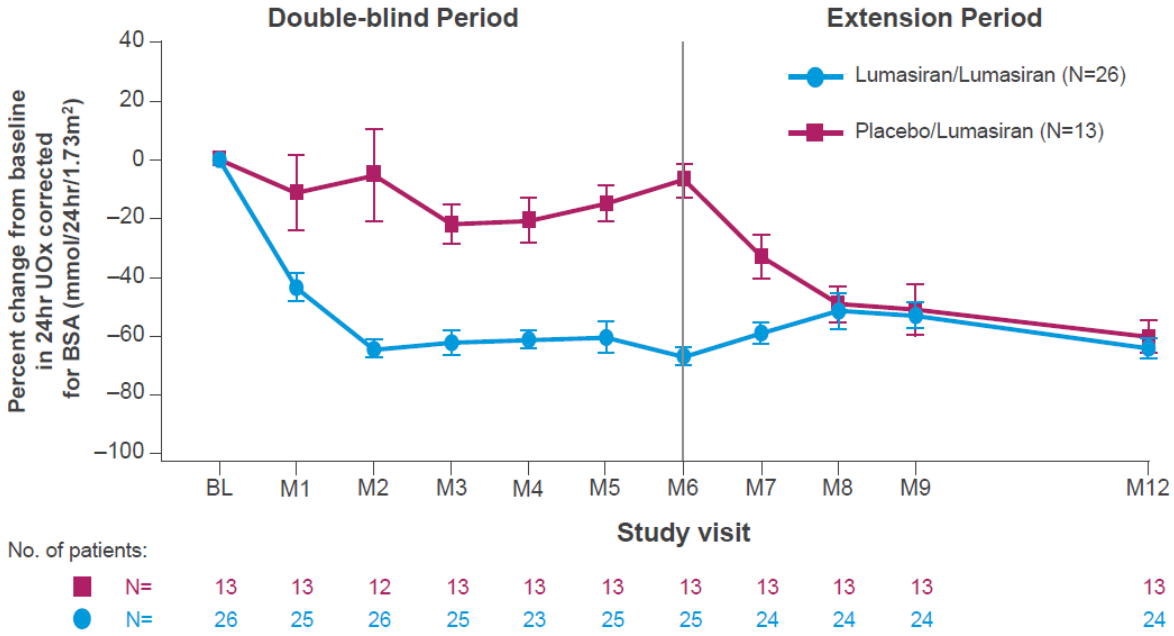
4.2.1.2.2 Efficacy

Interim results from the ILLUMINATE-A extension period provided further efficacy and safety data for lumasiran in PH1.

Oxalate levels in urine

Patients initially randomised to lumasiran and who remained on lumasiran had a sustained reduction in 24-hour urinary oxalate (corrected for BSA) through month 12. The mean reduction from baseline to month 12 in this lumasiran/lumasiran group was 64.1% (versus 65.4% observed to month 6 in the primary analysis).[15, 83] Patients initially randomised to placebo and who crossed over to lumasiran (i.e. placebo/lumasiran group) demonstrated a similar time course and magnitude of 24-hour urinary oxalate reduction following 6 months of lumasiran treatment; the mean reduction relative to the first dose of lumasiran was 57.3%, see Figure 4.7.[83]

Figure 4.7: ILLUMINATE-A extension period: percent change from baseline to month 12 in 24-h urinary oxalate (corrected for BSA)



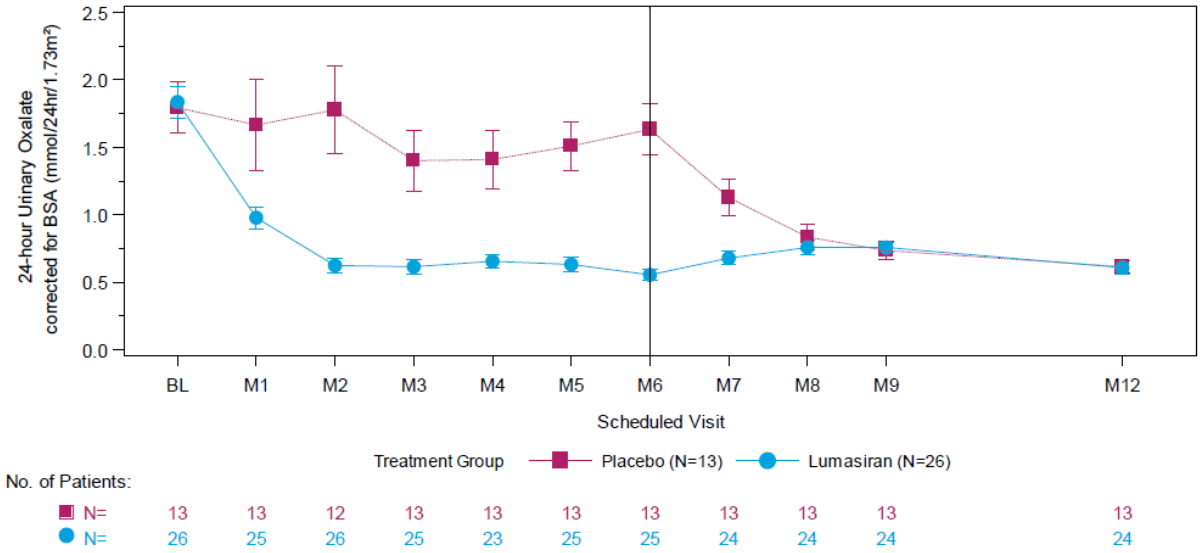
Based on CS[1] with primary source: Hulton et al. 2021[83]

BL = baseline; BSA = body surface area; CS = company submission; M = month; UOx = urinary oxalate

[redacted]

Continued treatment with lumasiran maintained the proportion of patients achieving near-normalisation or normalisation (≤1.5×ULN) of 24-hour urinary oxalate. A total of 84.0% and 87.5% in the lumasiran/lumasiran group achieved near-normalisation or normalisation at months 6 and 12, respectively. Similarly, 76.9% in the placebo/lumasiran group achieved near-normalisation or normalisation at month 12, after 6 months of treatment with lumasiran (compared to 0% at the time of crossover from placebo to lumasiran at month 6.[15, 83])

Figure 4.8: ILLUMINATE-A extension period: absolute change from baseline to month 12 in 24-h urinary oxalate (corrected for BSA)



Based on CS[1] with primary source: Hulton et al. 2021[83]

BL = baseline; BSA = body surface area; CS = company submission; M = month; UOx = urinary oxalate

Oxalate levels in plasma

Sustained percent and absolute reductions in plasma oxalate were maintained to month 12 in patients continuing treatment with lumasiran. The LSM (SEM) percent change from baseline was −36.9% (4.9%) at month 6 and −35.0% (6.1%) at month 12 in the lumasiran/lumasiran group, see Figure 4.9.[83]

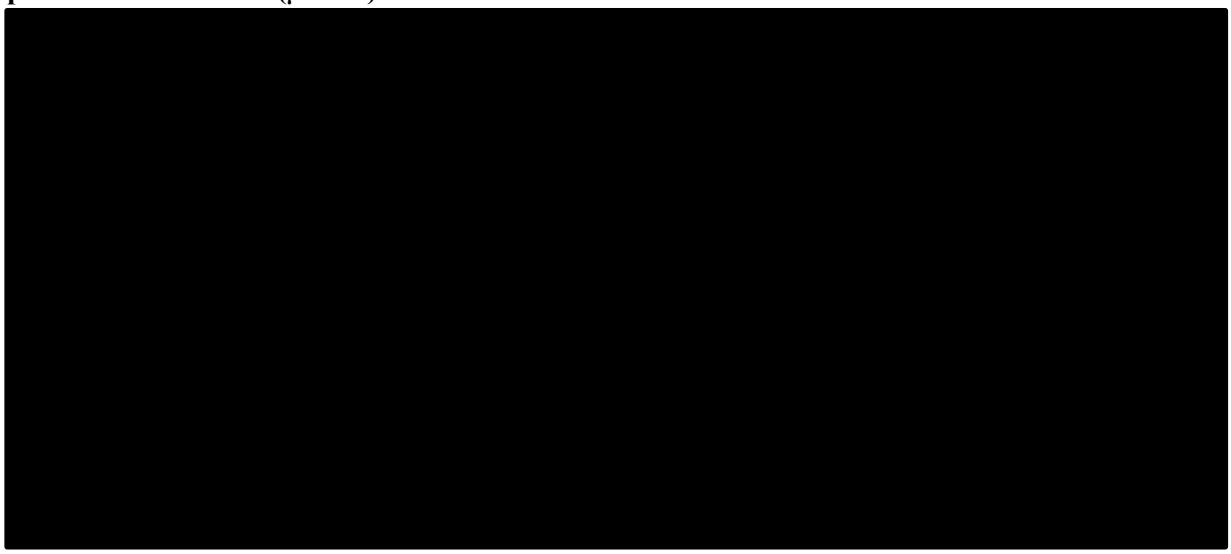
[redacted]

Reduction in plasma oxalate was replicated by placebo/lumasiran crossover patients after 6 months of lumasiran treatment, at study month 12. The LSM (SEM) percent and absolute changes from baseline were −48.9% (5.1%) and [redacted] Note that these differences from baseline are calculated based on actual values at the prespecified timepoints, whereas the primary analysis averaged values over a 3-month period (months 3 to 6).

Figure 4.9: ILLUMINATE-A extension period: percent change from baseline to month 12 in plasma oxalate levels (µmol/l)

Based on CS1 with primary source: Alnylam, Data on File[84]
The plasma oxalate analysis set was defined as patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ was 5.55 µmol/l. ULN was 12.11 µmol/l.
BL = baseline; CS = company submission; LLOQ = lower limit of quantification; M = month

Figure 4.10: ILLUMINATE-A extension period: absolute change from baseline to month 12 in plasma oxalate levels (µmol/l)

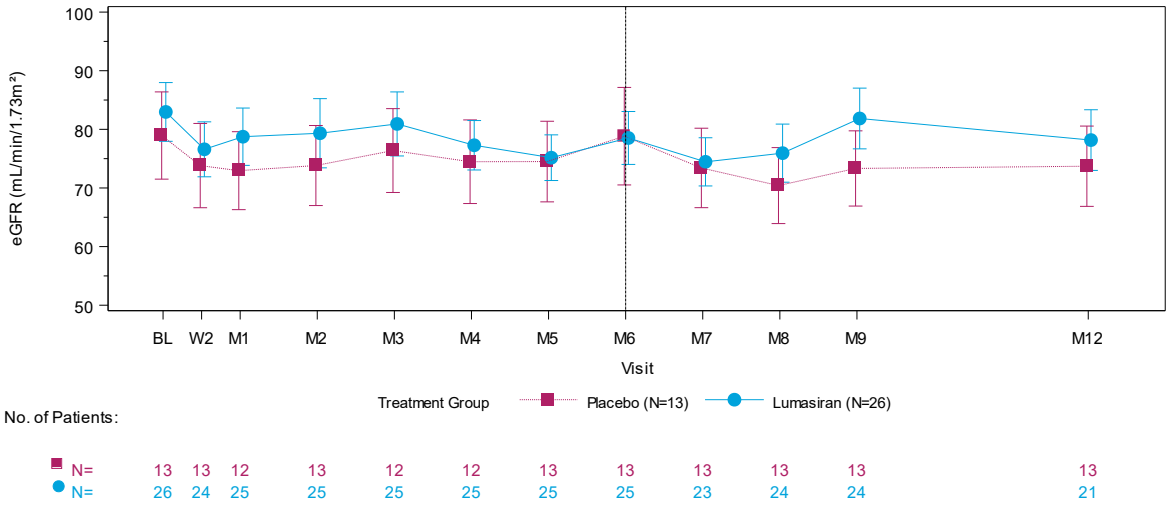


Based on CS[1] with primary source: Hulton et al. 2021[83]
The plasma oxalate analysis set was defined as patients who received any amount of study drug and had baseline plasma oxalate level ≥1.5×LLOQ. LLOQ was 5.55 µmol/l. ULN was 12.11 µmol/l.
BL = baseline; BSA = body surface area; CS = company submission; LLOQ = lower limit of quantification; M = month; ULN = upper limit of normal

Change in eGFR

Outcome eGFR remained stable in all patients through month 12, as shown in Figure 4.11.[83]

Figure 4.11: ILLUMINATE-A extension period: observed values for eGFR (ml/min/1.73 m^2) from baseline to month 12



Based on CS[1] with primary source: Hulton et al. 2021[83]
BL =baseline; CS = company submission; eGFR = estimated glomerular filtration rate; M = month; W = week

Need for liver transplant with or without a kidney transplant

This outcome was not covered.

Mortality

There were no deaths during the treatment extension period, see Section 4.2.2.1.[85]

Health related quality of life

No quality-of-life data for the extension period were found.

Outcomes out of scope

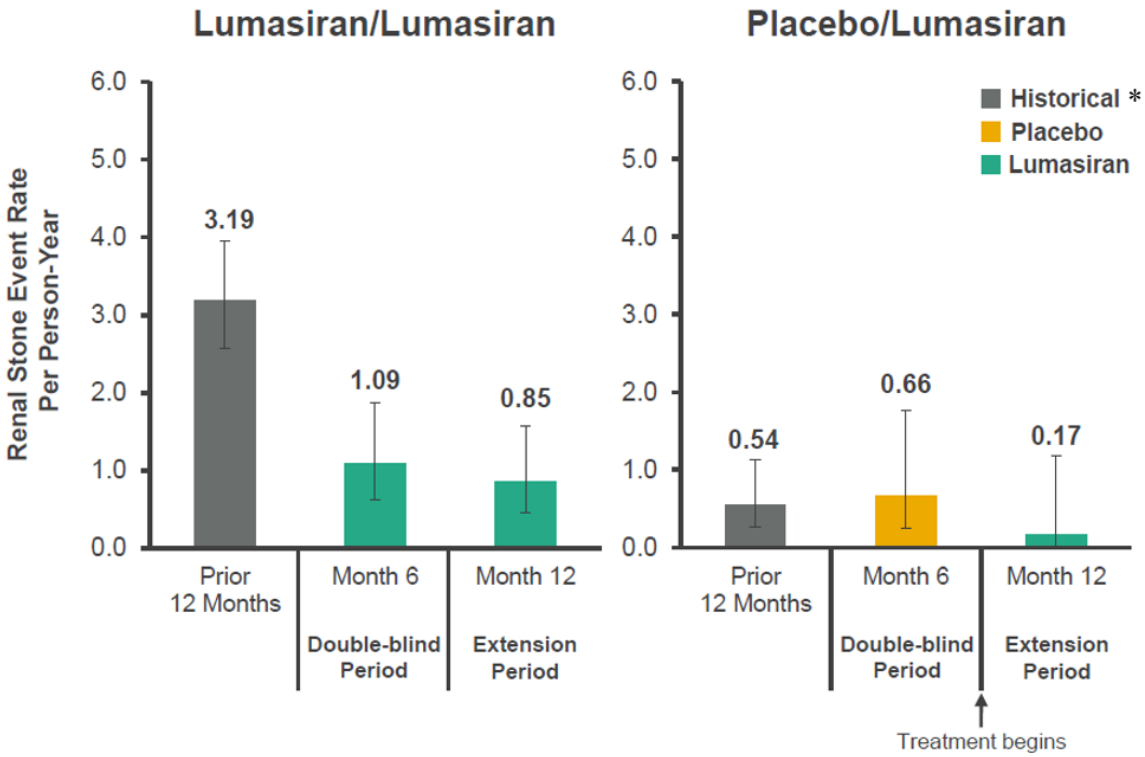
The company also reported 24-hour urinary oxalate:creatinine ratio, rate of renal stone events, and nephrocalcinosis (see pages 77 to 80 of the CS).[1] These outcomes are outside the NICE final scope and therefore most have not been included in the ERG report.

However, the ERG decided to include the rate of renal stone events in the ERG report, because, unlike many of the other outcomes considered, it is not a surrogate outcome and is directly related to the experience of the patient.

Rate of renal stone events

Renal stone event data continue to be collected during the ILLUMINATE-A extension period. In the lumasiran/lumasiran group, the reduction in renal stone frequency observed in the double-blind period was maintained with a further 6 months of lumasiran treatment. The renal stone event rates were 3.19 events per person-year in the 12 months prior to the study, 1.09 events from baseline to month 6, and 0.85 events from month 6 to month 12. In the placebo/lumasiran group, the renal stone event rates were 0.54 events per person-year in the 12 months prior to the study, 0.66 events during the 6-month placebo-treatment period, and 0.17 events during the ensuing 6 months of lumasiran treatment, see Figure 4.12.[83]

Figure 4.12: ILLUMINATE-A extension period: renal stone events following 6–12 months of treatment



Based on CS[1] with primary source: Hulton et al. 2021[83]
*Patient-reported history of renal stone events.
CS = company submission

4.2.1.2.3 Critical appraisal

The CS presents a critical appraisal table purporting to cover both the 6-month RCT and the 54-month open label extension periods in one evaluation (see Table 4.7).

ERG comment: On inspection, the evaluation carried out in the CS only applies to the 6-month RCT and does not apply to the 54-month open label extension, because the methodologies of the two parts of the project are distinct. Therefore, the CS has not provided a critical appraisal of the 54-month open label extension.

A critical appraisal specific to the extension period is therefore provided by the ERG as follows. As for any single-arm trial, any threats to internal validity will remain uncontrolled. For example, any effects relating to placebo effects will not be possible to extricate from treatment effects in a single arm trial, whereas in a controlled trial (and in particular a *blinded* controlled trial) such extraneous effects may cancel out from a relative effect measure if they occur to a similar extent in both arms. Nevertheless, given the nature of the condition and the outcomes chosen, as well as the pattern of results up to 12 months observed in Saland 2020, it seems unlikely that the results observed in the extension period are completely spurious.[80]

The group that had received lumasiran during the randomised phase continued to show a very similar pattern of results during the following 12 months, and their effects were very closely mirrored by effects in the group that had been previously receiving placebo, but which were now receiving lumasiran (the slight reduction in efficacy observed until month 8 in the lumasiran group may be explained by the use of 2 months of placebo in the 3-month transition period). This high level of correlation between the two

groups after adoption of the same therapy suggests that results may reflect a treatment effect. Although it is theoretically possible that placebo effects could explain the pattern of results seen, this is highly unlikely given the nature of the outcome. Therefore, selection bias should not be regarded as the serious problem normally encountered in a single-arm situation, and overall bias is regarded as not significantly inferior` to that of the 6-month trial.

4.2.1.3 ILLUMINATE-B: 6-month primary analysis

ILLUMINATE-B (ALN-GO1-004) project also comprised two parts.

The first part was a 6-month primary analysis. The second part, which was a continuation of the first part, involving the same participants, was an open label extension period where all participants had the study drug and there was no comparator. Because the possible level of inference about treatment effects will be very different from these two Sections the two parts will be dealt with separately. The information below is taken from the information in the CS, and information inferred, or taken directly, from the included papers.[1]

4.2.1.3.1 Study characteristics

Table 4.10 summarises the characteristics of the study for the ILLUMINATE-B 6-month primary analysis.

Table 4.10: Study characteristics for ILLUMINATE-B 6-month primary analysis

Study	Michael, 2020 [78]
Study type	International, multicentre, open-label, single-arm, phase 3 study. (6-month primary analysis)
Number of participants selected	18 Treatment discontinuations (not based on full 60-month follow-up period): lumasiran: 0 Study withdrawals (not based on full 60-month follow-up period): lumasiran: 0
Study sites	Nine study centres from across five countries (UK (one site), France (two), Germany (one), Israel (three), USA (two)). The one UK site was at the Great Ormond Street Hospital, London. [redacted].
Inclusion	• Have reached at least 37 weeks estimated gestational age (full-term infant) but <6 years of age at consent • Documented PH1 as determined by genetic analysis • Urinary oxalate:creatinine ratio > ULN based on age on at least two of three single-void collections during screening • Pyridoxine: allowed if patient was on a stable regimen for >90 days before screening and able to remain on this stable regimen at least until month 6 visit (dose adjustments for interval weight gain are acceptable) • Legal guardian(s) is (are) willing and able to comply with study requirements and provide written informed consent Note that all patients continued their PH1 established clinical management (including hyperhydration, crystallisation inhibitors, and pyridoxine) through month 6 of the study, after which adjustments could be made according to the recommendations of the treating physician.
Exclusion	• Clinical evidence of extrarenal systemic oxalosis • ALT or AST >2×ULN • Total bilirubin >1.5×ULN (patients with elevated total bilirubin that was secondary to documented Gilbert's syndrome were eligible if the total bilirubin was <2×ULN) • Known active human immunodeficiency virus infection, or evidence of current or chronic hepatitis C virus or hepatitis B virus infection • If ≥12 months old, has an eGFR ≤45 ml/min/1.73m^2 at screening (calculation was based on the Schwartz Bedside Formula); if <12 months old, has serum creatine value per the central laboratory above the ULN for age at screening • Investigational agent within the last 30 days or five half-lives, whichever was longer, or are in follow-up of another clinical study prior to randomisation • Has undergone renal or liver transplantation or a liver transplant is anticipated in the 6 months after the initial dose of lumasiran

Study	Michael, 2020 [78]
	• Other medical conditions or comorbidities, which in the opinion of the Investigator, would interfere with study compliance or data interpretation • History of allergic reaction to an oligonucleotide or GalNAc • History of intolerance to subcutaneous injection(s) • For female patients who may achieve menarche during the study, is unwilling to comply with the contraceptive requirements during the study period
Baseline differences	**≥10% difference in distribution of age between groups** (Age category (years), lumasiran <10 kg/≥10 to <20 kg/≥20 kg, n (%)) • 0 to <1: 2 (66.7)/0/0 • 1 to <2: 1 (33.3)/1 (8.3)/0 • 2 to <6: 0/11 (91.7)/3 (100) **≥10% difference in distribution of race between groups** (Race, lumasiran <10 kg/≥10 to <20 kg/≥20 kg, n (%)) • White: 1 (33.3)/12 (100)/3 (100) • Other: 2 (66.7)/0/0 **≥10% difference in distribution of region between groups** (Region, lumasiran <10 kg/≥10 to <20 kg/≥20 kg, n (%)) • Europe: 2 (66.7)/5 (41.7)/1 (33.3) • North America: 0/0/2 (66.7) • Other: 1 (33.3)/7 (58.3)/0
Randomisation	No randomisation.
Intervention	Lumasiran SC (N=18) **Loading dose (day 1, month 1, month 2) based on weight:** • <10 kg: 6.0 mg/kg QM×3 • ≥10 to <20 kg: 6.0 mg/kg QM×3 • ≥20 kg: 3.0 mg/kg QM×3 **Maintenance dose (month 3 and beyond) based on weight:** • <10 kg: 3.0 mg/kg QM

Study	Michael, 2020 [78]	
	• ≥10 to <20 kg: 6.0 mg/kg Q3M • ≥20 kg: 3.0 mg/kg Q3M Patients did not switch back to lower-weight dosing schedules if their body weight decreased on trial.	
Comparator	No comparator	
Baseline demographics		**Lumasiran (n=18)**
	Age, median (range), months	50.1 (3–72)
	Age at diagnosis, mean (SD), months	16.3
	Female, n (%)	10 (56)
	Weight, median (range) or mean (SD), kg	14.5 (6.2–24.3)
	Ethnicity – Asian	N/A
	Ethnicity – White	16 (89)
	Ethnicity – Other	2 (11)
	Region – Europe	8 (44)
	Region – Middle East	N/A
	Region – North America	2 (11)
	Region – Other	8 (44)
	24-hour urinary oxalate excretion (corrected for BSA), mean (SD), mmol/24 hours/1.73 m^2	2.083 (0.7087)
	24-hour urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	0.3406 (0.10929)
	Spot urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	0.631 (0.43)
	Plasma oxalate, mean (SD), µmol/l	13.24 (6.5)
	eGFR, mean (SD), ml/min/1.73 m^2	112.802 (27.63)
	CKD stage by eGFR, n (%), ml/min/1.73 m2 ≥90	N/R
	CKD stage by eGFR, n (%), ml/min/1.73 m 260 to <90	N/R
	CKD stage by eGFR, n (%), ml/min/1.73 m 230 to <60	N/R

Study	Michael, 2020 [78]	
	Renal stone events	3 (17)
	Lithotripsy/stone removal procedures in the 12 months prior to consent	2 (11.1)
	Pyridoxine use at baseline	11 (61)
	Pyelonephritis	2 (11)
	Urinary tract infections	4 (22)
	Nephrocalcinosis	14 (78)
	Symptomatic renal stone events in the 12 months prior to consent, n (%):1 to 5	N/R
	Symptomatic renal stone events in the 12 months prior to consent, n (%):6 to 10	N/R
	Symptomatic renal stone events in the 12 months prior to consent, n (%):>10	N/R
	Presenting symptoms – Asymptomatic (familial screening)	5 (28)
	Presenting symptoms – renal stone	5 (28)
	Presenting symptoms – ESKD	N/A
	Presenting symptoms – nephrocalcinosis	8 (44)
	Presenting symptoms – other	5 (28)
	Genotype – PR/any genotype of PR, M or N	3 (17)
	Genotype – M/M or M/N	10 (56)
	Genotype – N/N	5 (28)

Based on Tables C4 and C6 of the CS[1] tables C4 and C6.
*Baseline characteristics were derived from baseline in the parent phase 1/2 study.
ALT =alanine transaminase; AST =aspartate transaminase; BSA = body surface area; CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; GalNAc = N-Acetylgalactosamine; M = missense; N = nonsense; N/A = not applicable; N/R = not reported; PH1 = primary hyperoxaluria type 1; PR = pyridoxine responsive; RCT = randomised control trial; SD = standard deviation; UK = United Kingdom; ULN=upper limit of normal; USA = United States of America

The lumasiran phase 3 trial ILLUMINATE-B is an ongoing, international, multicentre, open-label study to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of lumasiran in infants and young children.

4.2.1.3.2 Subgroup and sensitivity analyses

Prespecified subgroup analyses were performed for the primary endpoint in the following subgroups:[54]:

- Age group: zero to <one year, one to <six years
- Weight-based dosing category: zero to <10 kg, ≥10 to <20 kg, and ≥20 kg

Three prespecified sensitivity analyses were performed to support the primary endpoint and included percent change from baseline for the:[54]

- Spot urinary oxalate:creatinine ratio by visit for the efficacy analysis set
- Spot urinary oxalate:creatinine ratio from month 3 to month 6 for the safety analysis set
- Ratio of measured spot urinary oxalate:creatinine to ULN from month 3 to month 6 for the efficacy analysis set

4.2.1.3.3 Efficacy

The clinical efficacy of lumasiran was evaluated in the single-arm ILLUMINATE-B trial in patients <six years of age with PH1 and relatively intact renal function. ILLUMINATE-B assessed the efficacy of lumasiran on several outcomes, although only some were relevant to the NICE scope.

Table 4.11 summarises the ILLUMINATE-B efficacy results for the 18 patients who completed the 6-month primary analysis period, for the outcomes that were within the NICE scope.[78, 86]

Table 4.11: Outcomes from published and unpublished studies – ILLUMINATE-B

Study	**ILLUMINATE-B (ALN-GO1-004), NCT03905694, EudraCT 2018-004014-17**				
Size of study groups	Lumasiran (n=18)				
Study duration	60 months				
Outcome Name (unit)	Effect Size		Statistical test		Comments
	Value	95% CI	Type	P value	
Percent change in plasma oxalate from baseline to month 6, %, LSM*	–31.7	(–39.5, –23.9)	MMRM	N/R	Secondary endpoint; EAS; statistical analysis was performed similarly to the primary endpoint
Absolute change in plasma oxalate from baseline to month 6, µmol/l, LSM*	–5.2	(–6.2, –4.2)	MMRM	N/R	Secondary endpoint; EAS; statistical analysis was performed similarly to the primary endpoint
Proportion of patients with spot urinary oxalate excretion ≤ULN at month 6, %‡	6	N/R	N/A	N/A	Secondary endpoint; EAS; descriptive statistics
Proportion of patients with spot urinary oxalate excretion ≤1.5×ULN at month 6, %‡	50	N/R	N/A	N/A	Secondary endpoint; EAS; descriptive statistics
Change from baseline in eGFR (ml/min/1.73m^2), mean (SD)*	−0.3 (15)	N/R	N/A	N/A	Secondary endpoint; EAS; descriptive statistics

Based on Table C11 of the CS[1]

*In patients with baseline plasma oxalate ≥1.5× lower limit of quantitation (n=13; mean, 15.6; range, 8.7–30.6 µmol/l at baseline), LSM reduction from the average of month 3 to month 6 was 39.4% (95% CI, 29.3%, 49.4%) or 6.9 µmol/l (95% CI, 5.5, 8.3 µmol/l); † Age-dependent ULN; ‡N=16. eGFR was only calculated in patients ≥12 months of age at baseline.

CI = confidence interval; CS = company submission; EAS = efficacy analysis set; eGFR = estimated glomerular filtration rate; LSM = least squares mean; MMRM = Mixed-effect model repeated measures; N/A = not applicable; N/R = not reported; PK = pharmacokinetic; SD = standard deviation; SEM = standard error of the mean; ULN = upper limit of normal

Oxalate levels in urine

Lumasiran led to clinically meaningful and sustained reductions in urinary oxalate excretion across all weight ranges in infants and young children enrolled in ILLUMINATE-B.[54, 86]

Overall, the treatment effect observed for urinary oxalate and plasma oxalate is consistent with that seen in the placebo-controlled ILLUMINATE-A RCT, indicating similar efficacy and suitable dosing regimens across all ages of patients with PH1. The clinical benefit of oxalate reduction is further supported by the low incidence of renal stone events and reversal of nephrocalcinosis.[15, 86] 24-hour urinary oxalate (corrected for BSA) was available for two patients. The percent changes from baseline to month 6 were −74.0% and −62.8%, respectively, for these two patients

ERG comment: No details of results were provided for most participants.

Oxalate levels in plasma

The LSM (95% CI) percent change in plasma oxalate from baseline to month 6 (average of months 3 to 6) was −31.7% (−39.5% to −23.9%), while the absolute change was −5.2 µmol/l (−6.2 to −4.2). In patients with a plasma oxalate level of ≥1.5×LLOQ (n=13) at baseline, the LSM (95% CI) percent change to month 6 (average of months 3 to 6) was −39.4% (−49.4% to −29.3%), while the absolute change was −6.9 µmol/l (−8.3 to −5.5).[86]

Change in eGFR

Renal function in the youngest patients generally followed the expected trajectory for healthy children of similar ages. The mean (SD) change from baseline to month 6 was −0.3 (15) ml/min/1.73 m^2.[86]

Need for liver transplant with or without a kidney transplant

No data provided in any of the data sources.

Mortality

No deaths occurred.

Health related quality of life

No data were provided in the CS. The study report[54] stated that '*no notable differences between initial weight dose groups were observed for the Caregiver Experience Survey and for the Patient and Caregiver Impact Questionnaire over this period'*.

Outcomes out of scope

The company also reported 24-hour urinary oxalate:creatinine ratio, rate of renal stone events, and nephrocalcinosis (see pages 82 to 84 of the CS).[1] These outcomes are outside the NICE final scope and therefore most have not been included in the ERG report.

However, the ERG decided to include the rate of renal stone events in the ERG report, because, unlike many of the other outcomes considered, it is not a surrogate outcome and is directly related to the experience of the patient.

Rate of renal stone events

Low rates of renal stone events in ILLUMINATE-B patients were unchanged between the 12-month historical recall and the first 6 months of treatment. A total of four renal stone events were reported by three patients in the 12 months prior to providing informed consent (0.24 event rate per person-year). Two patients each had a single postbaseline mild renal stone event within the 6-month treatment period (0.24 event rate per person-year).[54, 86]

4.2.1.3.4 Critical appraisal

The CS critically appraised the project, see Table 4.12.

Table 4.12: Critical appraisal of ILLUMINATE-B

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Not clear	Minimal details reported of eligibility to the study
Was the exposure accurately measured to minimise bias?	Not clear	No details of doses given
Was the outcome accurately measured to minimise bias?	Not clear	Minimal safety outcomes only reported in abstract
Have the authors identified all important confounding factors?	No	No discussion of confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	No	No discussion of confounding factors
Was the follow-up of patients complete?	No	Interim analysis only
How precise (for example, in terms of confidence interval and p values) are the results?	No	No precision estimates provided
Based on Table C9 of the CS[1] Adapted from CASP: Making sense of evidence: 12 questions to help you make sense of a cohort study[74] CASP = Critical Appraisal Skills Programme; N/A = not applicable; CS = company submission		

ERG comment: The CS evaluation of quality was a fair assessment, based on the unpublished and necessarily brief 'PowerPoint presentation' data by Michael 2020.[78] However the 'in press' publication by Sas 2021 provides far more methodological detail.[86] Based on the additional data provided, the ERG has provided an extra critical appraisal, see Table 4.13.

Table 4.13: Updated critical appraisal of ILLUMINATE-B

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Clear details reported of eligibility to the study
Was the exposure accurately measured to minimise bias?	Yes	Details of doses given, based on children's weights
Was the outcome accurately measured to minimise bias?	Yes	Efficacy and safety outcomes measured at least monthly
Have the authors identified all important confounding factors?	No	No discussion of confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	No	No discussion of confounding factors. The main limitation is the lack of any comparator group, making it impossible to extricate extraneous factors from the treatment effect.

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the follow-up of patients complete?	No	Interim analysis only
How precise (for example, in terms of confidence interval and p values) are the results?	Precise	Precision estimates provided
Adapted from CASP: Making sense of evidence: 12 questions to help you make sense of a cohort study[74] CASP = Critical Appraisal Skills Programme; N/A = not applicable; CS = company submission		

As stated above, the chief limitation is the lack of any comparator group, making it impossible to separate extraneous factors from the treatment effect. Although it is highly unlikely that extraneous factors will explain the entire magnitude and direction of clinical efficacy outcomes, it is likely that at least some of the observed effect will be influenced by intervening variables, and the degree of such confounding is uncertain. Interpretation of results should bear this in mind, and it is certainly not appropriate to unequivocally conclude that improvements in an outcome are wholly due to a treatment effect, as the CS appears to have done (for example, page 84 in the CS).[1]

4.2.1.4 ILLUMINATE-B: 60-month follow-up

4.2.1.4.1 Study characteristics

The participant characteristics are identical to those of the 6-month primary study (Table 4.10).

4.2.1.4.2 Clinical efficacy

Oxalate levels in urine

No data provided.

Oxalate levels in plasma

[redacted] versus LS mean [95% CI] percent change of –31.7% (–39.5% to –23.9%) at month 6.[78] [redacted]

Figure 4.13: ILLUMINATE-B extension period: percent change from baseline plasma oxalate

Based on CS[1] with primary source: Alnylam, Data on File[87]
Data are expressed as mean (SEM).
BL = baseline; CS = company submission; M = month; SEM = standard error of the mean

Change in eGFR

Need for liver transplant with or without a kidney transplant

No data provided.

Mortality

No deaths occurred.

Health-related quality of life

No data provided.

Outcomes out of scope

The company also reported 24-hour urinary oxalate:creatinine ratio, rate of renal stone events, and nephrocalcinosis (see page 84 of the CS).[1]) These outcomes are outside the NICE final scope and therefore most have not been included in the ERG report.

However, the ERG decided to include the rate of renal stone events in the ERG report, because, unlike many of the other outcomes considered, it is not a surrogate outcome and is directly related to the experience of the patient.

Rate of renal stone events

The rate of renal stone events was 0.12 events per person-year between month 6 and month 12 (versus 0.24 events from baseline to month 6 and 0.24 events in the 12 months prior to providing informed consent.[78, 81]

4.2.1.4.3 Critical appraisal

No critical appraisal was made of the extended period of ILLUMINATE-B in the CS.[1]

ERG comment: A critical appraisal of the unpublished Sas 2021[81] PowerPoint presentation is shown in Table 4.14.

Table 4.14: Critical appraisal of ILLUMINATE B-extension period

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Clear details reported of eligibility to the study
Was the exposure accurately measured to minimise bias?	Yes	Details of doses given, based on children's weights
Was the outcome accurately measured to minimise bias?	No	No outcomes measured post 6 months (despite being cited by CS as a relevant source for the extended period)
Have the authors identified all important confounding factors?	No	No discussion of confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	No	No discussion of confounding factors. The main limitation is the lack of any comparator group, making it impossible to extricate extraneous factors from the treatment effect.
Was the follow-up of patients complete?	No	Interim analysis only
How precise (for example, in terms of confidence interval and p values) are the results?	Precise	Precision estimates provided
Adapted from CASP: Making sense of evidence: 12 questions to help you make sense of a cohort study[74] CASP = Critical Appraisal Skills Programme; N/A = not applicable; CS = company submission		

4.2.1.5 ILLUMINATE-C

ILLUMINATE-C (ALN-GO1-004) project aimed to evaluate the efficacy, safety, PK, and PD of lumasiran (ALN-GO1) in patients with PH1 and advanced renal disease. The information below is taken from the information in the CS[1], and information inferred, or taken directly, from the included papers.

4.2.1.5.1 Study characteristics

Table 4.15 summarises the characteristics of the ILLUMINATE-C primary analysis.

Table 4.15: Study characteristics for ILLUMINATE-C primary analysis

Study	ILLUMINATE-C primary analysis
Study type	International, multicentre, open-label, single-arm, phase 3 study comprising two cohorts: • Cohort A: patients who do not yet require dialysis. Patients who experience progression of renal impairment over time and require dialysis therapy will cross over to Cohort B • Cohort B: patients who are on dialysis January 2020 to August 2025 (estimated completion date) 60-month follow-up (6-month primary analysis, 54-month long-term extension period)
Number of participants selected	N=21 (Cohort A = six, Cohort B = 15)
Study sites	15 study centres across 10 countries
Inclusion	• Have reached at least 37 weeks estimated gestational age (full-term infant) at consent • Documented PH1 as determined by genetic analysis • eGFR ≤45 ml/min/1.73 m^2 (calculated using the MDRD formula if ≥18 years or Schwartz Bedside Formula if ≥12 months to <18 years), or patients aged <12 months with serum creatinine that is considered elevated for age at consent • Mean plasma oxalate level from the first three collections at least seven days apart during screening ≥20 µmol/l • Pyridoxine: allowed if patient is on a stable regimen for >90 days before consent and able to remain on this stable regimen at least until month 6 visit (dose adjustments for interval weight gain are acceptable) • Willing to comply with study requirements; written informed consent from patient or legal guardian(s) • For patients who require dialysis (Cohort B): on a stable haemodialysis regimen for >four weeks prior to screening plasma oxalate assessment and able to maintain this regimen through month 6, with changes permitted only when medically indicated
Exclusion	• ALT or AST >2×ULN for age • Total bilirubin >1.5×ULN (patients with elevated total bilirubin that was secondary to documented Gilbert's syndrome were eligible if the total bilirubin was <2×ULN) • INR >1.5 (patients on oral anticoagulant (e.g. warfarin) with an INR <3.5 were allowed) • Known active human immunodeficiency virus infection, or evidence of current or chronic hepatitis C virus or hepatitis B virus infection • Investigational agent within the last 30 days or five half-lives, whichever was longer, or are in follow-up of another clinical study prior to randomisation

Study	ILLUMINATE-C primary analysis
	• History of allergic reaction to an oligonucleotide or GalNAc • Conditions other than PH1 contributing to renal insufficiency (i.e. glomerulonephritis, nephrotic syndrome, or lupus nephritis) • Other medical conditions or comorbidities, which in the opinion of the Investigator, would interfere with study compliance or data interpretation, or prevent participation in at least 12 months of the study • Unwilling or unable to limit alcohol consumption; alcohol intake of >two units per day was excluded during the study (unit: 1 glass of wine (125 ml) = one measure of spirits (one fluid ounce) = ½ pint of beer (284 ml)) • History of alcohol abuse within the last 12 months before screening • Has undergone liver transplantation or a liver transplant is anticipated within six months • Has undergone renal transplant and is currently receiving immunosuppression to prevent transplant rejection • Maintained on a peritoneal dialysis regimen • Plans to start dialysis replacement therapy within six months • Unwilling to comply with the contraceptive requirements during the study period • Pregnant, planning a pregnancy, or breast-feeding
Baseline differences	**≥10% difference in distribution of age between Cohorts** (Age category (years), lumasiran Cohort A/lumasiran Cohort B, n (%)) • 2 to <6: 0/3 (20.0) • 6 to <18: 3 (50.0)/5 (33.3) **≥10% difference in distribution of race between Cohorts** (Race, lumasiran Cohort A / lumasiran Cohort B, n (%)) • White: 4 (66.7)/12 (80.0) • Other: 1 (16.7)/0 **≥10% difference in distribution of region between Cohorts** (Region, lumasiran Cohort A / lumasiran Cohort B, n (%)) • Europe: 0/8 (53.3) • Middle East: 5 (83.3)/5 (33.3) **≥10% difference in body weight between Cohorts** Body weight, lumasiran Cohort A/lumasiran Cohort B, mean (SD), kg: 47.08 (45.00) / 35.72 (31.14)
Randomisation	No randomisation

Study	**ILLUMINATE-C primary analysis**			
Intervention	Lumasiran SC (N=21) **Loading dose (day 1, month 1, month 2) based on weight:** • <10 kg: 6.0 mg/kg QM×3 • ≥10 to <20 kg: 6.0 mg/kg QM×3 • ≥20 kg: 3.0 mg/kg QM×3 **Maintenance dose (month 3 and beyond) based on weight:** • <10 kg: 3.0 mg/kg QM • ≥10 to <20 kg: 6.0 mg/kg Q3M • ≥20 kg: 3.0 mg/kg Q3M			
Comparator	No comparator			
Baseline demographics		**Lumasiran Cohort A, n=6**	**Lumasiran Cohort B, n=15**	**Overall, N=21**
	Age, median (range), years	9.0 (0–40)	6.0 (1–59)	8.0 (0–59)
	Age at diagnosis, mean (SD), months	[redacted]	[redacted]	[redacted]
	Female, n (%)	3 (50)	6 (40)	9 (42.9)
	Weight, median (range) or mean (SD), kg	[redacted]	[redacted]	[redacted]
	Ethnicity - Asian	[redacted]	[redacted]	[redacted]
	Ethnicity - White	[redacted]	[redacted]	[redacted]
	Ethnicity - Other	[redacted]	[redacted]	[redacted]
	Region - Europe	[redacted]	[redacted]	[redacted]
	Region - Middle East	[redacted]	[redacted]	[redacted]
	Region - North America	[redacted]	[redacted]	[redacted]
	Region - Other‡	[redacted]	[redacted]	[redacted]
	24-hour urinary oxalate excretion (corrected for BSA), mean (SD), mmol/24 hours/1.73 m^2	[redacted]	[redacted]	[redacted]

Study	ILLUMINATE-C primary analysis			
	24-hour urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	[redacted]	[redacted]	[redacted]
	Spot urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	[redacted]	[redacted]	[redacted]
	Plasma oxalate, mean (SD), mmol/l	[redacted]	[redacted]	[redacted]
	eGFR, mean (SD), ml/min/1.73 m^2	[redacted]	[redacted]	[redacted]
	CKD stage by eGFR, n (%), ml/min/1.73 m2 ≥90	N/R	N/R	N/R
	CKD stage by eGFR, n (%), ml/min/1.73 m 260 to <90	N/R	N/R	N/R
	CKD stage by eGFR, n (%), ml/min/1.73 m 230 to <60	N/R	N/R	N/R
	Renal stone events	[redacted]	[redacted]	[redacted]
	Lithotripsy/stone removal procedures in the 12 months prior to consent	N/R	N/R	N/R
	Pyridoxine use at baseline	[redacted]	[redacted]	[redacted]
	Pyelonephritis	[redacted]	[redacted]	[redacted]
	Urinary tract infections	[redacted]	[redacted]	[redacted]
	Nephrocalcinosis	[redacted]	[redacted]	[redacted]
	Symptomatic renal stone events in the 12 months prior to consent, n (%):1 to 5	N/R	N/R	N/R
	Symptomatic renal stone events in the 12 months prior to consent, n (%):6 to 10	N/R	N/R	N/R
	Symptomatic renal stone events in the 12 months prior to consent, n (%):>10	N/R	N/R	N/R
	Presenting symptoms - Asymptomatic (familial screening)	[redacted]	[redacted]	[redacted]
	Presenting symptoms – renal stone	[redacted]	[redacted]	[redacted]

Study	ILLUMINATE-C primary analysis			
	Presenting symptoms - ESKD	[redacted]	[redacted]	[redacted]
	Presenting symptoms - nephrocalcinosis	[redacted]	[redacted]	[redacted]
	Presenting symptoms - other	[redacted]	[redacted]	[redacted]
	Genotype – PR/ any genotype of PR, M or N	[redacted]	[redacted]	[redacted]
	Genotype – M/M or M/N	[redacted]	[redacted]	[redacted]
	Genotype – N/N	[redacted]	[redacted]	[redacted]

Based on Tables C5 and C6 of the CS[1]

* Baseline characteristics were derived from baseline in the parent phase 1/2 study; † 24-hour urinary oxalate was performed in a limited subset of patients who were able to complete a 24-hour urine collection (n=five for 24-hour urinary oxalate excretion and n=six for 24-hour urinary oxalate:creatinine ratio); ‡ 24-hour urinary oxalate was performed in five out of six patients in Cohort A and in one out of 15 patients in Cohort B of ILLUMINATE-C; §Based on the plasma oxalate analysis set of ILLUMINATE-A comprising 23 patients in the lumasiran arm and 10 patients in the placebo arm; ¶ Symptomatic renal stone events; ǀ History of renal stone events in the 12 months prior to the study; ** Includes all symptoms that a patient had experienced prior to diagnosis. A patient may check more than one category; therefore, percentages may exceed 100%
ALT = alanine transaminase; AST = aspartate transaminase; BSA = body surface area; CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; GalNAc = N-Acetylgalactosamine; M = missense; N = nonsense; n = number; N/A = not applicable; N/R = not reported; PH1 = primary hyperoxaluria type 1; PR = pyridoxine responsive; SD = standard deviation; ULN=upper limit of normal

The lumasiran phase 3 trial ILLUMINATE-C is an ongoing, international, multicentre, open-label study to evaluate the efficacy, safety, PK, and PD of lumasiran in patients with PH1 and advanced renal disease (eGFR ≤45 ml/min/1.73 m^2), including patients requiring haemodialysis.[88]

ILLUMINATE-C included a cohort of patients who did not yet require dialysis (Cohort A) and a cohort of patients who were on dialysis (Cohort B). The study design specified inclusion of at least six patients in each cohort at baseline, with patients in Cohort A who experienced progression of renal impairment and required dialysis therapy able to cross over to Cohort B.[88] Twenty-one patients enrolled in ILLUMINATE-C, six patients in Cohort A and 15 patients in Cohort B.

4.2.1.5.2 Subgroup and sensitivity analyses

Prespecified subgroup analyses were performed for the primary endpoint in the following subgroups:[89]

- Age group: zero to <two years, two to <six years, six to <18 years, ≥18 years
- Weight-based dosing category: zero to <10 kg, ≥10 to <20 kg, and ≥20 kg

The following sensitivity analysis was performed in ILLUMINATE-C:

- Percent change in plasma oxalate (Cohort A) or pre-dialysis plasma oxalate (Cohort B) from baseline to month 6 for the safety analysis sets

4.2.1.5.3 Clinical efficacy

Table 4.16 summarises the outcomes from ILLUMINATE C that were in line with the NICE scope.

Table 4.16: Outcomes from ILLUMINATE-C

Study	**ILLUMINATE-C (ALN-GO1-005), NCT04152200, EudraCT 2019-001346-17[90]**						
Size of study groups	Lumasiran Cohort A—patients not yet on dialysis (n=6) Lumasiran Cohort B—patients on dialysis (n=15)						
Study duration	60 months (6-month primary analysis period plus 54-month extension)						
Outcome name (unit)	Effect size Cohort A		Effect size Cohort B		Statistical test		Comments
	Value	95% CI	Value	95% CI	Type	p value	
Percent change in plasma oxalate from baseline to month 6, %*	-33.33	(-81.82 to 15.16)	-42.43	(-50.71 to -34.15)	MMRM	[redacted]	Primary endpoint; FAS; statistical analyses were primarily descriptive
Absolute change in plasma oxalate from baseline to month 6, µmol/l*	-35.28	(-56.32 to -14.24)	-48.33	(-55.85 to -40.80)	MMRM	N/A	Secondary endpoint; FAS; statistical analyses were primarily descriptive
Percent change in plasma oxalate AUC (0–24 hours) between dialysis sessions from baseline to month 6, %	N/A	N/A	-41.4	(-51.0 to -31.8)	MMRM	N/A	Secondary endpoint; Cohort B FAS
Percent change in BSA-corrected 24-hour urinary oxalate from baseline to month 6, %†	10.557	(-31.986 to 10.871)	N/A	N/A	MMRM	N/A	Secondary endpoint; Cohort A FAS
Absolute change in BSA-corrected 24-hour urinary oxalate from baseline to month 6, mmol/24 hours/1.73 m^2 †	0.533	(-0.888 to -0.179)	N/A	N/A	MMRM	N/A	Secondary endpoint; Cohort A FAS

Based on Table C12 of the CS[1]
* Predialysis plasma oxalate in Cohort B; † Based on a subgroup of urine-producing patients in Cohort A (n=5).
AUC = area under the curve; BSA = body surface area; CI = confidence interval; CS = company submission; FAS = full analysis set; MMRM = mixed-effect model repeated measures; N/A = not applicable

Oxalate levels in urine

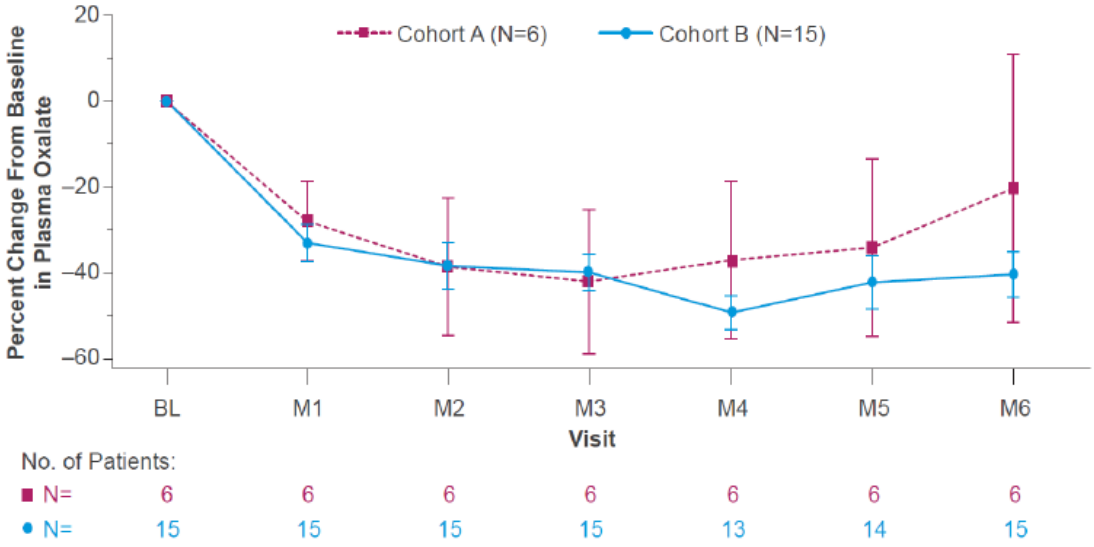
This was assessed in Cohort A. Treatment with lumasiran was associated with a reduction in:[90]

- BSA-corrected 24-hour urinary oxalate from baseline to month 6 (average of months 3 to 6). The LSM (95% CI) percent change from baseline was −10.557% (−31.986%, 10.871%). The LSM (95% CI) absolute change from baseline was −0.533 mmol/24 hours/1.73 m^2 (−0.888, −0.179)

Oxalate levels in plasma

The primary endpoint was percent change in plasma oxalate from baseline to month 6, which was measured as pre-dialysis plasma oxalate in Cohort B. At 6 months, the LSM (95% CI) change in plasma oxalate from baseline was −33.33% (−81.82% to 15.16%) in Cohort A. The LSM (95% CI) change in pre-dialysis plasma oxalate from baseline was −42.43% (−50.71% to −34.15%) in Cohort B. A clinically meaningful magnitude of percent plasma oxalate reduction from baseline to month 6 was observed in both cohorts, as shown in Figure 4.14.[90]

Figure 4.14: ILLUMINATE-C primary analysis: percent change in plasma oxalate from baseline to month 6



Based on CS[1] with primary source: Alnylam Pharmaceuticals 2021[91]
Data are expressed as least squares mean (SEM), estimated by MMRM.
BL = baseline; CS = company submission; M = month; MMRM = mixed-effect model repeated measures; SEM = standard error of the mean

A reduction in plasma oxalate was observed irrespective of patients' baseline characteristics in the larger Cohort B, as demonstrated by the subgroup analysis of the primary endpoint. Note that baseline plasma oxalate values were higher in Cohort B; median (range) values were 57.9 (22.7–134.0) µmol/l in Cohort A and 103.7 (56.3–167.0) µmol/l in Cohort B (Figure 4.15).[90]

Figure 4.15: ILLUMINATE-C primary analysis: Forest plots of percent change in plasma oxalate from baseline to month 6 in patient subgroups

Cohort A (N=6)

Cohort B (N=15)

Based on CS[1] with primary source: ILLUMINATE-C [ALN-GO1-005] CSR 1[55]
Estimated by MMRM.
CI = confidence interval; CS = company submission; CSR = clinical study report; LS = least squares; MMRM = mixed-effect model repeated measures

The secondary endpoint of absolute change in plasma oxalate from baseline to month 6 (average of months 3 to 6) was analysed in both cohorts. The LSM (95% CI) absolute change from baseline was −35.28 µmol/l (−56.32, −14.24) in Cohort A and −48.33 µmol/l (−55.85, −40.80) in Cohort B.[90]

The secondary endpoint of percent change from baseline to month 6 (average of months 3 to 6) in plasma oxalate $AUC_{(0–24\ h)}$ measured between dialysis sessions was assessed in patients receiving dialysis (i.e. Cohort B). This endpoint is used to evaluate the effect of lumasiran on patients' systemic

exposure to plasma oxalate between dialysis sessions. The LSM (95% CI) percent change from baseline was −41.4% (−51.0%, −31.8%).[90]

Change in eGFR

No data were provided.

Need for liver transplant with or without a kidney transplant

No data were provided.

Mortality

No deaths occurred.

Health related quality of life

No data were presented in the CS.

ERG comment: A report on quality-of-life data was found in the study report.[55] The reader is initially directed to Tables 14.2.5.20 and 14.2.5.21 but these were not possible to find in the document. It was stated that '*interpretation of the measures is difficult due to small sample sizes resulting from the applicability of the Pediatric Quality of Life Inventory (PedsQL) and the KDQOL-36 to an age-specific subset of the overall study population, among other factors*'. Therefore, no statement of actual results is made. Later in the document, in Section 11.2.1.3.7, further tables are referenced for the EQ-5D-Y, EQ-5D-5L, PedsQL, Kidney Disease Quality of Life-36 items (KDQOL-36) quality of life tools, but again these tables are not available in the document, and the report states that results are difficult to interpret.

Outcomes out of scope

The company also reported 24-hour urinary oxalate:creatinine ratio, cardiac outcomes, rate of renal stone events, and nephrocalcinosis (see page 89 of the CS).[1]). These outcomes are outside the NICE final scope and therefore most have not been included in the ERG report. However, the ERG decided to include the rate of renal stone events in the ERG report, because, unlike many of the other outcomes considered, it is not a surrogate outcome and is directly related to the experience of the patient.

Rate of renal stone events

[redacted]

4.2.1.5.4 Critical appraisal

A critical appraisal was not carried out in the CS.

ERG comment: A critical appraisal of Michael 2021, the main reference for ILLUMINATE-C, has been performed by the ERG and is reported in Table 4.17.[90]

Table 4.17: Critical appraisal of randomised control trials – ILLUMINATE-C

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Not clear	Minimal details reported of eligibility to the study
Was the exposure accurately measured to minimise bias?	Not clear	No details of doses given
Was the outcome accurately measured to minimise bias?	Yes	Efficacy and safety outcomes addressed
Have the authors identified all important confounding factors?	No	No discussion of confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	No	No discussion of confounding factors
Was the follow-up of patients complete?	No	Interim analysis only
How precise (for example, in terms of confidence interval and p values) are the results?	Precise for efficacy data	No precision estimates provided for safety data
Adapted from CASP: Making sense of evidence: 12 questions to help you make sense of a cohort study[74] CASP = Critical Appraisal Skills Programme; N/A = not applicable; CS = company submission		

4.2.1.6 ILLUMINATE-C: extended period

No data for the extended period were presented in the CS.[1]

4.2.1.7 ALN-GO1-001B

ALN-GO1-001 Part B (ALN-GO1-001B) was a phase 1/2, randomised, placebo-controlled, single-blind, multi-dose study to evaluate lumasiran in patients aged ≥six years with PH1 with urinary oxalate ≥0.7 mmol/1.73m^2/day and eGFR >45 ml/min/1.73m^2 (N=20). The primary study endpoint was safety; secondary study endpoints included change in 24-hour urinary oxalate.[92]

4.2.1.7.1 Study characteristics

20 adults and children aged six to 64 years with a diagnosis of PH1 and eGFR >45 ml/min/1.73m^2 were randomised 3:1 to one of three doses of lumasiran, or placebo (Part B). A group of healthy adult volunteers were also included in another part of the study (Part A) but this is not described here. The sample sizes and doses were as shown below:[92]

- Lumasiran, n=9
  - 1 mg/kg SC QM (n=3)
  - 3 mg/kg SC QM (n=3)
  - 3 mg/kg SC Q3M (n=3)
- Placebo, n=3
  - one patient for each lumasiran arm

Open-label expansion (OLE) cohorts (lumasiran 1 mg/kg SC QM (n=4), lumasiran 3 mg/kg SC Q (n=4)) were also mentioned by the CS but no reports of results for these were found.

4.2.1.7.2 Efficacy

Efficacy results were presented in tabular form in the supplement of Frishberg, 2021[77] and have been reproduced below. Results for percentage change from baseline to day 85 have been presented as these are the longest follow up results that contain placebo data.

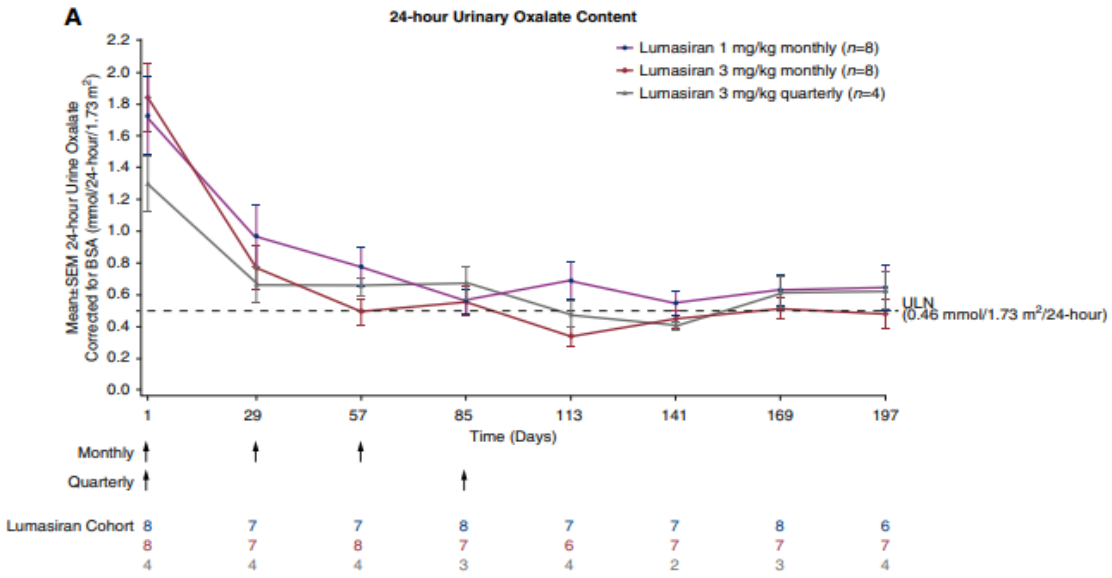
Urinary oxalate levels

Table 4.18 and Figure 4.16 summarise the results for urinary oxalate levels.

Table 4.18: Urinary oxalate levels

	Placebo	1 mg/kg once monthly	3 mg/kg once monthly	3 mg/kg, once every 3 months
24-hour urinary oxalate excretion (mmol/24 hours/1.73 m^2)	9.1 (n=1)	-65.6 (16.6) (n=8)	-68.4(10.6) (n=7)	-53.3(3.7) (n=3)
Adapted from data in supplement section of Frishberg 2021[77]				

Figure 4.16: Urinary oxalate assessments after multiple doses of lumasiran in patients with primary hyperoxaluria type 1 (part B). 24-hour urinary oxalate excretion (mmol per 24 hours per 1.73 m^2)



Taken from primary source: Frishberg 2021[77]
ULN = upper limit of normal

Plasma oxalate levels

Table 4.19 summarises results for plasma oxalate levels.

Table 4.19: Plasma oxalate levels

	Placebo	1 mg/kg once monthly	3 mg/kg once monthly	3 mg/kg, once every 3 months
Plasma oxalate (micromol/l)	-18.7 (n=1)	-75.3 (26) (n=2)	-53.2 (62.4) (n=5)	-
Adapted from data in supplement section of Frishberg 2021[77]				

Change in eGFR

No data provided.

Need for liver transplant with or without a kidney transplant

No data provided.

Mortality

No deaths occurred.

Health related quality of life

No data provided.

Outcomes out of scope

The company also reported 24-hour urinary oxalate:creatinine ratio, and 24-hour urinary glycolate:creatinine ratio; however, these outcomes are outside the NICE final scope and have not been included in the ERG report.

4.2.1.7.3 Critical appraisal

ERG comment: The CS provided minimal information about the ALN-GO1-001 study, and so the data extraction and critical appraisal of the key paper were carried out by the ERG, see Table 4.20.

Table 4.20: Critical appraisal of Frishberg 2021

Study type	RCT (doses and placebo)
Number of participants randomised	(Part B only)
Country	Israel, France, Germany, the United Kingdom, and the Netherlands
Inclusion	Eligible participants for Part B were patients aged six to 64 years with a diagnosis of primary hyperoxaluria type 1 confirmed by genetic analysis or reduced AGT enzyme activity. Additional inclusion criteria for Part B included 24-hour urinary oxalate excretion >0.7 mmol/24 hours per 1.73 m^2 (ULN is 0.46 mmol/24 hours per 1.73 m^2) and eGFR.45 ml/min per 1.73 m^2 calculated on the basis of the Modification of Diet in Renal Disease formula for adults and the Schwartz bedside formula for children. These criteria ensured kidney function was sufficient for urinary oxalate excretion to reliably reflect hepatic oxalate production
Exclusion	Not reported
Age mean (sd)	15 (10)
Gender	65% female
Ethnicity	75% white; 0% black, 20% Asian, 5% other
Other baseline characteristics	BMI 21 kg/m^2; pyridoxine use 65%; 24-hour urine oxalate excretion 0.60 mmol/24 hours per 1.73m^2; eGFR: 78 ml/min per 1.73 m^2; plasma oxalate 8.8 micromol/l
Selection bias	The clinical study centre pharmacy staff randomised the participants in accordance with a cohort-specific, computer-generated randomisation list generated by the contract research organisation biostatistician. This suggests some form of allocation concealment but does not confirm it, as there is no explicit statement that the recruiters were unaware of the next allocation in the random allocation sequence when deciding to recruit the next patient. Randomised treatment assignment was on the basis of permuted block randomisation method with a block size of four with a ratio of 3:1 (lumasiran to placebo). Block size was not known to the investigators.
Performance bias	Patients blinded, but no health care professional blinding, so potential performance bias
Attrition bias	No reports of loss of data
Detection bias	No assessor blinding, so potential detection bias
Intervention	1 mg/kg lumarisan qM q28dx3 SC, 3 mg/kg lumarisan qM q28dx3 SC, 3 mg/kg lumarisan q3M q84dx2 SC
Comparator	Placebo

Comments	Although this is a randomised trial, which should reduce the risk of systematic selection bias (though please note the comment on the unclear allocation concealment), the extremely small numbers of participants mean that random mixing of characteristics across groups in extremely unlikely. Therefore, random selection bias is highly likely to remain.

AGT = alanine-glyoxylate aminotransferase; BMI = body mass index; eGFR = estimated glomerular filtration rate; Q3M = every three months; RCT = randomised controlled trial; SC = subcutaneous; ULN = upper limit of normal

4.2.1.8 ALN-GO1-002

ALN-GO1-002 was a phase 2 multicentre OLE study to evaluate the long-term administration of lumasiran in patients with PH1 aged six to 64 years who were previously enrolled in ALN-GO1-001B (N=20).[77, 93, 94] Patients initiated dosing with SC lumasiran at the same dosing regimen as they received in ALN-GO1-001B (1 mg/kg monthly (n=8), 3 mg/kg monthly (n=7), or 3 mg/kg every 3 months (n=5)).[77, 93] Patients who received 1 mg/kg monthly were subsequently transitioned to 3 mg/kg every 3 months to align with the intended phase 3 maintenance dose.[94]

The primary study objective was to evaluate the long-term safety of multiple doses of lumasiran. Secondary objectives included the assessment of changes in 24-hour urinary oxalate (corrected for BSA), 24-hour urinary oxalate:creatinine ratio, and eGFR.[94]

4.2.1.8.1 Study characteristics

The CS provided baseline characteristics for ALN-GO1-002 but no other details concerning study type, inclusion, exclusion, baseline differences, and so these have been added to Table 4.21 based on ERG perusal of the primary sources.[77, 93]

Table 4.21: Study characteristics for ALN-GO1-002

Study type	Phase 2 multicentre OLE study	
Number of participants selected	20 adults and children aged six to 64 years with diagnosis of PH1 who participated in the ALN-GO1-001 phase 2 multi-dose study of lumasiran (NCT02706886): • 1 mg/kg SC QM (n=3) • 3 mg/kg SC QM (n=7) • 3 mg/kg SC Q3M (n=10)	
Study sites	Israel, France, Germany, the UK, and the Netherlands	
Inclusion	As for ALN-GO1-002. Eligible participants were patients aged six to 64 years with a diagnosis of primary hyperoxaluria type 1 confirmed by genetic analysis or reduced AGT enzyme activity. Additional inclusion criteria for Part B included 24-hour urinary oxalate excretion >0.7 mmol/24 hours per 1.73 m^2 (ULN is 0.46 mmol/24 hours per 1.73 m^2) and eGFR.45 ml/min per 1.73 m^2 calculated on the basis of the Modification of Diet in Renal Disease formula for adults and the Schwartz bedside formula for children. These criteria ensured kidney function was sufficient for urinary oxalate excretion to reliably reflect hepatic oxalate production	
Exclusion	Not reported	
Baseline differences	Not reported	
Randomisation	No comparator	
Intervention	Patients initiated dosing with SC lumasiran at the same dosing regimen as they received in ALN-GO1-001B (1 mg/kg monthly (n=8), 3 mg/kg monthly (n=7), or 3 mg/kg every 3 months (n=5)). Patients who received 1 mg/kg monthly were subsequently transitioned to 3 mg/kg every 3 months to align with the intended phase 3 maintenance dose	
Comparator	No comparator	
Baseline demographics		**Lumasiran (n=20)**
	Age, median (range), years	11.5 (6–43)
	Age at diagnosis, median (range), years	3.8 (−0 to 13)[†]
	Female, n (%)	7 (35)
	Weight, median (range) or mean (SD), kg	42.8 (21.3–112.5)
	Ethnicity - Asian	4 (20.0)
	Ethnicity - White	15 (75.0)

	Ethnicity - Other	1 (5.0)
	Region - Europe	N/R
	Region - Middle East	N/R
	Region - North America	N/R
	Region - Other‡	N/R
	24-h urinary oxalate excretion (corrected for BSA), mean (SD), mmol/24 hours/1.73 m^2	2.242 (0.9956)
	24-h urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	0.2793 (0.12977)
	Spot urinary oxalate:creatinine ratio, mean (SD), mmol/mmol	N/R
	Plasma oxalate, mean (SD), µmol/l	N/R
	eGFR, mean (SD), ml/min/1.73 m^2	77.341 (22.1113)
	CKD stage by eGFR, n (%), ml/min/1.73 m^2 ≥90	N/R
	CKD stage by eGFR, n (%), ml/min/1.73 m^2 60 to <90	N/R
	CKD stage by eGFR, n (%), ml/min/1.73 m^2 30 to <60	N/R
	Renal stone events	N/R
	Lithotripsy/stone removal procedures in the 12 months prior to consent	N/R
	Pyridoxine use at baseline	13 (65.0)
	Pyelonephritis	N/R
	Urinary tract infections	N/R
	Nephrocalcinosis	N/R
	Symptomatic renal stone events in the 12 months prior to consent, n (%):1 to 5	N/R

	Symptomatic renal stone events in the 12 months prior to consent, n (%):6 to 10	N/R
	Symptomatic renal stone events in the 12 months prior to consent, n (%):>10	N/R
	Presenting symptoms - Asymptomatic (familial screening)	N/R
	Presenting symptoms – renal stone	14 (77.8)
	Presenting symptoms - ESKD	N/A
	Presenting symptoms - nephrocalcinosis	10 (55.6)
	Presenting symptoms - other	5 (27.8)
	Genotype – PR/any genotype of PR, M or N	N/R
	Genotype – M/M or M/N	N/R
	Genotype – N/N	N/R

Based on Table C6 of the CS[1]
† Minimum reflects one patient with a prebirth diagnosis (−0.4 years in phase 2 OLE).
AGT = alanine-glyoxylate aminotransferase; BSA = body surface area; CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; M = missense; N = nonsense; N/R = not reported; OLE = open-label extension; PH1 = primary hyperoxaluria type 1; PR = pyridoxine responsive; Q3M = every three months; QM = every month; SC = subcutaneous; SD = standard deviation; UK = United Kingdom; ULN = upper limit of normal

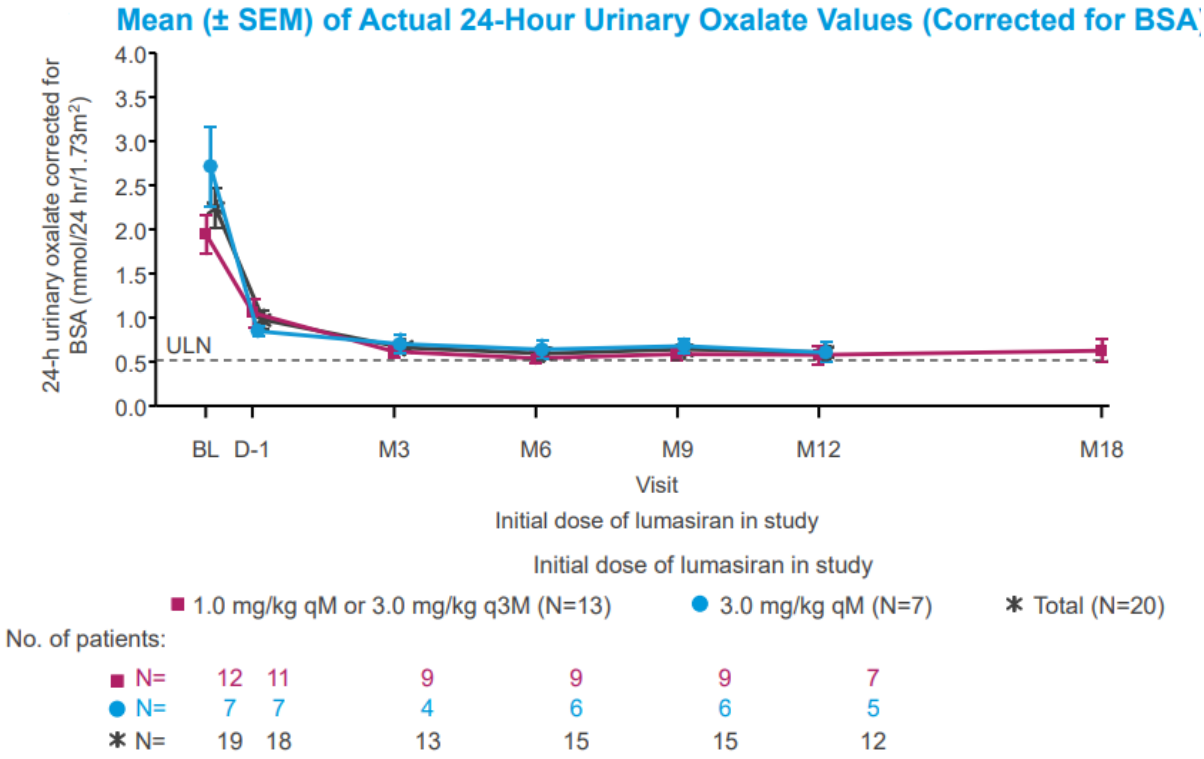
Patients with PH1 who completed the phase 1/2 lumasiran multi-dose study and met eligibility criteria were able to enrol in the phase 2 OLE and to continue receiving lumasiran 1.0 mg/kg SC monthly, 3.0 mg/kg SC monthly, or 3.0 mg/kg SC quarterly (depending on their original regimen in the parent phase 1/2 study) for up to 1,600 days.[77, 93, 95] Patients who received 1 mg/kg monthly were subsequently transitioned to 3 mg/kg every 3 months to align with the intended phase 3 maintenance dose.[94] All patients enrolled in ALN-GO1-001B (the parent phase 1/2 trial) completed this parent trial and subsequently enrolled in the phase 2 OLE (N=20).[93]

4.2.1.8.2 Efficacy

Urinary oxalate levels

Patients experienced sustained reductions in urinary oxalate excretion, with similar responses between dosage regimens. Mean maximal reduction in urinary oxalate of 74.5% (range 35.7 – 88.3%) relative to phase 1/2 baseline (N=17). 17/18 patients achieved normal or near normal (≤1.5 x ULN) levels of urinary oxalate, see Figure 4.17.[76]

Figure 4.17: Mean of actual 24-hour urinary oxalate values corrected for BSA



Taken from primary source: Frishberg 2020[76]

BSA = body surface area; M = month; Q3M = once every three months; QM = once monthly; SEM = standard error of the mean; ULN = upper limit of normal

Plasma oxalate level

Plasma oxalate levels decreased (mean maximal reduction of 55.2%, N=19).

Change in eGFR

Mean eGFR values were stable over time.

Need for liver transplant with or without a kidney transplant

No data presented.

Mortality

No deaths occurred.

Health related quality of life

No data presented.

Outcomes out of scope

The company also reported 24-hour urinary oxalate:creatinine ratio; however, this outcomes is outside the NICE final scope and has not been included in the ERG report.

4.2.1.8.3 Critical appraisal

A critical appraisal was not carried out in the CS.

ERG comment: A critical appraisal of Frishberg 2020, the main reference for this project, has been performed by the ERG and is reported in Table 4.22.[76]

Table 4.22: Critical appraisal of randomised control trials

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Not clear	Minimal details reported of eligibility to the study
Was the exposure accurately measured to minimise bias?	Yes	Adequate details of doses given
Was the outcome accurately measured to minimise bias?	Yes	Efficacy and safety outcomes addressed
Have the authors identified all important confounding factors?	No	No discussion of confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?	No	No discussion of confounding factors
Was the follow-up of patients complete?	No	Interim analysis only
How precise (for example, in terms of confidence interval and p values) are the results?	Precise for efficacy data	No precision estimates provided for safety data
Adapted from CASP: Making sense of evidence: 12 questions to help you make sense of a cohort study[74] CASP = Critical Appraisal Skills Programme; N/A = not applicable; CS = company submission		

4.2.2 Adverse effects related to Lumasiran

This Section summarises the outcome data on AEs for the ILLUMINATE-A RCT, the ILLUMINATE-B interventional phase 3 study and the long-term safety of lumasiran treatment from the phase 2 OLE.

4.2.2.1 Adverse events associated with Lumasiran reported in ILLUMINATE-A RCT

The company provided safety and tolerability results of the ILLUMINATE-A trial concerning two data cut-offs: a primary analysis of the 6-month double blind (DB) period extending from the start of the trial to May 2019 (safety analysis set),[15] and analyses from a second data cut-off of 26 April 2021 (extended safety analysis set),[85] during the 54-month extension period of the trial. The extension period of the trial composed of a 3-month blinded treatment extension period and an OLE period of up to 51 months.[96] The safety analysis set (n=39) comprised by patients that received any amount of study drug (lumasiran or placebo), while all patients received lumasiran in the extended safety analysis set. A summary of the key safety results for both data sets is reported in Table 4.23 and the full results regarding the primary analysis are reported in Table 4.24.

In the DB period, at least one AE was reported by 85% (n=22/26) of patients in the lumasiran group and 69% (n=9/13) of patients in the placebo group. At the second data cut-off an elevated rate of [redacted] of the patients reported AEs. No serious or severe AEs were reported during the DB period, while in the extended period [redacted] One patient discontinued treatment after 3 months due to AEs (fatigue and disturbance in attention) that were not considered to be related with lumasiran.[1]

In the safety analysis set, according to the CS, treatment-related effects were experienced by 42.3% of participants (n=11/26) in the lumasiran group and 7.7% (n=1/13) in the control group.[1] In the lumasiran group, AEs comprised of injection-site reaction experienced by 23.1% (n=6/26), injection-site erythema by 11.5% (n=3/26), and injection-site pain by 11.5% (n=3/26). In the placebo group, none of the AEs were reported by ≥10% of the patients.[46] In the extended safety analysis set, [redacted] but no further details were not provided.

Injection-site reactions frequency was evaluated through an AEs' mapping analysis to the Medical Dictionary for Regulatory Activities (MedDRA = high-level term of Injection Site Reactions).[46] Similarly, the frequency of hepatic AEs was assessed via an AEs mapping analysis to the standardised MedDRA query (SMQ) Drug Related Hepatic Disorders. According to the CS, a set of liver function test (LFT) parameters were examined to assess hepatic AEs: alanine transaminase (ALT), aspartate transaminase (AST) values and total bilirubin values. In the safety analysis set, all three parameters were found to be within normal ranges for the majority of the lumasiran group, 80.8% (n=21/26), 96.2% (n=25/26) and 88.5% (n=23/26), respectively.

Table 4.23: Summary of AEs for ILLUMINATE-A RCT

Adverse events, n (%)	Double-blinded, placebo-controlled 6-month period (May 2019 data cut-off)		Extended period (26 April 2021 data cut-off)
	Lumasiran (n=26)	Placebo (n=13)	Lumasiran (n=39)
Any AE[a]	**22 (85)**	**9 (69)**	[redacted]
AE occurring in ≥10% of patients in any group			
Injection-site reactions[b]	10 (38)	0	[redacted]
Headache	3 (12)	3 (23)	[redacted]

Adverse events, n (%)	Double-blinded, placebo-controlled 6-month period (May 2019 data cut-off)		Extended period (26 April 2021 data cut-off)
	Lumasiran (n=26)	Placebo (n=13)	Lumasiran (n=39)
Rhinitis	2 (8)	2 (15)	
Upper respiratory infection	2 (8)	2 (15)	[redacted]
Abdominal pain	-	-	[redacted]
Pyrexia	-	-	[redacted]
Vomiting	-	-	[redacted]
AE leading to discontinuation of lumasiran or placebo	**1 (4)**	**0**	[redacted]
AE leading to withdrawal from the trial	0	0	[redacted]
Any SAE	**0**	**0**	[redacted]
Abdominal pain	-	-	[redacted]
Urosepsis	-	-	[redacted]
Post-procedural complication	-	-	[redacted]
Any severe AE	**0**	**0**	[redacted]
Urosepsis	-	-	[redacted]
Post-procedural complication	-	-	[redacted]
Death	**0**	**0**	[redacted]

Based on Section 9.7.2 and Table C13 of the CS[1] which in turn is based on[15]
[a] All AEs were mild or moderate in severity, [b] Includes AEs of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort.
AE = adverse event; CS = company submission; RCT = randomised controlled trial; SAE = serious adverse event

Table 4.24: AEs by system organ class, preferred term for ILLUMINATE-A RCT (primary analysis)

Adverse events, n (%)	Placebo (n=13)			Lumasiran (n=26)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
At least one adverse event	**7 (53.8)**	**2 (15.4)**	**0**	**15 (57.7)**	**7 (26.9)**	**0**
Blood and lymphatic system disorders	**0**	**0**	**0**	**1 (3.8)**	**0**	**0**
Iron deficiency anaemia	0	0	0	1 (3.8)	0	0
Congenital, familial and genetic disorders	**0**	**0**	**0**	**1 (3.8)**	**0**	**0**
Thalassaemia beta	0	0	0	1 (3.8)	0	0
Ear and labyrinth disorders	**0**	**0**	**0**	**1 (3.8)**	**0**	**0**
Ear pain	0	0	0	1 (3.8)	0	0

Adverse events, n (%)	Placebo (n=13)			Lumasiran (n=26)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Eye disorders	**0**	**0**	**0**	**1 (3.8)**	**0**	**0**
Vision blurred	0	0	0	1 (3.8)	0	0
Gastrointestinal disorders	**1 (7.7)**	**0**	**0**	**3 (11.5)**	**1 (3.8)**	**0**
Abdominal discomfort	1 (7.7)	0	0	1 (3.8)	0	0
Abdominal pain	0	0	0	2 (7.7)	0	0
Abdominal pain lower	0	0	0	1 (3.8)	0	0
Abdominal pain upper	0	0	0	2 (7.7)	0	0
Constipation	0	0	0	1 (3.8)	0	0
Nausea	0	0	0	0	1 (3.8)	0
General disorders and administration site conditions	**0**	**0**	**0**	**10 (38.5)**	**1 (3.8)**	**0**
Chest pain	0	0	0	1 (3.8)	0	0
Fatigue	0	0	0	0	1 (3.8)	0
Injection site discomfort	0	0	0	1 (3.8)	0	0
Injection site erythema	0	0	0	3 (11.5)	0	0
Injection site pain	0	0	0	3 (11.5)	0	0
Injection site reaction	0	0	0	6 (23.1)	0	0
Immune system disorders	**0**	**0**	**0**	**1 (3.8)**	**0**	**0**
Hypersensitivity	0	0	0	1 (3.8)	0	0
Infections and infestations	**4 (30.8)**	**1 (7.7)**	**0**	**7 (26.9)**	**4 (15.4)**	**0**
Fungal skin infection	0	0	0	1 (3.8)	0	0
Infected bite	0	0	0	1 (3.8)	0	0
Kidney infection	0	0	0	0	1 (3.8)	0
Nasopharyngitis	0	0	0	1 (3.8)	0	0
Otitis media acute	1 (7.7)	0	0	0	0	0
Pharyngitis	0	0	0	1 (3.8)	0	0
Pneumonia	0	0	0	1 (3.8)	1 (3.8)	0
Rhinitis	2 (15.4)	0	0	2 (7.7)	0	0
Tonsillitis	0	0	0	0	1 (3.8)	0
Tooth infection	0	1 (7.7)	0	0	0	0
Upper respiratory tract infection	2 (15.4)	0	0	2 (7.7)	0	0
Urinary tract infection	0	0	0	0	2 (7.7)	0

Adverse events, n (%)	Placebo (n=13)			Lumasiran (n=26)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Injury, poisoning and procedural complications	**2 (15.4)**	**0**	**0**	**1 (3.8)**	**1 (3.8)**	**0**
Contusion	1 (7.7)	0	0	0	0	0
Foot fracture	0	0	0	1 (3.8)	0	0
Gastrostomy tube site complication	1 (7.7)	0	0	0	0	0
Tibia fracture	0	0	0	0	1 (3.8)	0
Metabolism and nutrition disorders	**1 (7.7)**	**0**	**0**	**1 (3.8)**	**0**	**0**
Iron deficiency	1 (7.7)	0	0	0	0	0
Vitamin D deficiency	0	0	0	1 (3.8)	0	0
Musculoskeletal and connective tissue disorders	**2 (15.4)**	**0**	**0**	**5 (19.2)**	**0**	**0**
Back pain	1 (7.7)	0	0	2 (7.7)	0	0
Flank pain	0	0	0	1 (3.8)	0	0
Groin pain	0	0	0	1 (3.8)	0	0
Musculoskeletal chest pain	0	0	0	1 (3.8)	0	0
Musculoskeletal pain	0	0	0	1 (3.8)	0	0
Pain in extremity	1 (7.7)	0	0	0	0	0
Nervous system disorders	**2 (15.4)**	**1 (7.7)**	**0**	**6 (23.1)**	**1 (3.8)**	**0**
Disturbance in attention	0	0	0	0	1 (3.8)	0
Dizziness	0	0	0	1 (3.8)	0	0
Headache	2 (15.4)	1 (7.7)	0	3 (11.5)	0	0
Hypoaesthesia	0	0	0	1 (3.8)	0	0
Restless legs syndrome	0	0	0	1 (3.8)	0	0
Psychiatric disorders	**0**	**0**	**0**	**1 (3.8)**	**2 (7.7)**	**0**
Anxiety	0	0	0	1 (3.8)	0	0
Fear of injection	0	0	0	0	1 (3.8)	0
Irritability	0	0	0	0	1 (3.8)	0
Renal and urinary disorders	**0**	**0**	**0**	**1 (3.8)**	**1 (3.8)**	**0**
Polyuria	0	0	0	1 (3.8)	0	0
Renal pain	0	0	0	0	1 (3.8)	0

Adverse events, n (%)	Placebo (n=13)			Lumasiran (n=26)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Respiratory, thoracic and mediastinal disorders	**2 (15.4)**	**0**	**0**	**2 (7.7)**	**0**	**0**
Cough	0	0	0	1 (3.8)	0	0
Nasal congestion	1 (7.7)	0	0	1 (3.8)	0	0
Oropharyngeal pain	1 (7.7)	0	0	1 (3.8)	0	0
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**2 (7.7)**	**1 (3.8)**	**0**
Alopecia	0	0	0	1 (3.8)	0	0
Eczema	0	0	0	1 (3.8)	0	0
Erythema	0	0	0	1 (3.8)	0	0
Pruritus	0	0	0	0	1 (3.8)	0
Rash erythematous	0	0	0	1 (3.8)	0	0
Vascular disorders	**0**	**0**	**0**	**1 (3.8)**	**0**	**0**
Hypertension	0	0	0	1 (3.8)	0	0
Based on Table 5 of the response to the request for clarification[52]						

ERG comments:

- The company did not provide details on which AEs were treatment-related in the extended safety set of the ILLUMINATE-A study. Furthermore, no details on hepatic AEs were reported regarding the extended safety set.
- According to the Integrated Safety Summary for the extended safety set of the ILLUMINATE-A study, there were three patients (7.7%) who experienced AEs leading to treatment interruption, but no details are provided in the CS around these events.[85]

This above lack of detailed evidence in the submission resulted the ERG not being able to make an in-depth appraisal regarding the extended safety set.

The AEs experienced by the patients in the lumasiran group are noticeably elevated compared to the placebo group, e.g. the injection-site reactions. This observation is more obvious when all AEs (mild, moderate and severe), reported by system organ class and preferred term (Table 4.24), are taken into consideration.

4.2.2.2 Adverse events associated with Lumasiran reported in ILLUMINATE-B

The safety and tolerability results of the ILLUMINATE-B trial during the double-blind period along with the 12-month interim data are reported in Table 4.25. Full results regarding the primary analysis are presented in Table 4.26. All patients (100%, n=18) reported at least one AE in both periods. Most of the experienced AEs were mild. There was one SAE (viral infection) in the DB period, which was considered unrelated to the treatment, and one during the extension period. The nature of the latter was not specified in the CS.[1] No AEs were mapped to the Drug Related Hepatic Disorders SMQ. The company stated that the LFT and AST values were both >3× ULN.

There were no AEs leading to treatment discontinuation and no deaths in both periods. Three patients (17%) experienced TRAEs (two injection-site reaction and one headache) in the primary analysis and four patients in the extended period.

Table 4.25: Summary of AEs for ILLUMINATE-B trial

Adverse events, n (%)	<10 kg (n=3)	10 to <20 kg (n=12)	≥20 kg (n=3)	All lumasiran-treated (N=18)	Extension period (12-month interim results)
AE	**3 (100)**	**12 (100)**	**3 (100)**	**18 (100)**	[redacted]
AEs occurring in ≥3 patients overall[a]					
Pyrexia	1 (33)	4 (33)	1 (33)	6 (33)	[redacted]
Rhinitis	1 (33)	3 (25)	0	4 (22)	
URTI	0	2 (17)	1 (33)	3 (17)	[redacted]
Vomiting	1 (33)	2 (17)	0	3 (17)	[redacted]
Injection-site reaction	-	-	-	-	[redacted]
Headache	-	-	-	-	[redacted]
AEs leading to discontinuation of study treatment	**0**	**0**	**0**	**0**	[redacted]
AEs leading to withdrawal from the trial	**0**	**0**	**0**	**0**	[redacted]
Death	**0**	**0**	**0**	**0**	[redacted]
Serious AE	**0**	**0**	**1 (33)[b]**	**1 (6)[b]**	[redacted]
Severe AE	**0**	**0**	**0**	**0**	[redacted]

Based on Section 9.7.2 and Table C14 of the CS[1] which in turn is based on Sas et al. 2021[97]

[a] AEs occurring in ≥10 patients for extension period, [b] Viral infection, considered unrelated to the study drug by the Investigator

AE = adverse event; CS = company submission; URTI = upper respiratory tract infection

Table 4.26: AEs by system organ class, preferred term for ILLUMINATE-B (primary analysis)

Adverse events, n (%)	<10 kg (n=3)			10 to <20 kg (n=12)			≥20 kg (n=3)			All lumasiran treated (N=18)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild ‘n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
At least 1 adverse event	**1 (33.3)**	**2 (66.7)**	**0**	**11 (91.7)**	**1 (8.3)**	**0**	**1 (33.3)**	**2 (66.7)**	**0**	**13 (72.2)**	**5 (27.8)**	**0**
Blood and lymphatic system disorders	**0**	**2 (66.7)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2 (11.1)**	**0**
Anaemia	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0
Iron deficiency anaemia	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0
Congenital, familial and genetic disorders	**1 (33.3)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (5.6)**	**0**	**0**
Factor XII deficiency	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Ear and labyrinth disorders	**1 (33.3)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (5.6)**	**0**	**0**
Ear pain	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Gastrointestinal disorders	**0**	**2 (66.7)**	**0**	**5 (41.7)**	**0**	**0**	**1 (33.3)**	**0**	**0**	**6 (33.3)**	**2 (11.1)**	**0**
Abdominal pain	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Anal pruritus	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Aphthous ulcer	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Diarrhoea	0	0	0	2 (16.7)	0	0	0	0	0	2 (11.1)	0	0
Mouth ulceration	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Nausea	0	0	0	1 (8.3)	0	0	1 (33.3)	0	0	2 (11.1)	0	0
Teething	0	2 (66.7)	0	0	0	0	0	0	0	0	2 (11.1)	0
Vomiting	0	1 (33.3)	0	2 (16.7)	0	0	1 (33.3)	0	0	3 (16.7)	1 (5.6)	0

Adverse events, n (%)	<10 kg (n=3)			10 to <20 kg (n=12)			≥20 kg (n=3)			All lumasiran treated (N=18)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild ‘n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
General disorders and administration site conditions	**1 (33.3)**	**2 (66.7)**	**0**	**5 (41.7)**	**0**	**0**	**1 (33.3)**	**1 (33.3)**	**0**	**7 (38.9)**	**3 (16.7)**	**0**
Influenza like illness	0	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0
Injection site reaction	0	0	0	2 (16.7)	0	0	1 (33.3)	0	0	3 (16.7)	0	0
Pyrexia	1 (33.3)	1 (33.3)	0	4 (33.3)	0	0	0	1 (33.3)	0	5 (27.8)	2 (11.1)	0
Infections and infestations	**1 (33.3)**	**1 (33.3)**	**0**	**10 (83.3)**	**1 (8.3)**	**0**	**1 (33.3)**	**1 (33.3)**	**0**	**12 (66.7)**	**3 (16.7)**	**0**
Asymptomatic bacteriuria	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Bronchitis	0	0	0	0	1 (8.3)	0	1 (33.3)	0	0	1 (5.6)	1 (5.6)	0
Conjunctivitis bacterial	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Croup infectious	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Ear infection	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Gastroenteritis	0	0	0	2 (16.7)	0	0	0	0	0	2 (11.1)	0	0
Influenza	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Nasopharyngitis	1 (33.3)	0	0	0	0	0	1 (33.3)	0	0	2 (11.1)	0	0
Oral herpes	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Pharyngitis	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Pneumonia	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Rhinitis	0	1 (33.3)	0	3 (25.0)	0	0	0	0	0	3 (16.7)	1 (5.6)	0
Tonsillitis	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Upper respiratory tract infection	1 (33.3)	0	0	2 (16.7)	0	0	0	1 (33.3)	0	3 (16.7)	1 (5.6)	0

Adverse events, n (%)	<10 kg (n=3)			10 to <20 kg (n=12)			≥20 kg (n=3)			All lumasiran treated (N=18)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild ‘n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Urinary tract infection	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Viral infection	0	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0
Viral pharyngitis	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Injury, poisoning and procedural complications	**2 (66.7)**	**0**	**0**	**0**	**0**	**0**	**1 (33.3)**	**0**	**0**	**3 (16.7)**	**0**	**0**
Arthropod bite	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Arthropod sting	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Fall	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Investigations	**0**	**0**	**0**	**1 (8.3)**	**0**	**0**	**0**	**1 (33.3)**	**0**	**1 (5.6)**	**1 (5.6)**	**0**
Blood creatinine increased	0	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0
Urine analysis abnormal	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Metabolism and nutrition disorders	**1 (33.3)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (5.6)**	**0**	**0**
Iron deficiency	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Nervous system disorders	**0**	**0**	**0**	**0**	**0**	**0**	**2 (66.7)**	**0**	**0**	**2 (11.1)**	**0**	**0**
Headache	0	0	0	0	0	0	2 (66.7)	0	0	2 (11.1)	0	0
Psychiatric disorders	**1 (33.3)**	**0**	**0**	**0**	**0**	**0**	**1 (33.3)**	**0**	**0**	**2 (11.1)**	**0**	**0**
Behaviour disorder	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Irritability	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0

Adverse events, n (%)	<10 kg (n=3)			10 to <20 kg (n=12)			≥20 kg (n=3)			All lumasiran treated (N=18)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild ‘n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Renal and urinary disorders	**0**	**0**	**0**	**1 (8.3)**	**0**	**0**	**0**	**0**	**0**	**1 (5.6)**	**0**	**0**
Haematuria	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Reproductive system and breast disorders	**0**	**0**	**0**	**1 (8.3)**	**0**	**0**	**0**	**0**	**0**	**1 (5.6)**	**0**	**0**
Gynaecomastia	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0
Respiratory, thoracic and mediastinal disorders	**1 (33.3)**	**1 (33.3)**	**0**	**3 (25.0)**	**0**	**0**	**1 (33.3)**	**0**	**0**	**5 (27.8)**	**1 (5.6)**	**0**
Cough	0	1 (33.3)	0	1 (8.3)	0	0	0	0	0	1 (5.6)	1 (5.6)	0
Nasal congestion	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Oropharyngeal pain	0	0	0	2 (16.7)	0	0	0	0	0	2 (11.1)	0	0
Rhinorrhoea	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Skin and subcutaneous tissue disorders	**1 (33.3)**	**0**	**0**	**1 (8.3)**	**0**	**0**	**1 (33.3)**	**0**	**0**	**3 (16.7)**	**0**	**0**
Eczema	1 (33.3)	0	0	0	0	0	0	0	0	1 (5.6)	0	0
Rash	0	0	0	0	0	0	1 (33.3)	0	0	1 (5.6)	0	0
Rash maculo-papular	0	0	0	1 (8.3)	0	0	0	0	0	1 (5.6)	0	0

Based on Table 6 of the response to the request for clarification[52]
AE = adverse event

ERG comments: There is a lack of detailed information regarding the hepatic-related AEs during the primary analysis period and the extended period where only a summary of the results is reported in text. For example, the results concerning the LFT, and AST values were not reported as was done for the ILLUMINATE-A study, thus hindering direct comparison of the results. While the data were provided (for the primary analysis alone) they were not referenced.[54].

This lack of data presentation and availability meant that the CS did not have optimal clarity in these Sections. In addition, details on the TRAEs experienced in the extended period were provided in the CS or in the Integrated Safety Summary.[85]

4.2.2.3 Adverse events associated with Lumasiran reported in ILLUMINATE-C

A summary of the AE analyses results for the two cohorts of the ILLUMINATE-C study are presented in Table 4.27. Patients in Cohort A did not yet require dialysis while patients in Cohort B were on dialysis. Full results of the AE analysis are presented in Table 4.28 by preferred term. TRAEs were experienced by 28.6% (n=6) of the patients and were all mild to moderate in severity, while [redacted] No post-baseline deaths were reported in the study. According to the company the AE profile in the study was consistent with PH1 and advanced renal disease.[55]

Table 4.27: Summary of AEs for ILLUMINATE-C trial

Adverse events, n (%)	Lumasiran Cohort A (n=6)	Lumasiran Cohort B (n=15)	Overall (N=21)
Any AE[a]	**5 (83.3)**	**12 (80.0)**	**17 (81.0)**
Any AE occurring in ≥10% of either cohort			
Pyrexia	1 (16.7)	5 (33.3)	6 (28.6)
Injection-site reactions*	1 (16.7)	4 (26.7)	5 (23.8)
Device-related infection	0	2 (13.3)	2 (9.5)
Diarrhoea	0	2 (13.3)	2 (9.5)
Lumasiran-related AEs leading to lumasiran discontinuation	**0**	**0**	**0**
Lumasiran-related AEs leading to study withdrawal	**0**	**0**	**0**
Death	**0**	**0**	**0**
Any serious AE	**1 (16.7)**	**5 (33.3)**	**6 (28.6)**
Any severe AE	**0**	**3 (20.0)**	**3 (14.3)**

Based on Section 9.7.2 and Table C15 of the CS[1] which in turn is based on Michael et al. 2021[90]
[a] Includes AEs of injection-site discoloration, erythema, and haematoma
AE = adverse event; CS = company submission

Table 4.28: AEs by system organ class, preferred term for ILLUMINATE-C (primary analysis)

Adverse events, n (%)	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
At least one adverse event	**4 (66.7)**	**1 (16.7)**	**0**	**4 (26.7)**	**3 (20.0)**	**6 (40.0)**	**8 (38.1)**	**4 (19.0)**	**6 (28.6)**
Blood and lymphatic system disorders	**0**	**0**	**0**	**0**	**1 (6.7)**	**1 (6.7)**	**0**	**1 (4.8)**	**1 (4.8)**
Anaemia	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Blood loss anaemia	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Spontaneous haematoma	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Endocrine disorders	**0**	**0**	**0**	**1 (6.7)**	**0**	**0**	**1 (4.8)**	**0**	**0**
Hyperparathyroidism tertiary	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Gastrointestinal disorders	**1 (16.7)**	**1 (16.7)**	**0**	**5 (33.3)**	**2 (13.3)**	**0**	**6 (28.6)**	**3 (14.3)**	**0**
Abdominal pain	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Abdominal pain upper	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Constipation	1 (16.7)	0	0	1 (6.7)	0	0	2 (9.5)	0	0
Diarrhoea	1 (16.7)	0	0	3 (20.0)	0	0	4 (19.0)	0	0
Gastritis	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Pancreatitis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Peptic ulcer	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Vomiting	0	1 (16.7)	0	1 (6.7)	0	0	1 (4.8)	1 (4.8)	0
General disorders and administration site conditions	**2 (33.3)**	**0**	**0**	**8 (53.3)**	**1 (6.7)**	**1 (6.7)**	**10 (47.6)**	**1 (4.8)**	**1 (4.8)**
Catheter site swelling	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0

Adverse events, n (%)	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Device related thrombosis	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Injection site reaction	1 (16.7)	0	0	4 (26.7)	0	0	5 (23.8)	0	0
Pyrexia	1 (16.7)	0	0	6 (40.0)	1 (6.7)	0	7 (33.3)	1 (4.8)	0
Swelling	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Hepatobiliary disorders	**0**	**0**	**0**	**1 (6.7)**	**1 (6.7)**	**0**	**1 (4.8)**	**1 (4.8)**	**0**
Cholecystitis acute	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Cholelithiasis	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Infections and infestations	**2 (33.3)**	**0**	**0**	**2 (13.3)**	**4 (26.7)**	**0**	**4 (19.0)**	**4 (19.0)**	**0**
Candida nappy rash	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Catheter site infection	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Clostridium difficile colitis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Conjunctivitis	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Device related infection	0	0	0	0	2 (13.3)	0	0	2 (9.5)	0
Ear infection	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Paronychia	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Roseola	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Sepsis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0

Adverse events, n (%)	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Upper respiratory tract infection	**1 (16.7)**	**0**	**0**	**1 (6.7)**	**0**	**0**	**2 (9.5)**	**0**	**0**
Urinary tract infection	**1 (16.7)**	**0**	**0**	**0**	**0**	**0**	**1 (4.8)**	**0**	**0**
Injury, poisoning and procedural complications	**2 (33.3)**	**0**	**0**	**1 (6.7)**	**2 (13.3)**	**1 (6.7)**	**3 (14.3)**	**2 (9.5)**	**1 (4.8)**
Arteriovenous fistula thrombosis	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Burns second degree	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Clavicle fracture	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Fibula fracture	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Head injury	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Humerus fracture	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Limb injury	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Radius fracture	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Skin scar contracture	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Upper limb fracture	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Investigations	**1 (16.7)**	**0**	**0**	**3 (20.0)**	**2 (13.3)**	**0**	**4 (19.0)**	**2 (9.5)**	**0**
Alanine aminotransferase increased	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Aspartate aminotransferase increased	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
Blood phosphorus increased	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Blood potassium increased	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Blood uric acid increased	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0

Adverse events, n (%)	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
General physical condition abnormal	0	0	0	0	1 (16.7)	0	0	1 (4.8)	0
International normalised ratio increased	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Liver function test increased	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
SARS-CoV-2 test positive	0	0	0	2 (13.3)	0	0	2 (9.5)	0	0
Staphylococcus test positive	0	0	0	1 (16.7)	0	0	1 (4.8)	0	0
Metabolism and nutrition disorders	**3 (50.0)**	**0**	**0**	**1 (6.7)**	**0**	**0**	**4 (19.0)**	**0**	**0**
Carnitine deficiency	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Hyperkalaemia	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Hypokalaemia	1 (16.7)	0	0	1 (6.7)	0	0	2 (9.5)	0	0
Iron deficiency	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Metabolic acidosis	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Vitamin D deficiency	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Nervous system disorders	**0**	**0**	**0**	**1 (6.7)**	**0**	**1 (6.7)**	**1 (4.8)**	**0**	**1 (4.8)**
Paraesthesia	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Seizure	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Product issues	**0**	**0**	**0**	**0**	**1 (6.7)**	**0**	**0**	**1 (4.8)**	**0**
Thrombosis in device	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Psychiatric disorders	**0**	**0**	**0**	**1 (6.7)**	**0**	**0**	**1 (4.8)**	**0**	**0**
Insomnia	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0

Adverse events, n (%)	Cohort A (n=6)			Cohort B (n=15)			Overall (N=21)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Renal and urinary disorders	**2 (33.3)**	**0**	**0**	**0**	**0**	**0**	**2 (9.5)**	**0**	**0**
Proteinuria	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Renal impairment	1 (16.7)	0	0	0	0	0	1 (4.8)	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**1 (6.7)**	**0**	**0**	**1 (4.8)**	**0**	**0**
Cough	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Surgical and medical procedures	**0**	**0**	**0**	**0**	**0**	**5 (33.3)**	**0**	**0**	**5 (23.8)**
Arteriovenous fistula operation	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Dialysis device insertion	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Renal and liver transplant	0	0	0	0	0	2 (13.3)	0	0	2 (9.5)
Renal transplant	0	0	0	0	0	1 (6.7)	0	0	1 (4.8)
Vascular disorders	**0**	**0**	**0**	**2 (13.3)**	**1 (6.7)**	**0**	**2 (9.5)**	**1 (4.8)**	**0**
Dialysis hypotension	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Haemorrhage	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0
Hypotension	0	0	0	1 (6.7)	0	0	1 (4.8)	0	0
Jugular vein thrombosis	0	0	0	0	1 (6.7)	0	0	1 (4.8)	0

Based on Table 7 of the response to the request for clarification[52]
AE = adverse event; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

ERG comment: No results were provided for the ILLUMINATE-C study beyond the 6-month primary analysis period although there the study also has a 54-month long-term extension period which started in June 2020.

While in ILLUMINATE-A and B the company only reported TRAEs in ILLUMINATEC they reported on TEAEs, it is not clear in the CS if the two terms are indistinguishable as described in ILLUMINATE-A CSR and in the statistical analysis plan.[46] The distinction between the two categories is not clearly reported in Table C15 which presents the results of the ILLUMINATE-C safety analyses.

Little detail is reported regarding the hepatic related AEs both in the parametrical tests used and in their results across both cohorts.

4.2.2.4 Adverse events associated with Lumasiran reported in the phase 2 OLE study

All patients (n=20) enrolled in the phase 1/2 ALN-GO1-001B trial completed it and subsequently enrolled in the phase 2 OLE (ALN-GO1-002).[93]

[redacted][85]

According to the CS and the response to the request for clarification, no severe TEAEs were experienced in any of the studies.[1, 52]

ERG comment: The ERG asked the company to provide further data on experienced AEs across all studies and specifically to provide tables of mild and moderate adverse events by preferred terms.[50] The company provided these tables of AEs, reproduced in Tables 4.24, 4.26, and 4.28.[51, 52]

There is no mention in the CS on how the severity of AEs was evaluated.[1] According to the ILLUMINATE-A and B CSRs *"adverse events that occurred during the study were assessed by the Investigator for severity (ie, mild, moderate, or severe)"* but no further details were provided.[46, 54] According to the ILLUMINATE-C study protocol, the only protocol provided by the company, severity of AEs is graded according to the three following categories:[88]

- Mild: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Severe: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an AE.

In addition, SAE have a separate regulatory definition[88] as defined in guidelines by the EMA[98] and the US Department of Health and Human Services[99]. The ERG assumes that the same definitions have been used in the rest of the studies as well.

According to the CSR of ILLUMINATE-A, renal stone events were not evaluated as AEs in the safety profile but included in the efficacy assessment.[46] Renal events are important since PH1 patients are considered to be at risk for recurrent kidney and bladder stones. Therefore, the safety profile of lumasiran should be looked at in combination to the renal stone events results as reported in the efficacy assessment.

The ERG asked that the company to further discuss hepatic AEs associated with lumasiran in patients with PH1.[50]. As highlighted in the ILLUMINATE-A CSR[46] hepatic events are crucial because lumasiran is directed to the liver. The company responded that *"hepatic events were infrequent during the lumasiran clinical development programme (Alnylam, data on file). On laboratory analysis, there have been no notable changes in liver function test (LFT) parameters related to lumasiran treatment. No elevations in LFT values had led to treatment interruption or discontinuation. Based on these results, there have been no hepatic safety concerns in clinical studies of lumasiran"*.[51, 52] The company has also provided some additional related data presented in Table 4.28.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparisons or multiple treatment comparisons were carried out.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As highlighted in Section 4.2, the ERG performed some critical appraisals.

4.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify studies on lumasiran for primary hyperoxaluria. Searches were conducted in June 2020 and updated in April 2021 and August 2021. Searches were transparent and reproducible, and comprehensive strategies were used. An extensive range of databases and grey literature resources were searched, and no date or language limits were applied.

The CS provided comprehensive data concerning several of the outcomes that were in the agreed scope.[1] The outcomes receiving most attention in the CS report were the surrogate outcomes of urinary oxalate levels, plasma oxalate levels and change in eGFR, which demonstrated that lumasiran may have benefits for patients with PH1 but are linked to uncertainty, see Section 4.1.2.[1] It should be noted that full CSRs were not available to the ERG, see Section 4.2.

In patients over the age of six years, this was based on randomised trial evidence that was relatively free from risk of bias. Most of the other evidence, however, was uncontrolled, and was subject to the influence of extraneous factors. Therefore, the ERG has limited confidence that some of the observed effects in the non-randomised evidence truly reflect the treatment effects of lumasiran.

Very importantly, there was a lack of any evidence that lumasiran improves quality of life to an extent that would make a difference to a patient. Quality of life data were referred to briefly in the CS in relation to the ILLUMINATE-A RCT, but this demonstrated differences that would probably not be

regarded as clinically meaningful.[1] This is a major drawback in the CS because if the treatment cannot be shown to affect quality of life it could be argued to have little clinical benefit. Furthermore, the agreed scope outcome of need for liver transplant with or without a kidney transplant was not covered by the CS at all, and no reasons were given for this.[1]

Several out-of-scope outcomes were presented by the CS, and most have not been considered by the ERG.[1] However, the outcome of renal stone events has been included in our report because, unlike most of the outcomes surveyed by the CS, it is not a surrogate outcome. This outcome suggested some improvement in renal stone events, although the effects were smaller in magnitude than those seen for the surrogate outcomes.

Overall, the CS provides some evidence that lumasiran is a potentially useful therapy for PH1, but it should be noted that the CS has considerably over-emphasised the methodological advantages the taken approach and has not demonstrated much appreciation of the possible effect of bias on observed effect sizes.

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

This Section provides an assessment of whether lumasiran for treating PH1 represents value for money for the National Health Service (NHS) in England. The main source of evidence used to inform this assessment is the CS and the electronic cost effectiveness model. This chapter provides a summary of the literature review performed by the company to search for economic evidence, the structure of the economic model, the evidence used to inform the input parameters of the economic analyses, the results of the company cost effectiveness analyses (CEAs) and a critique of all these aspects conducted by the ERG.

5.2 Review of existing economic analyses

5.2.1 Searches

The CS included a combined search for clinical as well as cost effectiveness evidence, please see Section 4.1.1.

5.2.2 Review process and results

The eligibility criteria for the economic SLR are shown in Section 4.1.2.

The SLR identified no UK-specific pharmacoeconomic models or CEAs.

Two studies (Perera 2011 and Perera 2009), both evaluating transplantation to treat PH1, reported HCRU data relevant to the UK.[100, 101] No cost data were identified in either of these publications.

Additionally, the SLR identified one study describing HRQoL evidence for PH1. Modersitzki 2019 published a conference abstract of their non-interventional study comparing HRQoL by time since last stone event at multiple timepoints in 56 pre-transplantation adults with PH enrolled in the Rare Kidney Stone Consortium (RKSC) registry.[102] This study was used in the CEA to model the utility decrement due to renal stone events.

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

Table 5.1 provides an assessment of the adherence of the company model to the NICE reference case.

Table 5.1: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE.	As per reference case.
Comparator	Therapies routinely used in the NHS, including technologies regarded as the current best practice.	The comparator is ECM, which may include an oxalate-controlled diet, hyperhydration, pyridoxine, and oral citrate supplements to inhibit calcium oxalate crystallisation. Furthermore, it may encompass haemodialysis and peritoneal dialysis and ultimately also combined or sequential liver–kidney transplantation may be warranted.

Element of economic analysis	Reference case	ERG comment
Perspective on costs	NHS and PSS.	As per reference case.
Perspective on outcomes	All health effects on individuals.	As per reference case
Type of economic evaluation	Cost effectiveness analysis.	As per reference case.
Time horizon	Sufficient to capture differences in costs and outcomes.	Lifetime perspective adopted.
Synthesis of evidence on outcomes	Based on a systematic review.	An SLR was conducted as per the reference case.
Measure of health effects	QALYs and life years.	Health outcomes are valued in terms of life years and QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers.	The health state utility values used in the model came from various sources. For CKD 1-3b, observed EQ-5D utilities from the ILLUMINATE-A study were used. Various disutilities were taken from literature. For uncontrolled CKD 4 and ESKD, vignettes describing health states were valued directly by members of the UK general population without patient measurement. Therefore, while the valuation aspect of the reference case was met, the measurement element was not always.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public.	
Discount rate	An annual rate of 3.5% on both costs and health effects.	As per the reference case.
Equity weighting	An additional weighting can be applied for incremental QALYs above 10 years.	The QALYs accumulated were [redacted]

BSC = best supportive care; CKD = chronic kidney disease; ERG = Evidence Review Group; ESKD = end-stage kidney disease; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

5.3.2 Model structure

As the literature search of the company did not reveal economic models for lumasiran or for other technologies used in UK clinical practice in the indicated population, a de novo cost effectiveness model was developed.

A Markov model was developed to assess costs and effects, life-years (LYs) and QALYs of lumasiran and ECM in a simulated cohort of patients with PH1. No disease-specific classification system exists for categorising disease severity in PH1.[20, 21] Since one of the main features of PH1 is the deterioration

of kidney function, and loss of kidney function is one of the most important endpoints to patients, the company choose to use CKD classes as health states. The CKD classes are defined by the eGFR (see Table 5.2), a lower eGFR indicates a worse kidney function and hence a higher CKD class.

Table 5.2: KDIGO Clinical Practice Guideline definitions of CKD stages

CKD stage	eGFR (ml/min/1.73m^2)	Description of eGFR category
1	≥90	Normal or high
2	60–89	Mildly decreased
3a	45–59	Mildly to moderately decreased
3b	30–44	Moderately to severely decreased
4	15–29	Severely decreased
5 (ESKD)	<15	Kidney failure

Based on KDIGO 2013[103]
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; KDIGO = Kidney Disease: Improving Global Outcomes

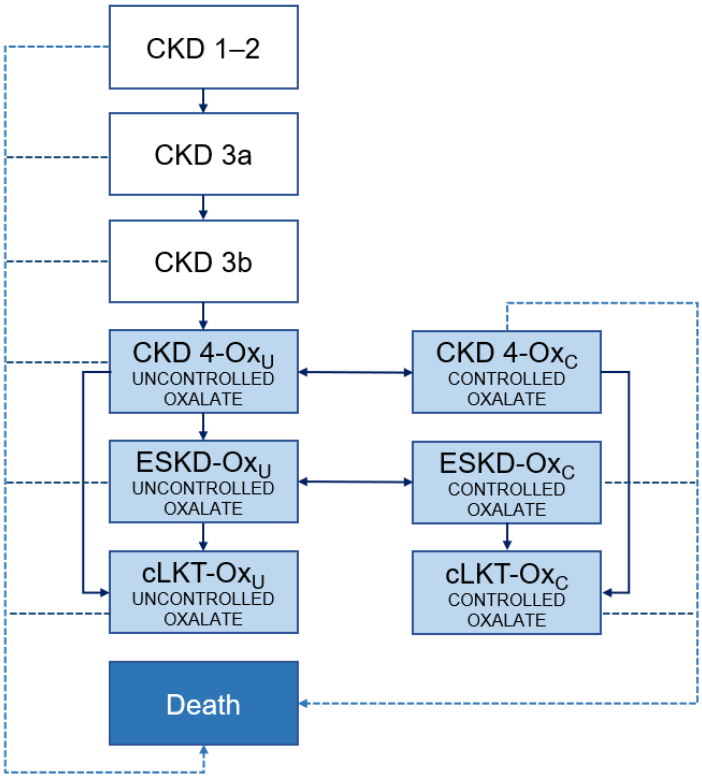
The model consists in total of nine health states defined by CKD stage, plasma oxalate levels, and/or transplant status, plus death. Figure 5.1 shows the design of this de novo Markov model.

CKD stage 4 and ESKD were each split in two, based on the plasma oxalate level, a threshold of 50 μmol/l plasma oxalate was used to distinguish between uncontrolled versus controlled oxalate levels, based on the use of this threshold in the literature to define a treatment target in PH1 and determine potential candidates for transplantation. An extra health state was added to reflect the state post-transplantation, again split into two to allow for either controlled or uncontrolled oxalate levels. Finally, the state 'Death' was added.

The model structure was used both for paediatric patients and adult patients, each population having their own set of model inputs. The company reports the results of this economic analysis as the weighted average of these two populations.

The model has a lifetime time horizon, and a cycle length of 6 months.

Figure 5.1: Model structure



Based on Figure D1 of the CS[1]
A threshold of 50 µmol/l was used to distinguish controlled versus uncontrolled oxalate based on the treatment target in PH1 identified from the literature.
CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS =company submission; ESKD = end-stage kidney disease; Ox_C = controlled oxalate levels; Ox_U = uncontrolled oxalate levels; PH1 = primary hyperoxaluria type 1

In each Markov cycle, a patient who had not yet undergone transplantation can progress to the next CKD stage or remain in the same CKD stage. For the late-stage health states (CKD 4 and ESKD), transition between the uncontrolled oxalate (Ox_U) and controlled oxalate (Ox_C) states is also permitted. In the cost effectiveness model, treatment with lumasiran is continued across all CKD stages. The company indicted though that it is currently unknown whether clinicians in real-world practice will initiate lumasiran in patients with early-stage disease without rapid signs of progression; furthermore, it is unknown how clinical practice will vary by patient characteristics, e.g. age, age at disease onset.[1]

Patients in the ECM cohort progressing beyond CKD 3b or entering the model with late-stage disease are assumed to have uncontrolled oxalate levels, only patients in the lumasiran cohort can move to the states with controlled oxalate levels.

Transition to a less severe CKD stage is not permitted in either cohort, based on evidence from other renal conditions that suggests that once renal function is lost, it cannot be recovered.

Patients in the CKD 4- Ox_C health state are assumed to be stable and not experience disease progression, i.e. these patients cannot transition to ESKD-Ox_C.

The model allows patients reaching CKD 4-Ox_U, CKD 4-Ox_C, ESKD-Ox_U, or ESKD-Ox_C to undergo combined/sequential liver–kidney transplantation (cLKT), in line with European clinical practice

guidelines for PH1.[3] Upon transplantation, these patients remain in the post-transplantation health state (cLKT) or move to the absorbing health state (i.e. death).

The cohort receiving transplant from CKD 4-Ox_U or ESKD- Ox_U transitions to cLKT-Ox_U and has worse post-transplant prognosis than the cohort receiving transplant from CKD 4-Ox_C or ESKD-Ox_C and transitioning to cLKT-Ox_C. This assumption is based on the effect of clinical status on post-transplant mortality from graft failure and other causes as observed over long-term follow-up in the study by Jamieson et al. 2005 study of PH1 patients.[104]

Besides the health states, the model also takes two other specific characteristics of PH1 into account, i.e., renal stone events and systemic oxalosis complications. Renal stone events are more likely to occur in the CKD 1-3b health states, and their event rates are treatment-specific. Systemic oxalosis complications are modelled only in CKD4 and ESKD, and their prevalence rates are again assumed to be treatment specific.

ERG comment: The ERG considers the model structure as fitting the disease and the potential impact lumasiran may have.

5.3.3 Evidence used to inform the company's model parameters

This Section presents a summary of the evidence sources used to inform the company's model parameters. The main sources used in the CS are the ILLUMINATE-A, -B and -C studies.[78, 80, 90, 105] A detailed description of model parameter values and sources is presented below.

5.3.3.1 Population

The patient population considered in the cost effectiveness model is defined as people with PH1. This is consistent with the final NICE scope and the decision problem.

Demographic data inputs to the CEA were obtained from the baseline characteristics of participants in these trials, see Table 5.3.[46, 54, 55]

Table 5.3: Baseline model cohort characteristics

Characteristic	Model input	Source
Initial age (years)		
Paediatric population	[redacted]	ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C at baseline,[46, 54, 55] children <18 years
Adult population	[redacted]	ILLUMINATE-A and ILLUMINATE-C at baseline,[46, 55] adults ≥18 years
Mean weight (kg)		
Paediatric population	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline,[46, 54, 55] children <18 years
Adult population	[redacted]	ILLUMINATE-A and ILLUMINATE-C at baseline,[46, 55] adults ≥18 years
Percentage of males	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline[46, 54, 55]
Percentage of paediatric patients	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline[46, 54, 55]

Based on Table D5 of the CS[1]
CKD =chronic kidney disease; CS = company submission; ESKD =end-stage kidney disease

5.3.3.2 Intervention and comparators

The cost effectiveness of the intervention, lumasiran plus ECM (referred to below as lumasiran), is compared against ECM alone, which, which may include an oxalate-controlled diet, hyperhydration, pyridoxine, and oral citrate supplements to inhibit calcium oxalate crystallisation.[3, 15, 21] Furthermore, it may encompass haemodialysis and peritoneal dialysis and ultimately also combined or sequential liver–kidney transplantation may be warranted.[3, 21, 22]

5.3.3.3 Initial patient distribution

The company used data from a study by Singh 2021 as estimates of the initial distribution of PH1 patients over the model health states.[106] That study is based on a retrospective review of all PH patients who were enrolled in the RKSC PH registry through February 2019. The RKSC PH registry is a voluntary registry where patients from >40 nationalities are represented. The USA was the country of birth for 62% of participants in the cohort, followed by 16% of patients from South Asia (India and Pakistan).

Patients reported by Singh 2021 to be in CKD 3 were assumed to be equally distributed between stages 3a and 3b.[106] Patients entering the model in the late-stage health states are assumed to have uncontrolled oxalate levels, i.e. higher than the threshold of 50 µmol/l. In response to the request for clarification, the company explained that clinical experts had been asked if the distribution as observed in Singh 2021. was representative of the distribution in the UK.[51, 52] The clinical experts confirmed that at the level of the overall population, the distribution of CKD stages reported by Singh 2021. for patients with PH1 in the RKSC PH registry is consistent with the distribution observed in the prevalent PH1 population in the UK. Nonetheless, the consultant paediatric nephrologist clarified that in the specific subpopulation of patients with infantile onset of PH1 in the UK, this distribution is skewed more heavily toward later CKD stages (0% in CKD 1 to 3b, 10% in CKD 4, and 90% in ESKD).

Table 5.4: Initial patient distribution model

Health state	Proportion
CKD 1–2	38.2%
CKD 3a	12.1%
CKD 3b	12.1%
CKD 4-Ox_U	9.7%
ESKD-Ox_U	27.9%
Total	**100%**

Based on Table D6 of the CS[1]
CKD = chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease; Ox_U = uncontrolled oxalate

5.3.3.4 Association between oxalate and kidney function in PH1

As the ILLUMINATE-A studies were designed to show a treatment effect with regards to plasma oxalate levels, the results could not be used directly to estimate the transition probabilities between CKD classes, which are defined by eGFR (a measure of filtration performance of kidney). Though the ILLUMINATE trials measured eGFR, the company considered this data unlikely to be representative of a true clinical effect. This is evident from the noisy eGFR data (i.e. wide CIs around point estimates; Section 9.6 of the CS), the small sample sizes, and the [redacted] (Section 9.9.2 of the CS).[1]

In Section 12.1.6 of the CS, the company sets out their argumentation why plasma oxalate can be regarded as a valid surrogate for kidney function.[1] An important problem in requiring for example change in eGFR or reaching ESKD as an RCT endpoint is that this would require larger and longer RCTs. Especially larger RCTs may not be feasible in an orphan disease.

Thus, the company set out to identify publications reporting on associations between oxalate and eGFR in PH1 through an SLR (Section 9.1 of the CS) and two targeted literature reviews. This yielded 11 studies in total, which were subsequently assessed for population, study design, study sample size, availability and robustness of reported eGFR and oxalate measurements, and the type of association between oxalate and eGFR reported (e.g. linear versus nonlinear; cross-sectional versus longitudinal). Longitudinal studies reporting regression equations and association figures were prioritised as they better reflect the complex association between oxalate and eGFR.[107]

Most studies did not report on urinary oxalate, thus the company focused on the association between plasma oxalate and eGFR. Based on the criteria above, four studies were considered for further analysis, i.e. Shah 2020,[34] Milliner 2020,[26] Milliner 2021,[108] and Perinpam 2017[109] were considered relatively high-quality studies, based on the evaluation criteria listed above. These studies were further analysed to characterise the association between plasma oxalate and eGFR.

Of these four studies, Shah 2020 was the only longitudinal follow-up of individual patients that established a temporal link between eGFR and plasma oxalate.[34] The company considered that the longitudinal design and availability of patient-level data makes Shah 2020 the preferred choice to model the relationship between eGFR and plasma oxalate.

Shah 2020 used generalised estimating equations (GEE) adjusting for time to evaluate the association between POx and eGFR throughout follow-up. There were 59 patients with a total of 369 plasma oxalate measurements and eGFR laboratory measures obtained within 3 months of each other throughout follow-up. The number of lab values per patient ranged from one to 20. After adjusting for follow-up time, eGFR was significantly lower among those with higher plasma oxalate level: eGFR reduced by 1.27 ml/min/1.73 m^2 for every 1 μmol increase in plasma oxalate ($P < 0.001$).

ERG comment: The ERG concurs with the company that of the papers found that try to quantify the relation between plasma oxalate and eGFR, the study by Shah 2020 is the preferred choice, as it has a longitudinal design and many measurements per patient.[34] However, it is surprising that in that paper, only the value of the slope is presented, without describing the whole model, e.g. it is unclear what other parameters were part of the GEE model. It is furthermore remarkable that no standard error or CI for the estimated slope was presented.

More importantly, the ERG considers it is possible that the one slope that indicates how much the eGFR decrease with each unit plasma oxalate increase is insufficient to describe the relation between plasma oxalate and kidney function. It seems plausible that having a constant high plasma oxalate level, so without any change, will also lead to a decrease in eGFR, depending on how long the plasma oxalate level is too high and how high it is.

The ERG mentioned this influence of time on the kidney function in their clarification letter and asked the company to justify the current approach of modelling transitions between CKD 1-2, CKD 3a, CKD 3b, i.e. based only on change in oxalate level, rather than also including exposure to above-normal levels of oxalate.

In response to the request for clarification, the company indicated that their modelling approach in the CS was the best possible solution given the available evidence from the literature, whilst acknowledging

its limitations.[51, 52] They did, however, undertake exploratory analyses to stratify the risk of progression through CKD stages in the model based on data from the ILLUMINATE studies. This revised exploratory approach partitions the CKD 1–3b cohort into two separate strata: (1) one corresponding to patients with normal or near-normal oxalate levels and (2) the other corresponding to patients with "above-normal" oxalate levels; the transition probabilities between CKD stages are differentiated for each stratum. The results with this version of the model were quite similar to the company's base case (see Section 6.1.2).

5.3.3.5 Transition and event probabilities

5.3.3.5.1 Transition probabilities in pre-ESKD health states - ECM arm

To estimate transition probabilities for the model, the company made use of changes in plasma oxalate as observed in the ILLUMINATE studies. In the ECM cohort, this was based on the available 6-month data from the placebo-arm of the ILLUMINATE-A trial. In this cohort, the absolute change in plasma oxalate over 6 months was 2.23 µmol/l increase. Using the link between eGFR and plasma oxalate determined by Shah et al. 2020 of a mean absolute eGFR decrease of 1.27 ml/min/1.73 m^2 per 1 µmol/l increase in plasma oxalate, it can be estimated that the eGFR would decrease by 2.83 ml/min/1.73 m^2 over 6 months (=1 model cycle). Based on this the transition rate per cycle across pre-ESKD health states (from CKD 1–2 to CKD 3a, from CKD 3a to CKD 3b, and from CKD 3b to CKD 4) in the ECM cohort could be derived.

To this end, the company assumed that each health state was to start at the mean eGFR observed among patients included in ILLUMINATE-A (placebo and lumasiran arms pooled) who were in that health state at baseline and progress to later states via modelled eGFR decline (Table 5.5). Table 5.5 also shows how much the eGFR needs to decrease from the observed mean eGFR before the next CKD class would be reached. By dividing this by 2.83, the decrease in eGFR per cycle, the number of cycles until reaching the next CKD class is found. Then finally, the probability of transitioning to the next more severe health state was estimated as the inverse of the mean number of cycles required to transition.

Table 5.5: eGFR by pre-ESKD CKD health states and eGFR distance to next CKD stage, transition probabilities for ECM

Pre-CKD health state	eGFR (ml/min/1.73 m^2)			Decrement to next health state	Cycles needed with eGFR increase (return period)	Probability per cycle
	Lower bound	Upper bound	Mean			
CKD 1–2	60.0	120.0	89.95*	37.68	13.30	0.075
CKD 3a	45.0	59.0	52.27*	15.25	5.38	0.186
CKD 3b	30.0	44.0	37.02*	15.02	5.30	0.189
CKD 4	15.0	29.0	22.00†	—		

Based on Table D7 of the CS[1] and electronic model v11.0[110]
* Mean eGFR was obtained from pooled lumasiran and placebo data from the ILLUMINATE-A trial; † Arithmetic mean of the lower and upper bound
CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease

Table 5.6: Transition matrix within the pre-ESKD health states, ECM arm

From↓ \ To→	CKD 1–2	CKD 3a	CKD 3b	CKD 4-OxC
CKD 1–2	0.925	0.075	0.000	0.000
CKD 3a	0.000	0.814	0.186	0.000

From↓ \ To→	CKD 1–2	CKD 3a	CKD 3b	CKD 4-OxC
CKD 3b	0.000	0.000	0.811	0.189

Based on Table D9 of the CS[1]
CKD = chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease; Ox_C = controlled oxalate

5.3.3.5.2 Transition probabilities in pre-ESKD health states—lumasiran arm

Modelling progression across pre-ESKD health states in the lumasiran arm was again based on the observed change in plasma oxalate, from the [redacted]. The company stated that they expect that the trend observed over 12 months would be maintained over time, based on:

1. Data from extension studies showing no loss of therapeutic effect over the duration of follow-up in patients treated with lumasiran;[76, 80, 81]
2. The mechanism of action of lumasiran, which selectively and durably silences the mRNA for the enzyme glycolate oxidase (GO) in the liver;[111]
3. Lack of evidence from preclinical or clinical studies to suggest the potential for tachyphylaxis (rapidly diminishing response to successive doses) with lumasiran; and
4. Lack of recognised mechanisms by which the biological pathways responsible for PH1 could adapt so that patients develop tolerance to chronic administration of hepatic GO enzyme ribonucleic acid interference (RNAi) silencing therapeutics.

No increase in eGFR (i.e. recovery of lost eGFR and thus improved kidney functioning) was permitted in the base-case analysis, which was, according to the company, a conservative assumption given the inverse relationship between oxalate and eGFR.[34]

Table 5.7 reports the transition matrix for the probabilities of progression across the pre-ESKD health states in the lumasiran arm. As there was no increase in plasma oxalate observed, there was also no decrease in eGFR estimated, meaning that patients will not progress to more severe health states. However, the model does allow for progression to more severe health states (i.e. CKD 4/ESKD) for the proportion of the CKD 1–3b cohort that discontinues lumasiran treatment, at which point ECM transitions are applied.

Table 5.7: Transition matrix within the pre-ESKD health states, lumasiran arm

From↓ \ To→	CKD 1–2	CKD 3a	CKD 3b	CKD 4-OxC
CKD 1–2	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table D8 of the CS[1]
CKD = chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease; Ox_C = controlled oxalate

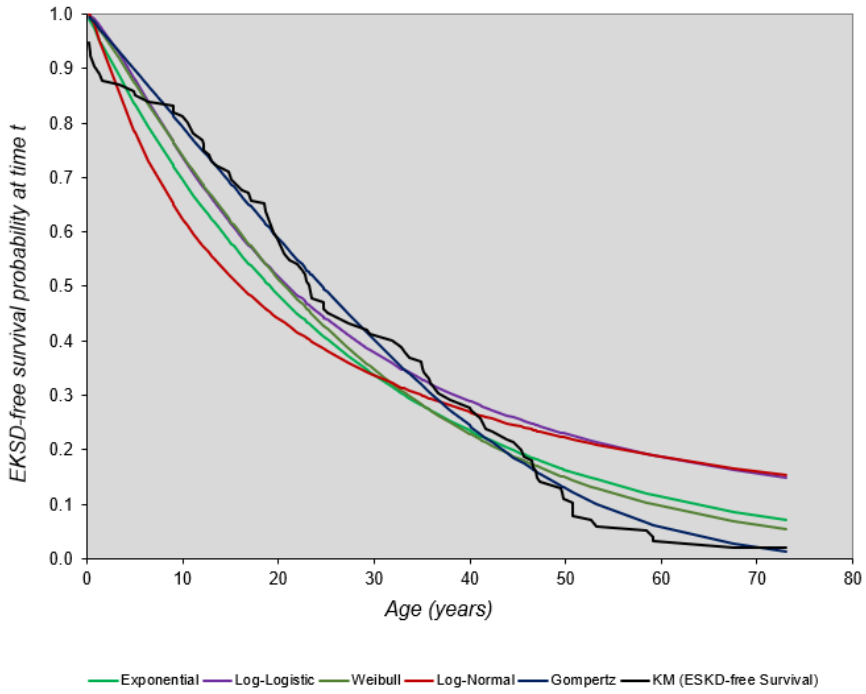
5.3.3.5.3 Transition probabilities from CKD 4 to ESKD - ECM arm

The transition from CKD 4-Ox_U to ESKD-Ox_U in the ECM cohort was modelled by the company using ESKD-free Kaplan-Meier (KM) survival curves published by Harambat 2010.[16] Harambat 2010 estimated time to ESKD by patient age in a large European PH1 cohort (n=155 for analysis). The

analysis revealed an increasing hazard of ESKD as patients age, indicating that over time, a greater proportion of pre-ESKD patients will progress to ESKD.

The company digitised the published ESKD-free KM survival curves and patient-level data were reconstructed via the Guyot method (Figure 5.2).[112] This patient-level data was then used to fit parametric distributions. Based on Akaike information criterion (AIC) estimators, the Gompertz model resulted in the best-fitting distributions for the KM survival curve (CS Table D13). The survival curve shown in Figure 5.2 reached zero, meaning that no extrapolation was required. However, the company opted to use this parametric curve to smooth the ESKD-free survival curve.

Figure 5.2: ESKD-free survival curve and parametric extrapolations



Based on Harambat et al. 2010[16]
ESKD = end-stage kidney disease; KM = Kaplan–Meier

The company used the resulting ESKD-free survival curve to calculate the per-cycle probability of transitioning from the CKD 4-Ox_U health state to the ESKD-Ox_U health state. It should be noted that the population in the Harambat study included a mix of patients including some in lower CKD stages than CKD 4, i.e. patients who were, on average, further from progression to ESKD when compared with a pure CKD 4-Ox_U cohort. Thus, the current approach likely represents a conservative approach.

The resulting proportions of the model cohort free from ESKD in the lumasiran and ECM arms are presented in Figure 5.3 for the adult and paediatric populations. Since a proportion of the overall cohort enters the model in ESKD, the proportion free of ESKD at the start is less than one. Note that the lumasiran cohort free from ESKD included the proportion of the cohort who discontinued treatment and to whom the probability of transition to ESKD was applied as for the ECM cohort.

Figure 5.3: Proportion of CKD 4-Ox_U cohort who have not reached ESKD over the time horizon of the CE model

A. Paediatric population

[redacted]

B. Adult population

[redacted]

Based on Figure D3 of the CS[1]
The proportion of the paediatric (A) and adult (B) cohorts who have not reached ESKD, based on 27.9% of the overall cohort entering the model in ESKD (Table 5.4).
CE = cost effectiveness; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease

5.3.3.5.4 Transition probabilities from CKD 4 to ESKD—lumasiran arm

[redacted], and data from extension studies show no loss of therapeutic effect over the duration of follow-up in patients treated with lumasiran.[76, 80] Thus, the company modelled no progression from CKD 4 to ESKD for the lumasiran cohort based on the observed reduction in plasma oxalate. The company assumed for the model that this decrease in plasma oxalate is expected to correspond to no reduction in eGFR (i.e. improvement in CKD stage), which is a conservative assumption.

5.3.3.5.5 Transition probabilities between CKD 4/ESKD health states differentiated by oxalate levels—lumasiran arm

Patients in the lumasiran cohort who start in late-stage health states with oxalate levels *above* 50 µmol/l (CKD 4-Ox_U or ESKD-Ox_U) can transition to health states with oxalate levels *below* 50 µmol/l (CKD 4-Ox_C or ESKD-Ox_C), as a result of the lumasiran treatment effect. The company assumes that the ECM cohort has no chance of transitioning to health states with oxalate levels below 50 µmol/l.

[redacted]

This was assumed to represent the mean plasma oxalate level in the CKD 4-Ox_U and ESKD-Ox_U health states.

The per-cycle probability of transitioning from CKD 4-Ox_U or ESKD-Ox_U health states to the corresponding health states with controlled oxalate levels was estimated for patients receiving lumasiran. The distance to health states with controlled oxalate levels was calculated (Table D10 in the CS). This distance was assumed to be identical across both late-CKD stages, i.e. CKD 4 and ESKD.

Table 5.8: Plasma oxalate in CKD 4 and ESKD health states and plasma oxalate distance to next CKD stage

	Mean plasma oxalate (µmol/l)	Plasma oxalate distance to health state with oxalate lower than threshold (µmol/l)*
CKD 4-Ox_U or ESKD-Ox_U	[redacted]	[redacted]
CKD 4-Ox_C or ESKD-Ox_C	[redacted]	[redacted]

Based on Table D10 of the CS[1]
CKD = chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease; N/A = not applicable; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

[redacted] (Table 5.8). Since at every next cycle the average starting plasma oxalate level is lower than in the preceding cycle, the resulting absolute reduction in plasma oxalate obtained by applying the percentage plasma oxalate reduction, will also be lower from one cycle to the next, see Table 5.9.

Table 5.9: Reduction in plasma oxalate for each cycle in CKD 4 and ESKD health states

	Reduction in plasma oxalate
Percent reduction in plasma oxalate, %	
Per-cycle	[redacted]
Absolute reduction in plasma oxalate, µmol/l	
Cycle 1	[redacted]
Cycle 2	[redacted]
Cycle 3	[redacted]
Cycle 4	[redacted]

Based on Table D11 of the CS[1]

	Reduction in plasma oxalate
CKD = chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease	

The company used the plasma oxalate distance from the health state with uncontrolled oxalate to the corresponding health state with controlled oxalate, together with the estimated average percent reduction from baseline in plasma oxalate per cycle, to calculate the mean number of years required to transition from the former to the latter state. Based on this analysis, there was a [redacted] probability per cycle of transitioning from health states with uncontrolled oxalate to health states with controlled oxalate during the first cycle of treatment and a probability of one at the second cycle, i.e. the cohort would take two cycles to reduce plasma oxalate levels to below the threshold (Table 5.10).

Table 5.10: Transition probability from uncontrolled oxalate to controlled oxalate CKD 4/ESKD health states

	Years needed to reach the threshold (return period)	Annual exceedance probability (1/return period)	Probability per 6-month cycle
Cycle 1	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]
Based on Table D12 of the CS[1] The maximum probability is capped at 1.00. CKD=chronic kidney disease; CS = company submission; ESKD=end-stage kidney disease			

ERG comment: At a few places in the calculations from the company, the ERG is not fully clear if the calculations are correct. In Table 5.9, [redacted].

In addition, the ERG considers an error has been made with regards to the time period that is considered in the calculation of the transition probability. [redacted] However, it appears to the ERG that only 1.12 cycles (of 6 months) are needed, which would mean that its reciprocal, 0.89, is not the annual exceedance probability but a 6-month exceedance probability.

For the ERG preferred base-case, we will assume a transition probability from uncontrolled oxalate to controlled oxalate CKD 4/ESKD health states of 0.89 rather than [redacted] in the first cycle.

5.3.3.5.6 Transition probabilities from CKD 4 or ESKD to transplantation

PH1 guidelines state that combined/sequential liver–kidney transplantation is an option for patients in CKD 4 or ESKD but are unclear regarding eligibility and timing.[3] In the company CE model, transition to the cLKT health state was permitted only from CKD 4 and ESKD in the lumasiran and ECM arms.

The company argues that the transition probabilities for late-stage CKD cohorts with controlled oxalate are expected to be similar to the transplantation rates observed across non-PH1 CKD patients, since patients with controlled oxalate are likely to be considered better candidates for transplantation than patients with uncontrolled oxalate. Rates of liver and kidney transplantation occurring within 3 years of the patient being listed on NHS transplant lists (children, 89% and 81%; adults, 82% and 66%) were derived from transplant activity in the UK and combined by multiplication to estimate 3-year rates of combined liver–kidney transplantation (children, 72%; adults, 54%).[113, 114] These transplantation rates were transformed into a 6-month cycle probability and applied to CKD 4 and ESKD health states with controlled oxalate (Table 5.11). It was assumed that 100% of patients in these health states would be placed on the waiting list for transplantation and therefore the transplantation rate is only dependent on organ availability.

For late-stage CKD cohorts with uncontrolled oxalate, the company estimated transplantation rates using data from the Compagnon 2014 study (Table 5.11).[115] Compagnon 2014 reported on 33 combined transplants performed in patients with PH1 in France over 31 years (from 1979 to 2010). The company then used data on file suggesting an average prevalence of [redacted] PH1 patients in France over the period covered by the study by Compagnon 2014 resulting in an estimated annual probability per patient is [redacted] (= [redacted] transplants/([redacted]× [redacted]) person-years). The annual probability was transformed into a cycle probability (6 months) of 0.00213 and applied to the CKD 4 and ESKD health states with uncontrolled oxalate for paediatric and adult cohorts, since there was no distinction in the Compagnon study between paediatric and adult patients or CKD 4 and ESKD.

In the request for clarification, the ERG pointed out that the estimated probability of transplantation in the uncontrolled group was not conditional on patients being in CKD 4 or ESKD.[50] In response, the company corrected their calculation by assuming, based on Singh[106] that of the 250 PH1 patients 38% would be in CKD 4 or ESKD, which leads to a per-cycle probability of 0.00696.[51, 52]

The company assumes that lumasiran treatment will continue until transplantation for the lumasiran cohort in CKD 4 or ESKD.

Table 5.11: Per-cycle probability of combined liver–kidney transplantation

Transition from	Per-cycle probability	Source
Paediatric cohort		
CKD 4-Ox_C ESKD-Ox_C	0.19204	NHS Blood and Transplant 2021;[113, 114] assuming that 100% of patients are placed on the transplant list
CKD 4-Ox_U ESKD-Ox_U	0.00696	Compagnon et al. 2014,[115], Singh et al. 2021[106]
Adult cohort		
CKD 4-Ox_C ESKD-Ox_C	0.12205	NHS Blood and Transplant 2021;[113, 114] assuming that 100% of patients are placed on the transplant list
CKD 4-Ox_U ESKD-Ox_U	0.00696	Compagnon et al. 2014,[115] Singh et al. 2021[106]

Based on Table D14 of the CS[1] and the response to the request for clarification[51]
Annual probability reported in Compagnon et al. 2014 was transformed into cycle probability.[115]
CKD = chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

ERG comment: The difference in transplantation probability between patients with controlled and uncontrolled plasma oxalate lacks face validity. If we use these probabilities to find out how long patients will have to wait for transplant, on average, we would come to 2.5 years for the paediatric cohort when controlled and 4 years for the adult cohort, compared to 83 years for both uncontrolled cohort. If this were indeed the case, PH1 patients who have been transplanted would be extremely rare. One of the potential explanations of this underestimate of the transplantation probability is the source that was used for estimation. The study by Compagnon 2014 reported on the period from 1979 to 2010.[115] It seems plausible that during these years a shift has taken place from predominantly kidney transplantations to combined liver and kidney transplantations. Also, the number of person-years that the company assumed for the calculations might be incorrect.

Unfortunately, there is a lack of alternative data to estimate the transplantation probabilities. So, for the ERG preferred base-case, we will assume that rather than 100%, as for controlled patients, only 50% of patients will be placed on the waiting list. Though this percentage is arbitrary, it appears far more realistic than the currently used estimate.

5.3.3.5.7 Probability of re-transplantation

Modelling of re-transplantation was based on data published by Compagnon 2014, which reported four instances of kidney re-transplantation over a maximum follow-up of 239 months.[115] Data on re-transplantation and follow-up duration were used to calculate the probability of re-transplantation per 6-month cycle for the cLKT-Ox_U health state, as shown in Table 5.12. For the cLKT-Ox_C health state, the per-cycle probability of re-transplantation was assumed to be equal the per-cycle probability observed in the cLKT-Ox_U health state, multiplied by the difference in the probability of graft failure between controlled and uncontrolled PH1 patients within the first 10 years of transplantation (0.2155) following reconstruction of patient-level data from the Jamieson 2005 publication.[104]

Table 5.12: Per-cycle probability of re-transplantation

Health state	Per-cycle probability	Source
cLKT-Ox_U	0.0032	Compagnon 2014[115]
cLKT-Ox_C	0.0007	Assumed to equal the per-cycle probability of re-transplantation in the Ox_U cohort (from Compagnon 2014[115]) multiplied by the probability of graft failure in controlled versus uncontrolled PH1 patients within the first 10 years of transplantation (from Jamieson 2005[104])
Based on Table D15 of the CS[1] Compagnon et al. 2014 reported that four of 33 transplantations required re-transplantation at a maximum follow-up of 239 months.[115] cLKT = combined liver–kidney transplantation; CS = company submission; OxC = controlled oxalate levels; OxU = uncontrolled oxalate levels; PH1 = primary hyperoxaluria type 1		

ERG comment: Since the same data source is used for the probability of re-transplantation as for the initial probability of transplantation, the same issues regarding the data source apply here. However, given the small number of patients that will require a re-transplant, the influence from an over- or underestimation of the probability of re-transplantation is likely to have only a limited impact on the ICER.

5.3.3.5.8 Renal stone events

[redacted]

[redacted] (Table 5.13).

For the CKD 4 and ESKD health states, the annualised rate of renal stone events for the ECM cohort was obtained from baseline data in the ILLUMINATE-C study. The annualised rate of renal stone events for the lumasiran cohort was obtained from ILLUMINATE-C 6-month data (i.e. after 6 months of lumasiran treatment). Annualised renal stone event rates were divided by two to obtain the rate of renal stone events per cycle (Table 5.13).

Table 5.13: Renal stone event rate by treatment and health state

	Mean	Standard error	Source
Annualised rate in CKD 1–3b			
Baseline	[redacted]	[redacted]	ILLUMINATE-A and ILLUMINATE-B, pooled pre-treatment historical rate
Renal stone event HR versus baseline rate in CKD 1–3b, by treatment			
ECM, any cycle	1.222	0.122	ILLUMINATE-A, 6 months
Lumasiran, Cycle 1	[redacted]	[redacted]	ILLUMINATE-A and ILLUMINATE-B, pooled 6 months
Lumasiran, Cycle 2+	[redacted]	[redacted]	ILLUMINATE-A and ILLUMINATE-B, pooled 12 months
Annualised rate in CKD 4/ESKD			
ECM, any cycle	[redacted]	[redacted]	ILLUMINATE-C, pre-treatment historical rate
Lumasiran, any cycle	[redacted]	[redacted]	ILLUMINATE-C, 6 months

Based on Table D16 of the CS[1]
CKD = chronic kidney disease; CS = company submission; ECM = established clinical management; HR = hazard ratio

5.3.3.5.9 Systemic oxalosis

Few studies exist that investigate the epidemiology and impact of systemic oxalosis in patients with PH1. The company therefore obtained the prevalence of complications associated with systemic oxalosis in patients with late-stage CKD and uncontrolled oxalate from a survey of UK clinical experts who treat PH1.

Furthermore, clinical experts suggested that the prevalence of systemic oxalosis would be [redacted] in patients in CKD 4 or ESKD with controlled oxalate (oxalate levels below 50 µmol/l), see Table 5.14. The probability of experiencing systemic oxalosis complications is assumed to be zero in CKD 1–3b

health states, since systemic oxalosis is associated with incomplete renal clearance of oxalate, which is typically observed after CKD 3b in PH1.

Table 5.14: Prevalence of systemic oxalosis complications in CKD 4 and ESKD health states

Systemic oxalosis complication	Prevalence per cycle			
	CKD 4-Ox_U	ESKD-Ox_U	CKD 4-Ox_C	ESKD-Ox_C
Bone	30%	80%	[redacted]	[redacted]
Cardiac	15%	40%	[redacted]	[redacted]
Cutaneous and vascular	15%	35%	[redacted]	[redacted]
Ophthalmic	18%	40%	[redacted]	[redacted]
Neurologic	18%	40%	[redacted]	[redacted]

Based on Table D17 of the CS[1]
CKD =chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease; Ox_C = controlled oxalate levels; Ox_U = uncontrolled oxalate levels

5.3.3.5.10 Dialysis

To estimate which group of patients would receive which type of dialysis with which frequency, the company commissioned a survey of UK clinical experts who treat PH1.

Table 5.15: Dialysis distribution

Population	Dialysis	Probability
High-intensity dialysis		
Paediatric	Haemodialysis, 7×week	[redacted]
	Haemodialysis, 6×week plus peritoneal dialysis 7×week	[redacted]
Adult	Haemodialysis, 7×week	[redacted]
	Haemodialysis, 6×week plus peritoneal dialysis 7×week	[redacted]
Normal-intensity dialysis		
Paediatric	Haemodialysis, 3×week	[redacted]
	Peritoneal dialysis 7×week	[redacted]
Adult	Haemodialysis, 3×week	[redacted]
	Peritoneal dialysis 7×week	[redacted]

Based on Table D18 of the CS[1]

In the model it is assumed that in the ECM cohort, 100% of the CKD 4 and 100% of the ESKD health states receive high-intensity dialysis as an add-on to ECM, based on PH1 clinical guidelines.[3] In the lumasiran cohort, 0% of the CKD 4 health state receives normal-intensity dialysis, since the kidney is functioning in CKD 4 and plasma oxalate is controlled by lumasiran. However, the company assumes that all patients with ESKD will require dialysis, but not higher-intensity dialysis to control oxalate, given the use of lumasiran for this purpose. Therefore, the proportion of the lumasiran cohort in ESKD with normal-intensity dialysis was set to 100%.

ERG comment: In the CS, it was stated that 100% of patients in the ECM cohort would receive high-intensity dialysis once they reach CKD class 4.[1] However, the clinical experts sought out by the company indicated that only rarely do patients in CKD4 dialysis (see also Section 5.3.3.9.4).[116] The

company did not provide any explanation why clinical guidelines were followed to estimate prevalence and frequency, rather than clinical expert opinion. To assess the impact of this change, the ERG included the expert's suggestion in the scenario analyses done after defining the ERG preferred base case.

5.3.3.5.11 Lumasiran treatment discontinuation

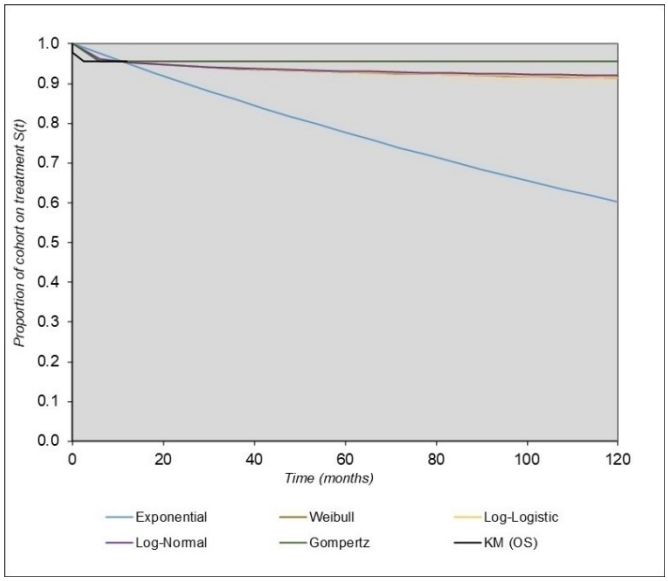
Treatment discontinuation represents unplanned interruption of lumasiran due to any reason and could occur within any of the early CKD health states (i.e. CKD 1–3b). The company used a time-on-treatment (ToT) curve derived from ILLUMINATE-A and ILLUMINATE-B patient-level data to simulate the proportion of the CKD 1–3b cohorts discontinuing treatment with lumasiran at each cycle of the model. Following treatment discontinuation, the cohort was assumed to experience the clinical effect observed in the ECM arm, specifically with respect to transition probabilities across all pre-ESKD health states, transition probabilities from pre-ESKD to ESKD, probabilities of transition to transplantation, the prevalence of systemic oxalosis complications, the renal stone event rate, and dialysis schedules.

Data on treatment discontinuation due to any reason in patients receiving lumasiran were obtained from the ILLUMINATE-A and ILLUMINATE-B trials at the 12-month cut-off. Beyond the trial period, ToT was extrapolated by fitting parametric models to observed time-to-event data. AIC and Bayesian information criterion (BIC) estimators were used to evaluate the relative fit of the parametric models considered, namely exponential, Weibull, Gompertz, log-normal, and log-logistic (CS Table D19).[1] The log-normal function was selected to inform the fraction of patients still on treatment at each time point in the simulation based on the goodness of fit. Figure 5.4 shows how the parametric curves compare for the extrapolation of the ToT for lumasiran. A piecewise approach was followed, where the KM points were used for the duration of directly observed follow-up available and thereafter the best-fitting parametric curve was used to define the probability of discontinuation.

No benefit of lumasiran treatment was assumed beyond treatment discontinuation; therefore, the effect of treatment was not applied for the proportion of the cohort who discontinued treatment.

A discontinuation rate of zero was applied to CKD 4 and ESKD cohorts since no discontinuations were observed in ILLUMINATE-C within the first 6 months.

Figure 5.4: Extrapolation of the ToT for lumasiran



Based on Figure D4 of the CS[1]

CS = company submission; KM = Kaplan–Meier; OS = overall survival; ToT = time on treatment

5.3.3.5.12 Mortality

General population mortality

General population mortality was defined as age- and gender-specific all-cause mortality and has been included in the model based on country-specific mortality tables for England.[117] The general mortality rate used in the model corresponded to the age of the cohort at each given cycle and was adjusted based on the proportion of males in the analysis.

CKD-related mortality

The CEA simulates CKD-related mortality in the model cohort by applying a higher risk of mortality with increasingly severe PH1 health states, applied over the time horizon of the model. The company used the relative risk of death in each model state versus the general population mortality as reported by Go et al.[118] They obtained these relative risks from a retrospective database analysis of longitudinal eGFR data. The company argues that it is appropriate to use relative risk–based multipliers from Go et al. (applied to general population mortality estimates) in this CE model even though they were not obtained within a PH1 population, because the aim of this aspect of the CE model was to quantify the mortality impact of renal dysfunction independently of the presence of PH1, to obtain the increased risk of death related to each CKD stage.

Table 5.16 presents the health-state–specific mortality multipliers used in the current analysis. The reference group (eGFR ≥60 ml/min/1.73m^2, or CKD 1–2) was assumed to have normal background mortality. The mortality multipliers are likely to be conservative estimates as they do not incorporate further mortality risk due to systemic oxalosis complications in the later stages of CKD in PH1.

Table 5.16: Mortality multiplier of model health states

Health state	Mortality relative risk versus general population
CKD 1–2	1.0
CKD 3a	1.2
CKD 3b	1.8
CKD 4	3.2
ESKD	5.9

Based on Table D20 of the CS[1]
Hazard ratio estimates were applied as CKD stage–specific multipliers of background (general population) mortality risk.
CKD = chronic kidney disease (stage); CS = company submission; ESKD = end-stage kidney disease

Transplant-related mortality (time to death from first transplant)

The company used data published by Jamieson 2005 to model overall survival following combined/sequential liver–kidney transplantation.[104] That study had estimated KM survival curves stratified according to pre-operative condition (very good, good, fair and poor). These KM curves were digitised, and patient-level data were reconstructed via the Guyot method (based on the published number at risk).[112]

After validation with clinical experts, the company used the average of the two KM curves referring to patients in *Very Good* and *Good* pre-operative condition to estimate the overall survival of patients in the post-cLKT health state with controlled oxalate. The average of the two KM curves referring to

patients in *Fair* and *Poor* pre-operative condition was used to estimate the overall survival of patients in the post-cLKT health state with uncontrolled oxalate.

Since the fitting of the extrapolation curves for some KM curves reported by Jamieson 2005 was very poor, the company used a piecewise approach whereby the average KM curve was used for the duration of observed follow-up available, after which the best-fitting extrapolation curve was used. If at the end of observed period survival was lower than that estimated with the best-fitting extrapolation curve, the last observed survival was applied until the time point at which it was matched by the estimate from the best-fitting extrapolation curve, after which values from the extrapolation curve were used (Table 5.17).

Table 5.17: Long-term risk of post-transplantation mortality

Time period	Estimation of post-transplantation mortality risk
Up to year 4 (short term)	Time point-specific probability of mortality was estimated from the parameterisation of overall survival curves for the cohort of interest (Very Good/Good Condition or Fair/Poor Condition) receiving combined/sequential liver–kidney transplantation (Jamieson 2005[104])
Years five to – 29 (medium term)	Fixed probability of mortality, calculated as the average over years five to 29 following the methodology described (estimation from Jamieson 2005 [104]), to avoid using more than 10 tunnel states
Year 30+ (long term)	Assumed to equal the age-specific mortality rate of the general population
Based on Table D21 of the CS[1] CS = company submission	

ERG comment: The study by Jamieson et al. report on 127 liver transplantations in 117 PH1 patients, reported between June 1984 and December 2004 by 35 European centres.[104] Thus, the survival reported in this paper is based on patients receiving ECM, which means that also the patients classified as in very good/good condition should be taken into account when deriving the post-transplantation survival for uncontrolled oxalate in CKD 4/ESKD. This will be done for the ERG preferred base case, see Section 6.2. Given the time period on which is reported in Jamieson et al., the question also arises how representative the estimated survival curves are for the present patients. Unfortunately, survival is not reported stratified by time period of the transplantation. A small note should also be made that the curves reported in Jamieson also include a few patients receiving only a liver transplant.

The ERG found a very recent publication from the OxalRegistry, reporting on a total of 267 patients with PH1 who underwent transplantation between 1978 and 2019.[119] The patient survival in this study appears to be (based on comparison of the survival curves) a few percent higher than in the Jamieson study.[104] In addition, this study also presents the survival curve for patients who underwent their transplantation after 1-1-2000, and this curve in turn appears to show again a slightly higher survival then the curve for all patients.

The above might explain why the survival curves in the model for controlled CKD4, ESKD and post-transplantation reveal that between cycle 10 and cycle 100, the probability of dying after a transplantation is (substantially) higher than when a patient is in CKD4 or ESKD, which does not seem plausible.

5.3.3.6 Adverse events

The incidences of AEs associated with lumasiran and ECM in the model were estimated on 6-month data from ILLUMINATE-A. The analysis included treatment-related AEs reported by at least 10% of

patients in either group, with adjustments to incidence made to account for the 6-month cycle length (Table 5.18). Note that all AEs were either mild or moderately severe.[46]

Table 5.18: Cycle probabilities of treatment-related AEs

	Lumasiran (cycle incidence)	ECM/placebo (cycle incidence)
Headache	0.115	0.231
Injection-site erythema	0.115	0.000
Injection-site pain	0.346	0.000
Injection-site reaction	0.385	0.000
Rhinitis	0.077	0.154
Upper respiratory infection	0.077	0.154

Based on Table D22 of the CS[1]
AE = adverse event; CS = company submission; ECM = established clinical management

5.3.3.7 Health-related quality of life

5.3.3.7.1 HRQoL evidence

[redacted] RSE and AE utility data were derived from the literature.[102, 120] For late-stage disease health states CKD 4 and ESKD utility values could not be obtained from the ILLUMINATE-A study since it did not include those patients, and HRQoL data from the ILLUMINATE-C study were not considered appropriate by the company given the small sample size (N=21) and the inclusion of very young patients (<2 years), the lack of face validity of available evidence, which would introduce unnecessary uncertainty into the CEA, and confounding factors such as the extent and severity of systemic oxalosis (SO) complications which would be challenging to control for.[1] Consequently, the company decided to use a health-state vignette study to obtain values for adult and paediatric patients in the CKD 4 and ESKD health states as recommended by the NICE Decision Support Unit (DSU) report on HRQoL when sufficient EQ-5D data are not available.[121] In the health-state vignette study, the company collected HRQoL data on two of the eight health states in the severe stages, namely CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis, which represents the ECM arm in the model. For the other health states, CKD 4/ESKD with uncontrolled oxalate and normal intensity dialysis and controlled oxalate and normal-/high-intensity dialysis, data from the ILLUMINATE-A study and literature were used to estimate utilities. Utilities for patients in the cLKT health states for the time after transplantation were also obtained from the vignette study. Additionally, a one-off disutility was applied for the burden of the transplantation for a set period of days (91.32), and was based on literature.[122] The company also applied an estimated disutility associated with graft failure for a set duration of days (91.32), which was derived from literature and based on the incidence of graft failure in the cLKT health states.[123]

Table 5.19: Utility values for CKD 1-3b

	Children (n=19)		Adults (n=17)	
	Mean	**SE**	**Mean**	**SE**
ILLUMINATE A at baseline (n=36)	[redacted]	[redacted]	[redacted]	[redacted]
ILLUMINATE A pooled baseline, m6 and m12 (n=89) – base-case	[redacted]	[redacted]	[redacted]	[redacted]

Based on Excel model v11.0[110]
m = month; SE = standard error

ERG comment: The DSU technical support document (TSD) 11 report states that alternative methods to generating health state utility values for CKD 4 and ESKD can be used when EQ-5D data are either unavailable or inappropriate.[124] Unavailability should be established from a SLR which was done by the company. The company argues that HRQoL data from the ILLUMINATE-C study was not appropriate given the small sample size and the inclusion of very young patients, the lack of face validity of available evidence, and the challenges with accounting for confounding factors such as the extent and severity of SO complications.

The ERG does not agree with the current arguments provided by the company. According to the CS, HRQoL data were measured with the EQ-5D-Y in the ILLUMINATE-C study.[1] The EuroQol 5-Dimension - Youth version (EQ-5D-Y) is considered an appropriate HRQoL measurement for children aged seven to 12 years and is recommended by the DSU.[125] In the CS, a median age of eight years is reported for the overall sample in the ILLUMINATE-C study. Since at least half of the sample in the ILLUMINATE-C study has reached the age considered suitable for measuring HRQoL with the EQ-5D-Y, the ERG questions the company's reasoning. ILLUMINATE-C study included 21 patients whereas the ILLUMINATE-A study included 39 patients. The ERG does not consider the difference in sample size sufficiently large to dismiss the HRQoL data from the sample from the ILLUMINATE-C study outright. Regarding the face validity of the HRQoL data in the ILLUMINATE-C study, the ERG cannot form an opinion given the lack of data provided on HRQoL in the CS. Thus, the ERG has to consider that the arguments of the company challenging the appropriateness of the HRQoL data collected in the ILLUMINATE-C study might not hold.

The company did not provide a rationale for using pooled utilities for the CKD 1-3b health states instead of baseline utilities. Also, the rationale for assigning one utility value across the early CKD health states (1-3b) are not clearly stated by the company.

5.3.3.7.2 Vignette/TTO study

The company conducted a vignette study in which various vignettes representing different health states associated with patients with PH1 were valued by members of the UK general population using three different approaches:

1. European Quality of Life-5 dimensions-5 levels (EQ-5D-5L) questionnaire,
2. A visual analogue scale (VAS), and
3. A time trade off (TTO) exercises. The development and valuation exercises are described below separately.

Vignette development

[redacted]

[redacted]

For the ESKD health state the company stated that the clinical experts agreed to a subset of manifestations of SO representative of the ESKD health state including bone, cutaneous, and vascular complications. For the paediatric population the experts included bone, cutaneous, vascular, and ophthalmologic manifestations of SO in the description of CKD 4 and ESKD. The company further reports that the vignettes only capture CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis that represents the ECM arm in the model.

Vignette exercise

The company states that a sample of [redacted] members of the general public were individually interviewed to value the health states. The members completed the EQ-5D-5L questionnaire for each vignette, ranked the severity of each vignette from zero (worst possible state) to 100 (full health) on a VAS, and completed a TTO exercise. The utility results are presented in Table 5.20 below for adult and paediatric patients. The company used the EQ-5D-5L questionnaire completed for each vignette and mapped to EQ-5D-3L to value utilities of the CKD and ESKD in the cost effectiveness model.

Table 5.20: HRQoL data derived from the health-state vignettes

	Adult			Child		
	EQ-5D-5L	**VAS**	**TTO**	**EQ-5D-5L**	**VAS**	**TTO**
CKD 1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3a	[redacted]	[redacted]	[redacted]			
CKD 3b	[redacted]	[redacted]	[redacted]			
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESKD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table C17 of the CS[1]
CKD = chronic kidney disease; cLKT = combined liver–kidney transplant; CS = company submission; EQ-5D-5L = European Quality of Life-5 dimensions-5 levels; ESKD = end-stage kidney disease; TTO = time trade off; VAS = visual analogue scale

Since the vignettes only captured CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis, the company used the utility decrement of CKD 4/ESKD relative to CKD 1–3b in non-PH1

populations obtained from the literature,[126, 127] and applied it to the utility values for adult and paediatric CKD 1–3b health states obtained from ILLUMINATE-A. To this base utility for CKD and ESKD, the company applied utility decrements for SO complications and dialysis. For CKD 4 and ESKD health states in which not all SO complications (i.e. bone, cardiac, cutaneous, and vascular, neurologic, and ophthalmologic) have been captured through the vignette study, utility decrements were based on literature[120, 128] and prevalence data collected from third party clinical expert surveys. The same SO prevalence rates were used for the adult and paediatric patient population. The company used a multiplicative approach to calculate disutility for patients with multiple manifestations of SO based on the prevalence of these conditions. Literature was also used to estimate the utility decrements for normal-/ and high-intensity dialysis for adult and paediatric patients.[129] In addition, like for the early CKD health states, per-event utility decrements due to AEs and RSE were applied to the CKD 4 and ESKD health states.

ERG comment: While the ERG agrees that the vignette utilities represent the preferences of the general public as the valuations were conducted in a representative sample of the general public, they fail to meet a different vital element of the NICE reference case which states that HRQoL must be measured/reported in patients. No patient HRQoL data are actually used to produce utilities in vignette studies. Members of the general public are given descriptions of health states which are intended to reflect the health of patients in different states in the model, and these descriptions are valued directly. No patients are involved and therefore one cannot be sure how reflective these descriptions or the utilities produced are of the patients in the trial.

Additionally, the DSU recommends in-depth interviews and/or focus-groups with the patients for a valid description of the vignettes.[125] Although the company used published testimonials from patients describing their experiences, the final vignettes were not validated with patients but only clinical experts resulting in a complete lack of direct input from patients on the vignette descriptions. The inclusion of patients who receive lumasiran in the development of the vignettes could have additionally resulted in vignettes also representing the controlled oxalate CKD 4 and ESKD states and not only the current standard of CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis.

In the base-case, the company makes use of the EQ-5D-5L questionnaire completed for each vignette to estimate the utility. The ERG asked the company to provide an option to use the utility values from the TTO. The company provided the requested option and noted an increase in the resulting ICER from £[redacted]/QALY in the base-case to £[redacted]/QALY representing a 37% increase with the TTO utilities scenario compared with the EQ-5D-5L utilities base-case. The company states that it does not believe the TTO scenario should be considered of relevance considering NICE guidelines stating EQ5D as the preferred valuation due to reasons of consistency across evaluations.[51, 52]

Although the ERG agrees on the preferred use of EQ-5D utilities, this preference is commonly for situations where patients fill in the questionnaire based on their own health. based on utilities derived directly from patients and not from the general public. As part of the recent revision of the NICE methods guide, a systematic review was done to investigate for which disease areas the EQ-5D might be less valid.[130] It was found that EQ-5D-5L may not be reliable in conditions affecting neurological or ophthalmologic properties of the patient. In the vignette study for paediatric patients, ophthalmologic manifestations of SO are used in the description of CKD 4 and ESKD. The ERG is therefore not sure about the face validity of EQ-5D-5L valued vignettes for the paediatric population.

In addition, the EQ-5D-3L baseline utility reported in the ILLUMINATE-A trial of [redacted] for the paediatric population in health states CKD 1-3b differs substantially from the vignette obtained EQ-5D-5L utility of [redacted] for these health states but aligns better with the utility obtained from the TTO

valuation of the vignettes ([redacted]). Likewise, the observed utilities for adults over health states CKD 1-2, CKD 3a and CKD 3b are more similar to the TTO values for the vignettes than the EQ-5D derived values.[1]

Given the questionable face validity of the EQ-5D-5L valuations of the vignettes indicated by the ILLUMINATE-A utility values for CKD 1-3b and the DSU recommendation not to use EQ-5D-5L valuation for vignettes that describe ophthalmologic conditions as well as the availability of TTO values with face validity, the ERG will use the TTO values in an ERG preferred base-case.

Due to the difficulty to describe a representative set of SO manifestations, the company used literature to estimate the disutility of those. The same prevalence data was used for the paediatric and adult population. At the request of the ERG, the company provided separate prevalence rates which were collected through a third-party survey with clinical experts. The company states that prevalence data was collected for each individual condition instead of sets of SO complications to reduce complexity and subsequently any combination of SO disorders was estimated using a multiplicative permutation approach assuming independence of disorders. The company further states that an average of prevalence data was used to reduce the complexity of the analysis and that prevalence data was not considered to differ much between the two population groups. Estimating the prevalence rate for each of the five SO manifestations for CKD 4 versus ESKD, Ox_C versus Ox_U and paediatric versus adult a total of 40 prevalence rates would have needed to be estimated. The company argues, that would make the estimation of HRQoL more complex since the total utility decrement associated with SO manifestations would need to be estimated separately for paediatric and adults in all health-states.

Whilst the ERG acknowledges the possible complexity of all 40 combinations of SO disorders, it disagrees with the company on the similarity of prevalence rates between paediatric and adult patients for at least two of the 10 conditions (in both CKD 4 and ESKD), which results in mean values that significantly under- or overestimate prevalence rates in the paediatric patient population and therefore associated disutilities. The cardiac disutility decrement is with -0.10 the 2nd largest utility decrement together with bone disorders and after neurological disorders. The ERG considers the additional effort to add prevalence data for paediatric patients for the uncontrolled and controlled CKD 4 and ESKD states, resulting in a total of four overall OS disutility values to be applied to CKD 4 and ESDR health states, worthwhile. Especially considering the model's clear differentiation between adult and paediatric patients in various other instances and the apparent difference in prevalence data for complications that is also associated with a relatively large utility decrement within the SO complications. The SO disutility additionally applied to the vignette study data, which was collected for adults and paediatric patients separately, is also based on the prevalence data of the average of adults and paediatric patients despite the availability of group-specific prevalence data, the relatively low effort of estimating another three combinations and the dominant percentage of paediatric patients in the model ([redacted]).

As for the multiplicative approach, the ERG asked the company to justify this approach and to provide a scenario with an additive approach. The company argues that a multiplicative, permutation-based approach, developed by Ara and Brazier 2017, was used to estimate the probability of each unique combination of SO manifestations and, therefore, assumes that the likelihood of occurrence of SO complications in one organ system is independent from the likelihood of occurrence of SO complications in any other organ system.[130] The company further states that the approach was chosen in consultation with John Brazier and the health-economic experts at Sheffield University and is a recommended approach by the International Society for Pharmacoeconomics and Outcomes Research Good Practices for Outcome Research Task Force.[81] A scenario was run by the company estimating the disutilities for SO complication using the additive approach (see Table 5.22) below for disutilities). The

impact on the ICER was reported as a 0.33% reduction compared with the base-case ICER ([redacted] versus [redacted]). The ERG concludes that the chosen method on estimating prevalence rates of combined OS complications has minimum influence on the results.

Table 5.21: Prevalence by systemic oxalosis manifestation obtained from the third-party survey with UK clinical experts

	Paediatric nephrologist	Adult nephrologist	Average
CKD 4			
Bone	0.30	0.30	0.30
Cardiac	0.00	0.30	0.15
Cutaneous and vascular	0.20	0.10	0.15
Ophthalmologic	0.30	0.05	0.18
Neurological	0.20	0.15	0.18
ESKD			
Bone	0.80	0.80	0.80
Cardiac	0.20	0.60	0.40
Cutaneous and vascular	0.40	0.30	0.35
Ophthalmologic	0.60	0.20	0.40
Neurological	0.40	0.40	0.40

Based on Table 15 of the response to request for clarification[51, 52]
CKD = chronic kidney disease (stage); ESKD = end-stage kidney disease

Table 5.22: Differences in disutilities of systemic oxalosis manifestation estimated using the multiplicative versus additive method

	Total systemic oxalosis manifestation disutility	
	Multiplicative approach	**Additive approach**
CKD 4-Ox_u, all	-0.101	[redacted]
ESKD-Ox_u, all	-0.233	[redacted]
Cardiac and neurological complications in CKD 4-Ox_u, children	-0.056	[redacted]
Cardiac and neurological complications in ESKD-Ox_u, children	-0.131	[redacted]
Cardiac, ophthalmologic and neurological complications in ESKD-Ox_u, adults	-0.145	[redacted]
CKD 4-Ox_c, all	-0.081	[redacted]
ESKD-Ox_c, all	-0.190	[redacted]

Based on Table 15 of the response to request for clarification[51, 52]
CKD = chronic kidney disease (stage); ESKD = end-stage kidney disease; OX_c = oxalate controlled; OX_u = oxalate uncontrolled

5.3.3.7.3 Carer disutility

The company applied caregiver disutilities for the severe health states CKD 4 and ESKD since [redacted]

[redacted][131] The company could not find any published study in caregiver disutilities for parental caregivers of children aged six to 17 years with PH1. The company used disutilities reported in an observational study on caregiver health status comparing the burden on caregivers responsible for children with abnormal kidney function versus those responsible for children with normal kidney function, yielding a disutility per caregiver of [redacted].[131] Number of caregivers per patient were retrieved from pooled observations in ILLUMINATE-A and ILLUMINATE-B trials. A mean of [redacted] caregivers were used to estimate utility decrements. The company states that in the pooled analysis observations where patients had at least one caregiver were included.

ERG comment: The company assumes that the caregiver tasks in health state CKD 4 and ESKD are the same resulting in the same burden on the caregiver and therefore, the same caregiver disutilities can be applied. However, the company does not provide any literature on this assumption. Furthermore, the company uses the estimated disutility regardless of the intensity of the dialysis being given. It is quite likely though, that the intensive dialysis leads to a higher burden for the caregiver than the normal dialysis. Since the lumasiran treated patients will only need the normal dialysis frequency and the ECM patients the intensive dialysis, applying the same disutility to all patients in CKD 4 and ESKD will lead to a conservative estimate of the ICER.

5.3.3.7.4 Impact of adverse events on HRQoL

The company stated that it could be expected that several AEs may have a negative impact on the HRQoL of patients, but the literature search did not result in data specifically on the relationship between AEs and HRQoL in patients with PH1.[1] Therefore, the company used the catalogues of EQ5D scores for the UK to model the impact of AEs (see Table 5.23).[120] For the QALY calculation, the company assumed that all AEs would last 14 days

Table 5.23: Utility decrements due to adverse events

Adverse event	Utility decrement	Source
Headache	−0.027	Sullivan 2011;[120] 084 Headache, Including Migraine
Injection-site erythema	−0.001	Assumed equal to rhinitis
Injection-site pain	−0.027	Assumed equal to headache
Injection-site reaction	−0.027	Assumed equal to headache
Rhinitis	−0.001	Sullivan 2011;[120] ICD-9 477 Allergic Rhinitis
Upper respiratory infection	−0.037	Sullivan 2011;[120] ICD-9 519 Other Respiratory System Diseases
Based on Table C18 of the CS[1] CS = company submission		

ERG comment: Given the reported paucity of data on the impact of AEs on the HRQoL of patients with PH1, the ERG agrees with the use of the catalogues of EQ-5D scores. The company however could not establish whether the loss in HRQoL due to AEs in health states CKD 1-3b was not already captured in the HRQoL collected in the ILLUMINATE-A study. Therefore, there is a small risk of double counting.

5.3.3.8 Resources and costs

The following cost categories were included in the analysis: drug acquisition costs, drug administration costs, dialysis costs, renal stone event costs, systemic oxalosis complications costs, transplantation-related costs, disease monitoring costs, adverse event costs, and end-of-life costs.

5.3.3.8.1 Drug acquisition costs

The drug acquisition costs for lumasiran are £61,068.98 per 94.5 mg vial at list price or [redacted] including the proposed Patient Access Scheme (PAS) discount of [redacted]. Treatment with lumasiran consists of an initial loading phase during the first 3 months and a subsequent maintenance phase. Dosage and number of administrations of lumasiran per quarter is dependent on body weight: patients with a body weight <10 kg receive three administrations of 6 mg/kg during the loading phase and three administrations of 3 mg/kg per quarter during the maintenance phase, patients with a body weight ≥10 to < 20 kg receive three administrations of 6 mg/kg during the loading phase and one administration of 6 mg/kg per quarter during the maintenance phase, patients with a body weight ≥ 20 kg receive three administrations of 3 mg/kg during the loading phase and one administration of 3 mg/kg per quarter during the maintenance phase. The average body weight of patients in the ILLUMINATE trials is [redacted] kg for the paediatric population and [redacted] kg for the adult population, with corresponding doses per administration of [redacted] mg and [redacted] mg respectively. [redacted]

The average cost of lumasiran for a paediatric patient is [redacted] for the first model cycle and [redacted] for subsequent 6-month cycles. The average cost of lumasiran for an adult patient is [redacted] for the first 6-month cycle and [redacted] for subsequent cycles. No vial sharing is assumed for lumasiran. On average 16.05 mg and 37.43 mg of lumasiran is wasted for the paediatric and adult population, with corresponding costs due to wastage of [redacted] and [redacted] per administration, respectively. The average per-cycle costs due to wastage for the paediatric and adult populations are [redacted] and [redacted] for the first model cycle, and [redacted] and [redacted] for subsequent model cycles, respectively.

The drug acquisition costs for pyridoxine, a component of ECM, are £21.93 per pack of 28 tablets of 50 mg. Dosage of pyridoxine is 8 mg/kg and it is assumed that 50% of patients in the lumasiran arm and 69% of patients in the ECM arm receive pyridoxine based on ILLUMINATE-A. This results in an average per-cycle cost of £1.96 for children and £5.48 for adults in the lumasiran arm, and £2.71 for children and £7.59 for adults in the ECM arm.

ERG comment: The ERG considers the costs due to drug wastage for lumasiran to be high. During the clarification phase, the ERG asked the company to demonstrate exactly the costs due to drug wastage. These are provided above. In response to the ERG's request, the company also included the option in the model to assume vial sharing (i.e. no drug wastage) for lumasiran. If vial sharing is included the company's base-case ICER amounts to [redacted]. In response to the ERG's question whether the company has plans to provide lumasiran in vials of smaller quantities to enhance dosing flexibility and reduce wastage, the company indicated that this will not be possible.

5.3.3.8.2 Drug administration costs

Lumasiran is administered subcutaneously. Administration costs amount to £43.44 per administration based on the NHS Reference costs 2019/2020 (currency code N02AF; District Nurse, Adult, Face to face).[132] The per-cycle administration cost for lumasiran is £169.86 in the first cycle and £84.93 in subsequent cycles for paediatric patients, and £509.57 in the first cycle and £254.79 in subsequent cycles for adult patients.

5.3.3.8.3 Dialysis costs

The weighted average costs of haemodialysis (HD) and peritoneal dialysis (PD) were calculated based on the NHS Reference costs 2019/2020 for paediatric and adult patients separately.[132] The unit costs were provided in Table 6 of Appendix 5 in the CS.[1]

For adult patients receiving high-intensity dialysis it was assumed that [redacted] receive daily HD alone and [redacted] receive HD six times per week in combination with PD seven times per week, based on a survey with UK clinicians.[116] [redacted] paediatric patients receiving high-intensity dialysis were assumed to receive daily HD alone, based on a survey with UK clinicians. The resulting per-cycle costs of high-intensity dialysis were £83,633 for paediatric patients and £32,372 for adult patients.

For both adult and paediatric patients receiving normal-intensity dialysis it was assumed that [redacted] receive HD alone three times per week and [redacted] receive daily PD alone, based on a survey with UK clinicians.[116] The resulting per-cycle costs of normal-intensity dialysis were £38,961 for paediatric patients and £13,022 for adult patients.

5.3.3.8.4 Renal stone event costs

The weighted average cost of a renal stone event was calculated as £806.64 based on the NHS Reference costs 2019/2020.[132] The unit costs were provided in Table 7 of Appendix 5 in the CS.[1]

5.3.3.8.5 Systemic oxalosis complications costs

The analysis included costs for the treatment of the following systemic oxalosis complications: 'bone', 'cardiac', 'cutaneous and vascular', 'ophthalmologic' and 'neurologic' complications. These costs were sourced from the literature and inflated to 2020/2021 using the NHS Cost Inflation Index (NHS CII) from the Personal Social Services Research Unit (PSSRU) 2020 (i.e. using an estimated index value for 2020/2021 based on the average index between 2017 and 2020).[133] The cost of treatment for bone complications amounts to £1,313.17 and was sourced from Borgström 2020,[134] assuming the UK-specific annual cost, adjusted to the 6-month cycle length of the current model, of distal forearm fractures in the year following the fracture (converted from EUR to GBP using the purchasing power parities at the year of costing). The cost of treatment for cardiac complications amounts to £1,948.67 and was sourced from Danese 2016,[135] assuming the UK-specific cost in the months 7 to 36 after an event of heart failure, adjusted for cycle length. The cost of treatment for cutaneous and vascular complications amounts to £3,937.46 and was sourced from Patel 2020,[136] assuming the annual NHS and PSS cost in subsequent years to the first year from stroke occurrence, adjusted for cycle length. The cost of treatment for ophthalmologic complications amounts to £625.77 and was sourced from Galvin 2020,[137] assuming the health-system cost in 2019 of inherited retinal diseases in the UK (i.e. £25 million divided by 20,815 cases), adjusted for cycle length. The cost of treatment for ophthalmologic complications amounts to £625.77 and was sourced from Galvin 2020,[137] assuming the health-system cost in 2019 of inherited retinal diseases in the UK (i.e. £25 million divided by 20,815 cases), adjusted for cycle length. The cost of treatment for neurologic complications amounts to £1,513.24 and was sourced from Liedgens 2020, assuming the cost in 2012 of neuropathic pain in the UK, adjusted for

cycle length.[138] An overview of the systemic oxalosis complications costs and assumptions is provided in Table 5.24.

Table 5.24: Systemic oxalosis complications costs.

Complication	Cost	Source
Bone	£1,313.17	Borgström 2020;[134] assumed equal to the annual cost of distal forearm fractures in the year following the fracture. EUR converted into GBP using the PPP at the year of costing.
Cardiac	£1,948.67	Danese 2016;[135] assumed equal to the per-cycle cost after an event of heart failure (months 7 to 36 after the event).
Cutaneous and vascular	£3,937.46	Patel 2020;[136] assumed equal to the annual NHS & PSS cost in subsequent years to the first year from stroke occurrence.
Ophthalmologic	£625.77	Galvin 2020;[137] assumed equal to the health-system cost of inherited retinal diseases in the UK (i.e. £25 million divided by 20,815 cases).
Neurologic	£1,513.24	Liedgens 2016;[138] assumed equal to the per-cycle cost of neuropathic pain.

Source: Table D31 in the CS.[1]
CE = cost effectiveness; EUR = Euro; GBP = British pound sterling; NHS = National Health Service; OWSA = one-way sensitivity analysis; PPP = purchasing power parities; PSA = probabilistic sensitivity analysis; PSS = Personal Social Services

5.3.3.8.6 Transplantation-related costs

The weighted average costs of cLKT were calculated for paediatric and adult patients separately based on the NHS Reference costs 2019/2020 for liver transplantation and kidney transplantation (including pre-transplantation).[132] The weighted average costs of re-transplantations were also calculated for paediatric and adult patients separately based on the NHS Reference costs 2019/2020.[132] The weighted average cost of post-cLKT monitoring was calculated based on the post-kidney transplantation costs from the NHS Reference costs 2019/2020 and applied as a per-cycle cost to all patients who received a cLKT.[132] In addition, a per-cycle cost of £102.70 was applied for post-cLKT immunosuppression with an assumed daily dosage of 16.3 mg based on Jones-Hughes 2016 and using a cost of £9,66 for a pack of 28 tablets containing 10 mg prednisolone each that was sourced from the Monthly Index of Medical Specialities (MIMS).[139, 140] The weighted average one-off cost of a graft failure was calculated based on the NHS Reference costs 2019/2020 for all patients.[132] The transplantation-related costs are summarised in Table D32 and Table D33 of the CS, and details on the unit costs that were sourced from the NHS Reference costs 2019/2020 are provided in Table 9 of Appendix 6 in the CS.[1] The cLKT and other transplantation-related costs as used in the company base-case analysis are shown in Table 5.25.

Table 5.25: Costs of combined liver and kidney transplantation and other transplantation-related costs as used in the company base-case model.

Cost	Paediatric population	Adult population	Source
Combined liver and kidney transplantation (one-off)	£56,566.33	£35,028.41	National Schedule of NHS Costs 2019/2020[132]
Post-transplant monitoring (per cycle)	£280.56		National Schedule of NHS Costs 2019/2020[132]
Post-transplant immunosuppression (per cycle)	£102.70		Assumed immunosuppressive treatment with prednisone. Jones-Hughes 2016 for dosing scheme (16.3 mg per day);[139] MIMS for drug price prednisone 10 mg × 28 tablets of £9.66.[140]
Graft failure (one-off)	£3,724.04		National Schedule of NHS Costs 2019/2020[132]
Re-transplantation (one-off)	£28,560.86	£17,765.26	National Schedule of NHS Costs 2019/2020[132]

Based on Table D33 of the CS[1]
CS = company submission; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service

5.3.3.8.7 Disease monitoring costs

The analysis included the costs of laboratory tests, procedures and visits for disease monitoring, for which the unit costs (i.e. provided in Table D34 of the CS) were sourced (as weighted averages where applicable) from the NHS Reference costs 2019/2020 and the frequencies of use (i.e. as provided in Table 10 and Table 11 in Appendix 5) were estimated for each health state in the model from a survey with UK clinical experts.[141] The total, per-cycle costs for disease monitoring are provided for each health state in the model in Table 5.26.

Table 5.26: Disease monitoring costs per health state

Health state	Paediatric population	Adult population
CKD 1–2	£215.24	£139.33
CKD 3a	£217.83	£141.92
CKD 3b	£220.41	£144.51
CKD 4	£1,525.57	£444.83
ESKD	£4,299.29	£747.08

Based on Table D35 of the CS[1]
CKD = chronic kidney disease; CS = company submission; ESKD = end-stage kidney disease

5.3.3.8.8 Adverse event costs

The costs of managing AEs were sourced from the NHS Reference costs 2019/2020 and are provided in Table 5.27 below.[132]

Table 5.27: Adverse event costs

Adverse event	Cost	Source
Headache	£403.42	National Schedule of NHS Costs 2019/2020[132]
Injection-site erythema	£266.93	
Injection-site pain	£266.93	
Injection-site reaction	£266.93	
Rhinitis	£266.93	
Upper respiratory infection	£324.94	
Based on Table D36 in the CS.[1] CS = company submission; NHS = National Health Service		

5.3.3.8.9 End-of-life costs

A one-off end-of-life cost was applied to all newly died patients in the model, which was sourced from the PSSRU 2020.[133] This cost of £4,200.00 was stated to be equivalent to the costs of five inpatient days with specialist palliative care of £398.00 per day and five outpatient medical specialist visits of £202.00 per visit.

5.3.3.9 Expert opinion elicitation

The company commissioned a study led by Tolley Health Economics to elicit clinical expert opinion that could be used to inform and validate the inputs used in the CEA model.[116] A structured expert exercise (SEE), using questionnaires and interviews, was conducted with three clinical experts from the UK that had recent experience in treating patients with PH1 in the UK and were considered to have the relevant, up-to-date, knowledge and experience of PH1. The experts were an adult nephrologist, a paediatric nephrologist and a transplant surgeon. These experts provided estimates for the frequencies of use of various health care resources (i.e. laboratory tests, procedures and visits), the use of specific dialysis regimens and resource use related to liver and combined liver and kidney transplantation. The two nephrologists provided estimates for all aspects, whereas the transplant surgeon only provided estimates for dialysis- and transplantation-related aspects.

5.3.3.9.1 Management of chronic kidney disease

The experts provided estimates for the frequencies of use (through a combination of estimates of frequencies for patients utilising each resource and proportions of patients utilising each resource) for various specialist visits, laboratory tests, and procedures for the management of CKD. Separate estimates were provided for CKD stages 1-3a (eGFR ≥45), CKD 3b (30 ≤ eGFR ≤44), CKD 4 (15 ≤ eGFR ≤ 29) and CKD 5 (eGFR < 15) / ESKD. The means and ranges of frequencies as estimated by the experts are provided in Tables 1 to 4 of the study report,[116] and the inputs as used in the CEA model are provided in Table 10 (monthly frequencies) and Table 11 (annual frequencies) of Appendix 5 in the CS.[1]

ERG comment: The ERG notes that the mean frequency estimates were rarely used as inputs in the model. Instead, for most resources the company opted to use the lowest estimates. In exceptional instances the company opted for the highest estimate or deviated from the expert estimates altogether. The same inputs were mostly used for both adult and paediatric patients, except for the ESKD health state. No justification was provided for the choices made in using the expert estimates as inputs for the CEA model. The ERG considers that in absence of a rationale to use either of the two estimates for a

given resource, the mean estimates would be most appropriate to use. Otherwise, it could have made sense to use the estimates from the adult nephrologist for the adult population and the estimates from the paediatric nephrologist for the paediatric population. The ERG considers the current use of expert opinion in the model to lack justification and can therefore not confirm its appropriateness. As such, this remains a source of uncertainty.

5.3.3.9.2 Rates of renal stone events

Data from ILLUMINATE-A indicate that for patients with CKD stages 1-3b who have non-normal UOx levels the annual rate of renal stone events is [redacted]. The experts were asked whether it is reasonable to assume the same rate for patients with CKD stages 4-5. The adult nephrologist agreed to this, whilst the paediatric nephrologist suggested a lower rate [redacted]. Aggregating the two estimates resulted in a mean annual rate of [redacted].

ERG comment: The company did not use expert opinion on the rates of renal stone events. Instead, the company used the inputs as provided in Table 5.13 in Section 5.3.3.5.8. The company did not further refer to the estimates as provided by the experts.

5.3.3.9.3 Proportions of patients with systemic oxalosis complications

The nephrologist experts provided estimates of the proportions of patients with systemic oxalosis complications in CKD stages 4 and 5, of which the mean values were used in the model for patients with uncontrolled oxalate levels. The company assumed a [redacted] reduction in proportions for patients with controlled oxalate levels, which they stated was based on clinical opinion, although no information on this was available from the study report. The proportions as used in the model are provided in Table 5.14 in Section 5.3.3.5.9.

The transplant surgeon, who did not provide estimates of the proportions of patients with systemic oxalosis complications in CKD stages 4 and 5, noted that an estimated 80% of patients would see a complete resolution of bone complications, usually within two years, whilst cardiac and cutaneous/vascular complications would be expected to be resolved in around 50% of patients' post-transplant. Patients who experienced ophthalmologic or neurological complications could experience symptoms or problems relating to these even 20 years post-transplant. This information was not referred to in the CS.[1]

ERG comment:

It is not clear what the assumed reduction for patients with controlled oxalate levels is based on. It is also not clear whether and, if so, how, the additional information provided by the transplant surgeon was used to inform the model.

5.3.3.9.4 Dialysis regimens used by patients with PH1

The experts provided estimates of the proportions of patients in CKD 4 and ESKD who make use of dialysis regimens (i.e. either haemodialysis, peritoneal dialysis or a combination thereof, for various days per week). The mean proportions are provided in Table 5.28. It was noted that there are currently [redacted] patients with PH1 receiving dialysis for six days per week. Still, the experts estimated that dialysis for six days a week may be considered for [redacted] of the patients and that peritoneal dialysis (for an expected seven days per week) may be considered for [redacted] of the patients in ESKD, i.e. but not in CKD stage 4.

Table 5.28: Mean estimated proportions of patients receiving dialysis regimens

Dialysis regimen	CKD stage 4	ESKD
Haemodialysis	[redacted]	[redacted]
6 days per week	[redacted]	[redacted]
4 to 5 days per week	[redacted]	[redacted]
≥3 days per week (minimum)	[redacted]	[redacted]
≤3 days per	[redacted]	[redacted]
Peritoneal dialysis	[redacted]	[redacted]
Proportion of patients receiving dual-modality; haemodialysis plus peritoneal dialysis (expected seven days a week at home)	[redacted]	[redacted]

Based on Table 7 in the Tolley Health Economics study report.[116]
CKD = chronic kidney disease; ESKD = end-stage kidney disease

The proportions of patients receiving various dialysis regimens that were assumed in the model are provided in Table 5.29. The company assumed that all patients in the ECM arm (i.e. both CKD 4 and ESKD) receive high-intensity dialysis. In the lumasiran arm no patients with CKD 4 receive any type of dialysis and all patients in ESKD receive normal-intensity dialysis.

Table 5.29: Proportions of patients receiving various dialysis regimens in the model

Population	Dialysis	Probability
High-intensity dialysis		
Paediatric	Haemodialysis, 7×week	[redacted]
	Haemodialysis, 6×week plus peritoneal dialysis 7×week	[redacted]
Adult	Haemodialysis, 7×week	[redacted]
	Haemodialysis, 6×week plus peritoneal dialysis 7×week	[redacted]
Normal-intensity dialysis		
Paediatric	Haemodialysis, 3×week	[redacted]
	Peritoneal dialysis 7×week	[redacted]
Adult	Haemodialysis, 3×week	[redacted]
	Peritoneal dialysis 7×week	[redacted]

Based on Table D18 of the CS[1]
CS = company submission

ERG comment: Despite the notion that there are currently [redacted] patients with PH1 receiving dialysis for six days per week and the experts' estimates that haemodialysis for six days a week may be considered for [redacted] of the patients and peritoneal dialysis (for an expected seven days per week) may be considered for [redacted] of the patients in CKD 5 (i.e. but not in CKD stage 4), the company assumed that all patients in the ECM arm in CKD 4 and ESKD receive dialysis (either haemodialysis or combined haemodialysis and peritoneal dialysis) for seven days per week. As such, this assumption is in sharp contrast with the

experts' estimates, lacks justification and can therefore not be considered plausible. It is not clear what the inputs for patients in the lumasiran arm receiving normal-intensity dialysis are based on.

5.3.4 Model evaluation

The health economic analyses results are presented in terms of the incremental QALYs and incremental costs for lumasiran compared to ECM. The CS also included the results of one-way deterministic sensitivity analyses and a probabilistic sensitivity analysis (PSA). In the deterministic one-way sensitivity analysis parameters were varied one by one using the upper and lower bounds of 95% CIs. If no standard error was available to calculate the 95% confidence interval, a standard error of 10% of the mean value was assumed. A list of all input including the upper and lower bounds and distributions for the PSA can be found in Table D24 of the CS.[1]

The ICER was recorded for each upper and lower bound, and the 10 parameters with the largest impact on the ICER were presented in a tornado diagram. In the PSA, probability distributions were assigned to the model input parameters to assess the uncertainty around all parameters simultaneously. The PSA was conducted using 1,000 simulations. Results were recorded in the form of incremental costs and incremental QALYs and were plotted on a cost-effectiveness plane. A cost effectiveness acceptability curve (CEAC) was estimated from the results of the PSA. Finally, several scenario analyses were also explored by the company to assess the impact of varying modelling assumptions on the cost effectiveness results.

5.4 Headline results reported within the CS

This Section summarises the results of the economic analyses as presented in the CS and, when relevant, in the response to the clarification letter.[1, 51, 52]

5.4.1 Deterministic results of the company (base-case)

The discounted company base-case results using the proposed PAS discount of [redacted]% for lumasiran are summarised in Table 5.30. Lumasiran accrued [redacted] incremental QALYs compared to ECM at an additional cost of [redacted]. This corresponds to an ICER of [redacted] per QALY gained. Note that the CE results were calculated as a weighted average of the results from the paediatric and adult cohorts, where the weighting was based on the proportion of paediatric patients obtained from the pooled ILLUMINATE-A and ILLUMINATE-B trials.

Table 5.30: Company discounted base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	22.78	[redacted]				
Lumasiran	[redacted]	23.94	[redacted]	[redacted]	1.16	[redacted]	[redacted]

Based on Table D37 of the CS[1]
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

The undiscounted company base-case results are presented in Table 5.31. These results are relevant because lumasiran accrued [redacted] undiscounted incremental QALYs compared to ECM. For highly specialised technologies with a gain in QALYs equal or above [redacted], a weighting of [redacted] can be used to calculate a weighted threshold.[142] In this case, the resulting threshold after applying a QALY weighting of [redacted] is [redacted] per QALY gained.

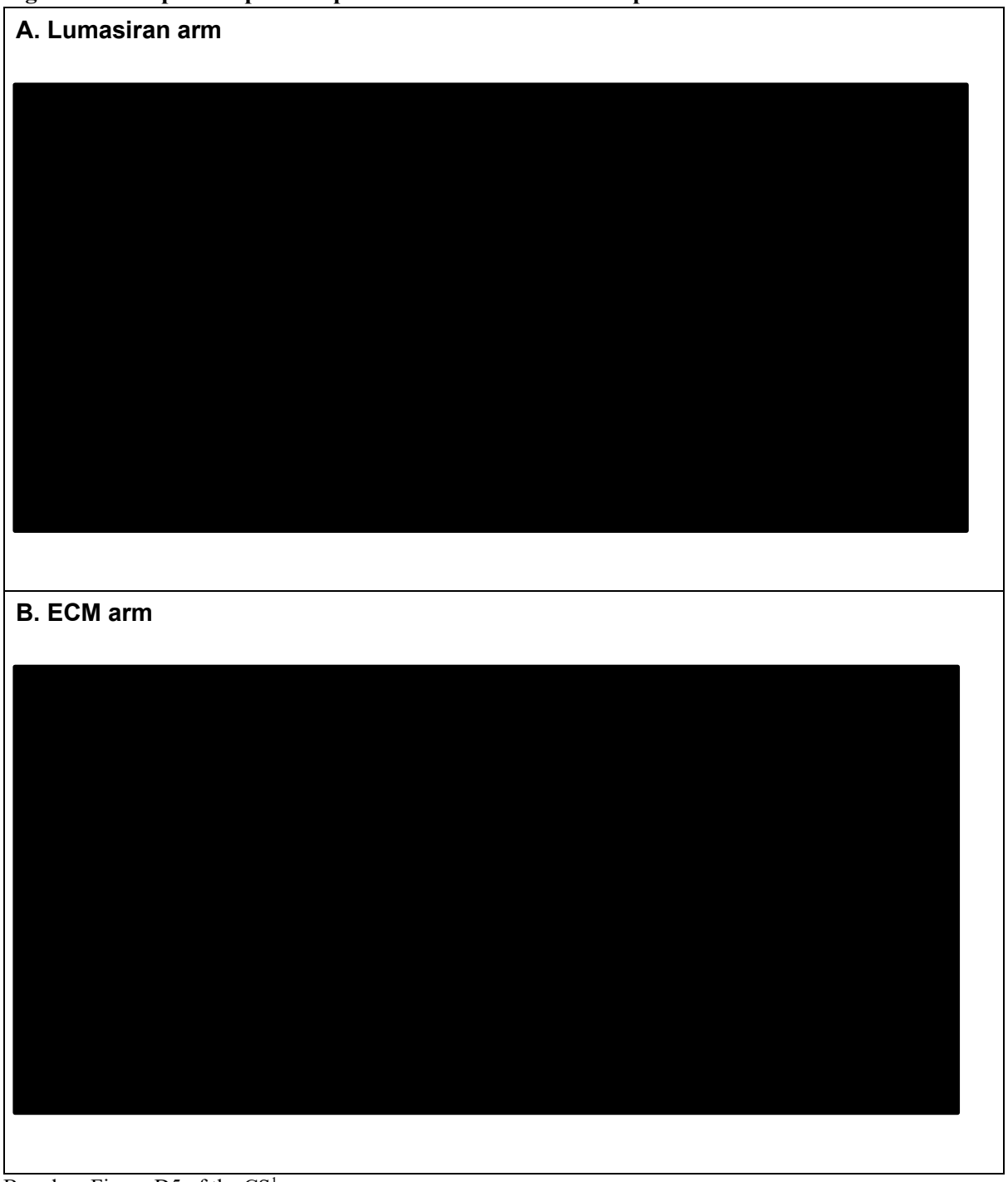
Table 5.31: Company undiscounted base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	49.03	[redacted]				
Lumasiran	[redacted]	57.48	[redacted]	[redacted]	8.45	[redacted]	[redacted]

Based on Table D37 of the CS[1]
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

The distribution of patients per health-state over time, in both the lumasiran and ECM arms, are shown in Figures 5.5 and 5.6 for the paediatric and the adult cohorts, respectively. The model predicts that more patients receiving lumasiran remain in the health state CKD 3b or better compared to ECM. Also, lumasiran patients spend more time in the "controlled" health states (CKD 4-Ox_C, ESKD-Ox_C and cLKT-Ox_C), as opposed to ECM patients being in the "uncontrolled" ones (CKD 4-Ox_U, ESKD-Ox_U and cLKT-OxU). The exact proportions of patients per health state over time of the overall cohort across for both arms are not presented here but can be found in Tables D38 and D39 of the CS, respectively.[1] The distribution of undiscounted LYG per health state is summarised in Table 5.32.

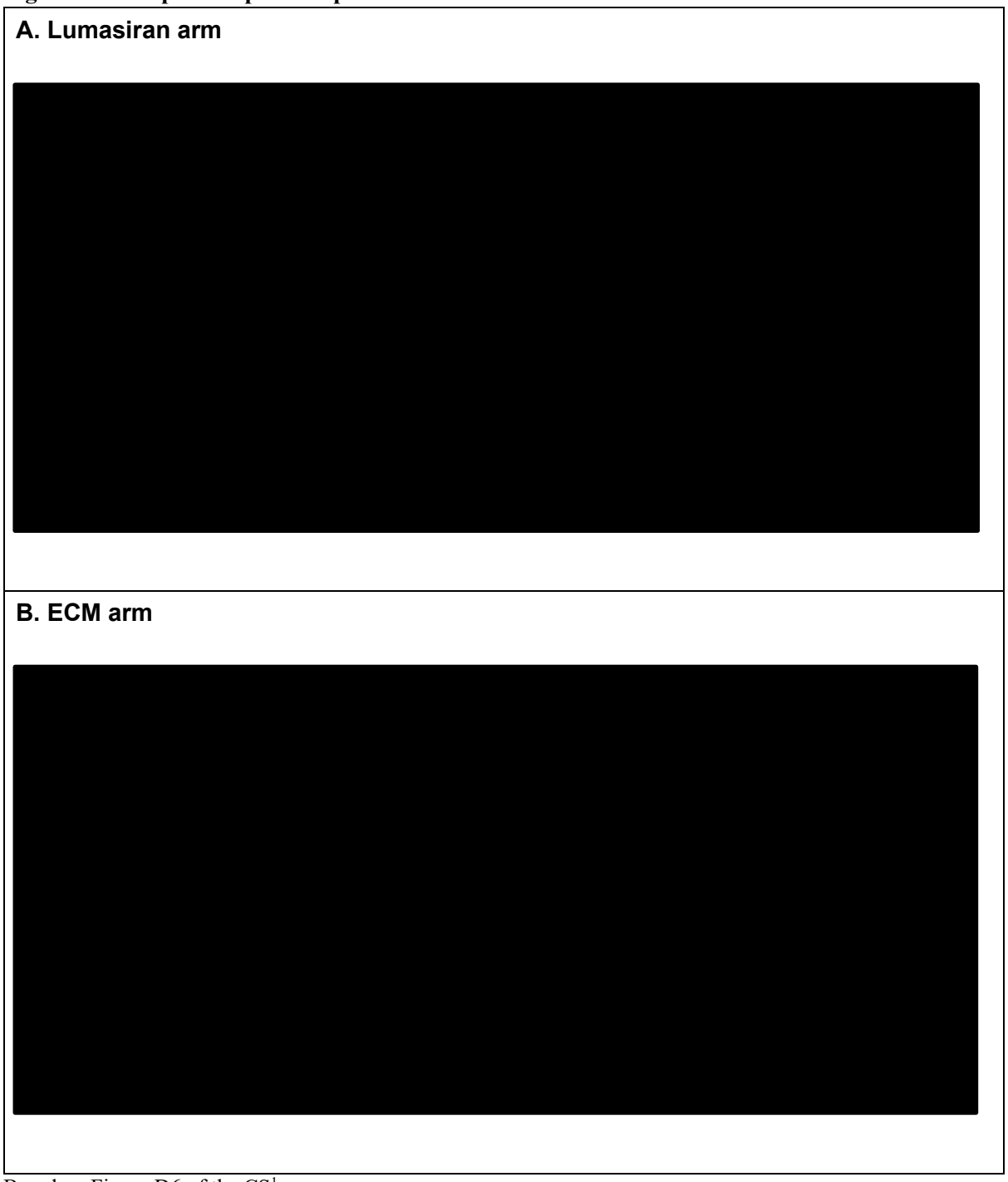
Figure 5.5: Proportion patients per health states over time – paediatric cohort



Based on Figure D5 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

Figure 5.6: Proportion patients per health states over time – adult cohort



Based on Figure D6 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

Table 5.32: Undiscounted LYG per health state

Technologies	CKD 1-2	CKD 3a	CKD 3b	CKD 4-Ox_C	CKD 4-Ox_U	ESKD-Ox_C	ESKD-Ox_U	cLKT-Ox_C	cLKT-Ox_U	Total
ECM	2.43	1.32	1.61	0.00	12.37	0.00	27.55	0.00	3.75	49.03
Lumasiran	23.22	7.25	6.85	0.29	1.04	0.84	1.33	16.44	0.22	57.48
Difference	20.78	5.93	5.23	0.29	–11.33	0.84	–26.22	16.44	–3.52	8.45

Based on Table D40 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; LYG = life-years gained; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

The distribution of discounted QALYs per health state over time, in both the lumasiran and ECM arms, are shown in Figures 5.7 and 5.8 for the paediatric and the adult cohorts, respectively. Since the model predicts that lumasiran patients remain in the better health states compared to ECM, it is not surprising that more QALYs are accrued for lumasiran. Also note, that since ECM patients spent a substantial numbers of life years in the "uncontrolled" health states (see Table 5.32), negative QALYs are accrued over time in the ECM arm. The distribution of undiscounted QALYs per health state over time is not presented here but can be found in Figure D9 and D10 of the CS for the paediatric and adult cohorts, respectively.[1] Disaggregated discounted QALYs per health state are summarised in Table 5.33. It can be seen that, [redacted] Disaggregated undiscounted QALYs are not presented here but can be found in Table D42 of the CS.[1]

Figure 5.7: Discounted QALYs over time – paediatric cohort

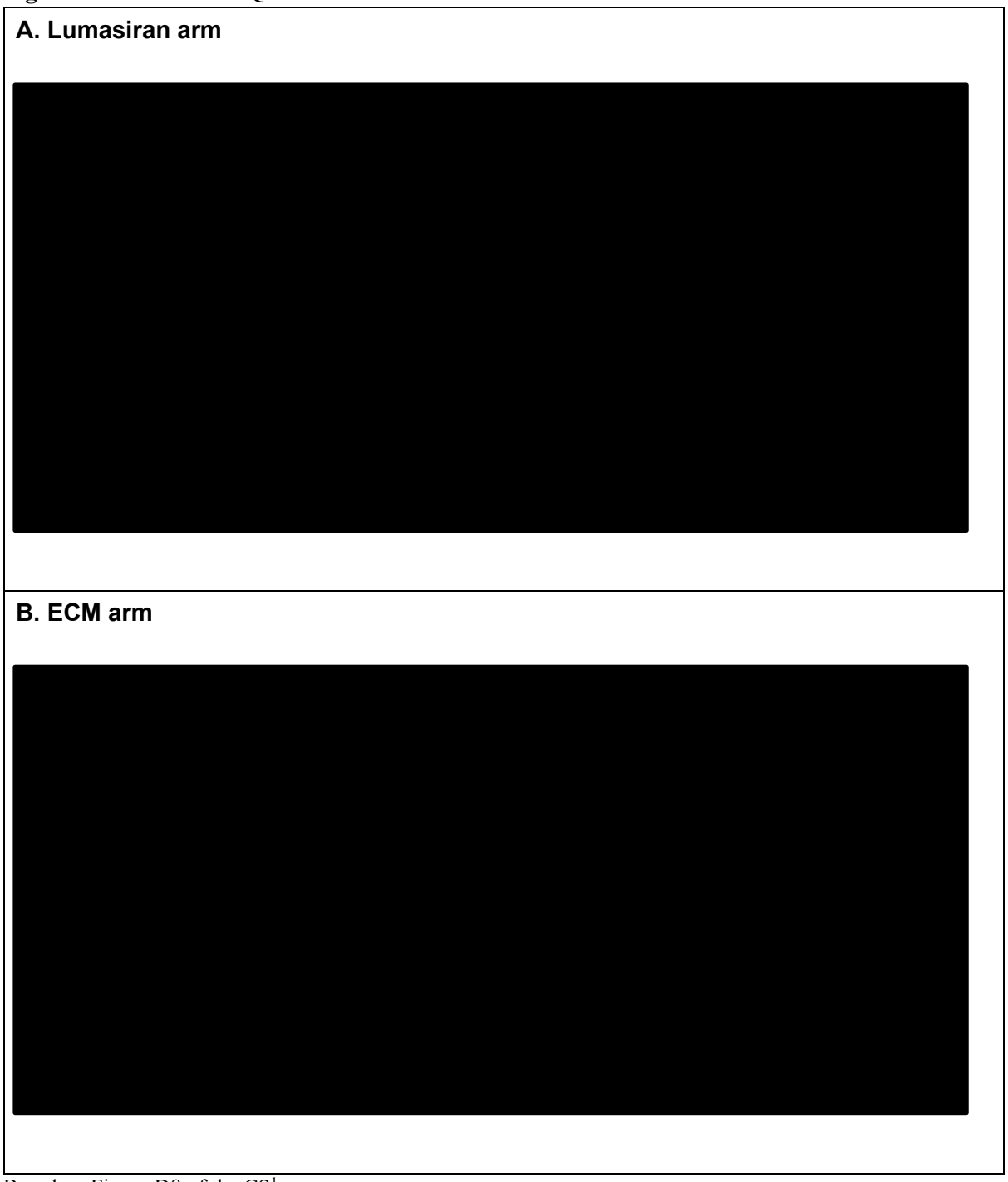
A. Lumasiran arm

B. ECM arm

Based on Figure D7 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate; QALY = quality-adjusted life-years

Figure 5.8: Discounted QALYs over time – adult cohort



Based on Figure D8 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate; QALY = quality-adjusted life-years

Disaggregated discounted costs per cost category and health state are presented in Tables 5.34 and 5.35, respectively. It can be seen that the vast majority of the additional costs associated to lumasiran are due to drug acquisition costs. On the other hand, lumasiran results in substantial cost savings compared to ECM in terms of dialysis avoided and, to a much lower extent, in the reduced number of systemic oxalosis complications. Disaggregated undiscounted costs per cost category and health state are not presented here but can be found in Table D43 and D45 of the CS, respectively.[1]

Table 5.33: Discounted QALYs per health state

Technologies	CKD 1-2	CKD 3a	CKD 3b	CKD 4-Ox_C	CKD 4-Ox_U	ESKD-Ox_C	ESKD-Ox_U	cLKT-Ox_C	cLKT-Ox_U	Total
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table D41 of the CS[1]
CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; LYG = life-years gained; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

Table 5.34: Discounted costs (£) per cost category

Category	Lumasiran	ECM	Difference
Drug	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Based on Table D44 of the CS[1]
AE = adverse event; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management

Table 5.35: Discounted costs (£) per health state

Technologies	CKD 1-2	CKD 3a	CKD 3b	CKD 4-Ox_C	CKD 4-Ox_U	ESKD-Ox_C	ESKD-Ox_U	cLKT-Ox_C	cLKT-Ox_U	Total
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table D46 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; LYG = life-years gained; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

5.4.2 Sensitivity analyses presented within the company's submission

The company conducted one-way deterministic and probabilistic sensitivity analyses, as well as a number of scenario and subgroup analyses. The results of these analyses are summarised in the remainder of this section. Only discounted results are discussed here.

5.4.2.1 One-way deterministic sensitivity analyses

The results of the deterministic one-way sensitivity analysis (OWSA) for lumasiran compared to ECM BSC are presented in the form of a tornado diagram in Figure 5.9, showing the 10 parameters with the largest impact on the ICER. [redacted].

Figure 5.9: One-way sensitivity analysis - ICER results

Based on Figure D11 of the CS[1]
CKD = chronic kidney disease; CS = company submission; ECM = estimated clinical management; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; ICER = incremental cost effectiveness ratio; POx = plasma oxalate; QALY = quality-adjusted life-year

5.4.2.2 Probabilistic sensitivity analysis

The company conducted a PSA using 1,000 Monte Carlo simulations. Average results can be seen in Table 5.36. In the PSA, [redacted]. Individual PSA simulations were plotted in the cost effectiveness (CE) plane shown in Figure 5.10. [redacted]. A CEAC was derived and shown in Figure 5.11. At the threshold ICER of £100,000 per QALY gained, the probability that lumasiran is cost effective compared to ECM was [redacted]%.

Table 5.36: Company probabilistic base-case results

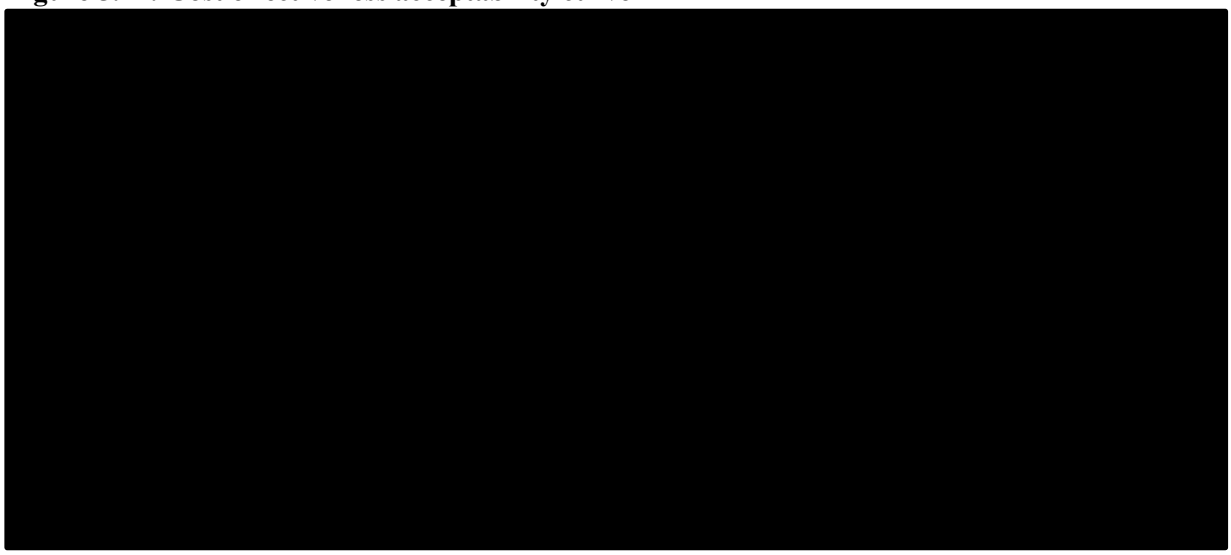
Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	NR	[redacted]				
Lumasiran	[redacted]	NR	[redacted]	[redacted]	NR	[redacted]	[redacted]

Based on electronic model in the original CS[110]
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; NR = not reported; QALY = quality-adjusted life year

Figure 5.10: Probabilistic sensitivity analysis scatterplot company base-case

Based on electronic model in the original CS[110]
CS = company submission; ECM = estimated clinical management; ICER = incremental cost effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 5.11: Cost effectiveness acceptability curve



Based on electronic model in the original CS[110]
CE = cost effectiveness; CS = company submission; QALY = quality-adjusted life-year; WTP = willingness-to-pay

5.4.2.3 Scenario analyses

The company only presented the results of four additional scenario analyses. The scenarios explored are described below and their results summarised in Table 5.37:

- Scenario 1: Differential discounting (1.5% outcomes and 3.5% costs).
- Scenario 2: Distribution at start from Singh 2021 in paediatric and adult separately.[106]
- Scenario 3: Model time to ESKD based on PH1 data from the US RSKC PH registry data by Singh 2021.[106]
- Scenario 4: Worsening of advanced renal disease in the CKD 4-OxC health state.

From the scenarios explored by the company, [redacted]

Table 5.37: Scenario analyses results

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)	Change versus base-case (%)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table D49 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year

ERG comment: Given the limited number of scenarios explored by the company in the main CS, the ERG asked the company in the clarification letter to conduct additional scenario analyses.[50] In their response to clarification question B9,[51, 52] the company identified an error in the economic model. The correction of this error led to a revised base-case, which together with the results of the scenario analyses included in the clarification letter response, are presented in Section 6.1 of the ERG report.

5.4.3 Subgroup analyses

CEAs were also presented for two subgroups of patients: 1) patients of all ages with infantile onset of PH1 and 2) infants with infantile onset of PH1. These subgroups were identified in the final NICE scope as relevant, given the detrimental clinical manifestations of PH1 in children, and the rapid progression to ESKD and greater mortality in patients with earlier clinical onset regardless their current age.[49] Results are presented separately for each subgroup in the remainder of this section. Note that only deterministic results are shown for each subgroup.

5.4.3.1 Patients of all ages with infantile onset of PH1

It is assumed that all patients in the model are paediatric patients since these patients are unlikely to reach adulthood without a transplantation. Values for the initial age and average weight of this subgroup are the same as those used for the paediatric population in the base-case analysis and was derived from ILLUMINATE data. The distribution of patients per CKD health state at baseline was also assumed to be the same as in the base-case analysis and was derived from Singh 2021.[106] Please refer to Table 5.3 for details.

The discounted company results for patients of all ages with infantile onset of PH1 are summarised in Table 5.38. Lumasiran accrued [redacted] incremental QALYs compared to ECM at an additional cost of [redacted]. This corresponds to an ICER of £[redacted] per QALY gained. This represents a [redacted] in the ICER compared to the base-case ICER (Table 5.30). Note that the undiscounted cost effectiveness results are not presented here but these can be seen in Table D50 of the CS.[1] Lumasiran accrued [redacted] undiscounted incremental QALYs compared to ECM, thus [redacted] compared to the base-case. The distribution of undiscounted LYG per health state is summarised in Table 5.39.

The distribution of discounted QALYs per health state over time, in both the lumasiran and ECM arms, are shown in Figure 5.12. The distribution of undiscounted QALYs per health state over time is not presented here but can be found in Figure D15 of the CS.[1] Disaggregated undiscounted QALYs per health state are summarised in Table 5.40. It can be seen that, [redacted] Disaggregated discounted QALYs were not presented in the CS.

Table 5.38: Company discounted base-case results, patients of all ages with infantile onset of PH1

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	24.20	[redacted]				
Lumasiran	[redacted]	24.80	[redacted]	[redacted]	0.60	[redacted]	[redacted]

Based on Table D50 of the CS[1]
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; LYG = life-years gained; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life year

Table 5.39: Undiscounted LYG per health state, patients of all ages with infantile onset of PH1

Technologies	CKD 1-2	CKD 3a	CKD 3b	CKD 4-Ox_C	CKD 4-Ox_U	ESKD-Ox_C	ESKD-Ox_U	cLKT-Ox_C	cLKT-Ox_U	Total
ECM	2.44	1.32	1.62	0.00	3.78	0.00	41.56	0.00	4.47	55.19
Lumasiran	25.90	8.10	7.70	0.25	0.35	0.73	2.36	17.73	0.26	63.37
Difference	23.46	6.78	6.07	0.25	–3.43	0.73	–39.21	17.73	–4.20	8.18

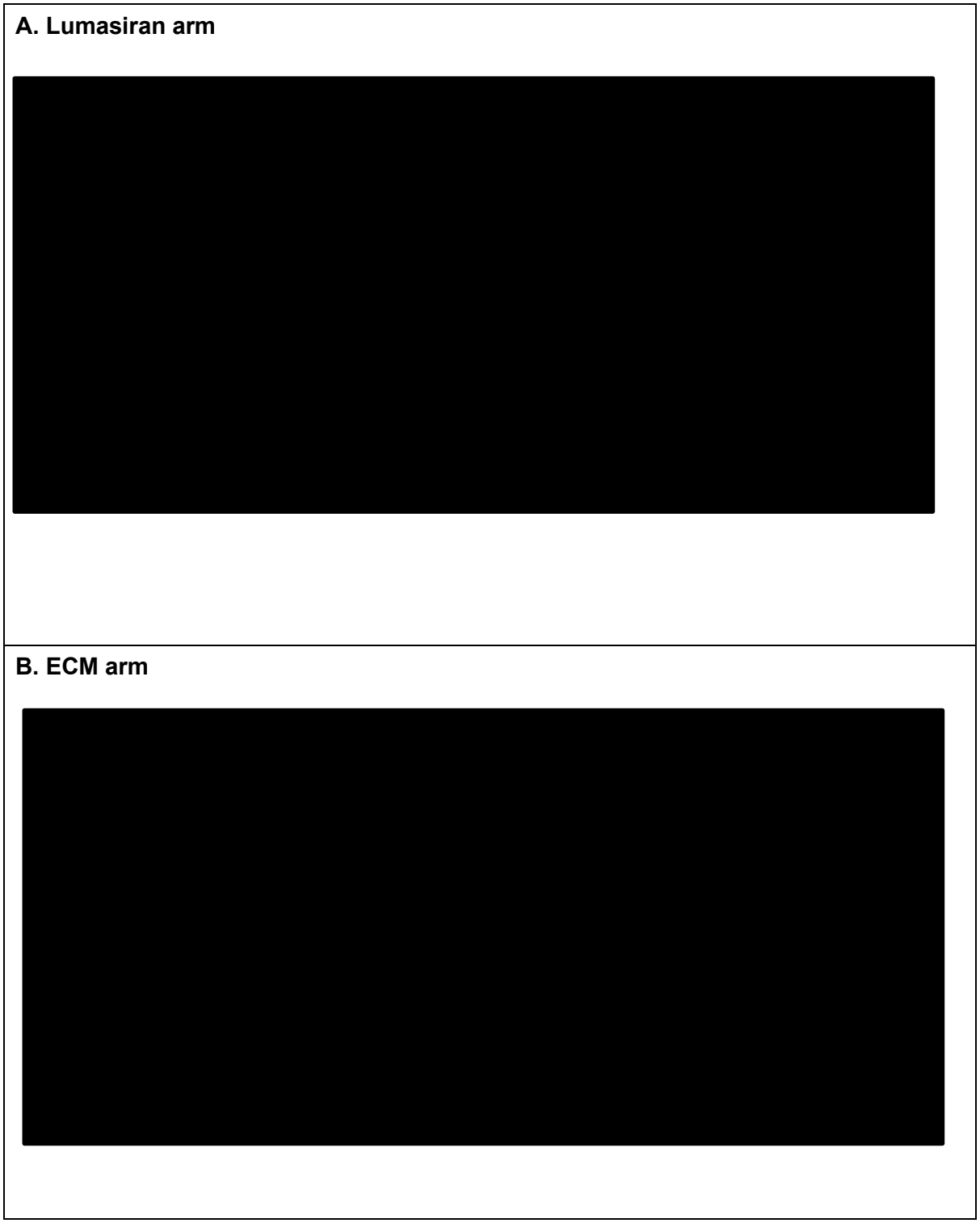
Based on Table D51 of the CS[1]
CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; PH1 = primary hyperoxaluria type 1; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

Table 5.40: Undiscounted QALYs per health state, patients of all ages with infantile onset of PH1

Technologies	CKD 1-2	CKD 3a	CKD 3b	CKD 4-Ox_C	CKD 4-Ox_U	ESKD-Ox_C	ESKD-Ox_U	cLKT-Ox_C	cLKT-Ox_U	Total
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table D52 of the CS[1]
CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; ECM = established clinical management; ESKD = end-stage kidney disease; PH1 = primary hyperoxaluria type 1; OxC = controlled oxalate; OxU = uncontrolled oxalate; QALY = quality-adjusted life years

Figure 5.12: Discounted QALYs over time – patients of all ages with infantile onset of PH1



Based on Figure D14 of the CS[1]
CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; PH1 = primary hyperoxaluria type 1; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate; QALY = quality-adjusted life-years

Disaggregated discounted costs per cost category are presented in Table 5.41. It can be seen that, as in the base-case, the majority of the additional costs associated to lumasiran are due to drug acquisition costs. Lumasiran also results in substantial cost savings compared to ECM in terms of dialysis avoided

and, to a much lower extent, in the reduced number of systemic oxalosis complications. Disaggregated undiscounted costs per cost category are not presented here but can be found in Table D53 of the CS.[1]

Table 5.41: Discounted costs (£) per cost category, patients of all ages with infantile onset of PH1

Category	Lumasiran	ECM	Difference
Drug	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Based on Table D54 of the CS[1]
AE = adverse event; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management

5.4.3.2 Infants with infantile onset of PH1

It is assumed that all patients in the model are infants with severe disease. The age at baseline for these patients was defined as the midpoint of the definition used for infant age, thus 0.5 years.[143] The value for the average weight of this subgroup is the same as the one used for the paediatric population in the base-case analysis and was derived from ILLUMINATE data, since infants are expected to become children within one cycle in the model. Please refer to Table 5.3 for details. The distribution of patients per CKD health state at baseline was assumed to be 10% for CKD 4 and 90% for ESKD. These estimates were based on UK clinical expert opinion as discussed in Section 5.3.3.3. Additionally, a hazard ratio (HR) of 6.0 for progression to ESKD was applied to infants with infantile onset of PH1 compared to patients with non-infantile onset. This HR was based on Harambat 2010.[16]

The discounted company results for infants with infantile onset of PH1 are summarised in Table 5.42. Lumasiran accrued [redacted] incremental QALYs compared to ECM and resulted in [redacted] savings in costs. Thus, lumasiran was dominant compared to ECM for infants with infantile onset of PH1. Note that the undiscounted cost effectiveness results are not presented here but these can be seen in Table D55 of the CS.[1] The distribution of undiscounted LYG per health state is summarised in Table 5.43.

Table 5.42: Company discounted base-case results, infants with infantile onset of PH1

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	24.41	[redacted]				
Lumasiran	[redacted]	21.67	[redacted]	[redacted]	–2.74	[redacted]	[redacted]

Based on Table D55 of the CS[1]
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; LYG = life-years gained; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life-year

The distribution of discounted QALYs per health state over time, in both the lumasiran and ECM arms, are shown in Figure 5.13. The distribution of undiscounted QALYs per health state over time is not presented here but can be found in Figure D17 of the CS.[1] Disaggregated undiscounted QALYs per health state are summarised in Table 5.44. It can be seen that, [redacted] Disaggregated discounted QALYs were not presented in the CS.

Table 5.43: Undiscounted LYG per health state, infants with infantile onset of PH1

Technologies	CKD 1-2	CKD 3a	CKD 3b	CKD 4-Ox_C	CKD 4-Ox_U	ESKD-Ox_C	ESKD-Ox_U	cLKT-Ox_C	cLKT-Ox_U	Total
ECM	0.00	0.00	0.00	0.00	0.67	0.00	52.73	0.00	5.69	59.08
Lumasiran	0.00	0.00	0.00	0.25	0.04	2.31	0.37	48.26	0.09	51.33
Difference	0.00	0.00	0.00	0.25	–0.63	2.31	–52.36	48.26	–5.59	–7.75

Based on Table D56 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; LYG = life-years gained; PH1 = primary hyperoxaluria type 1; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

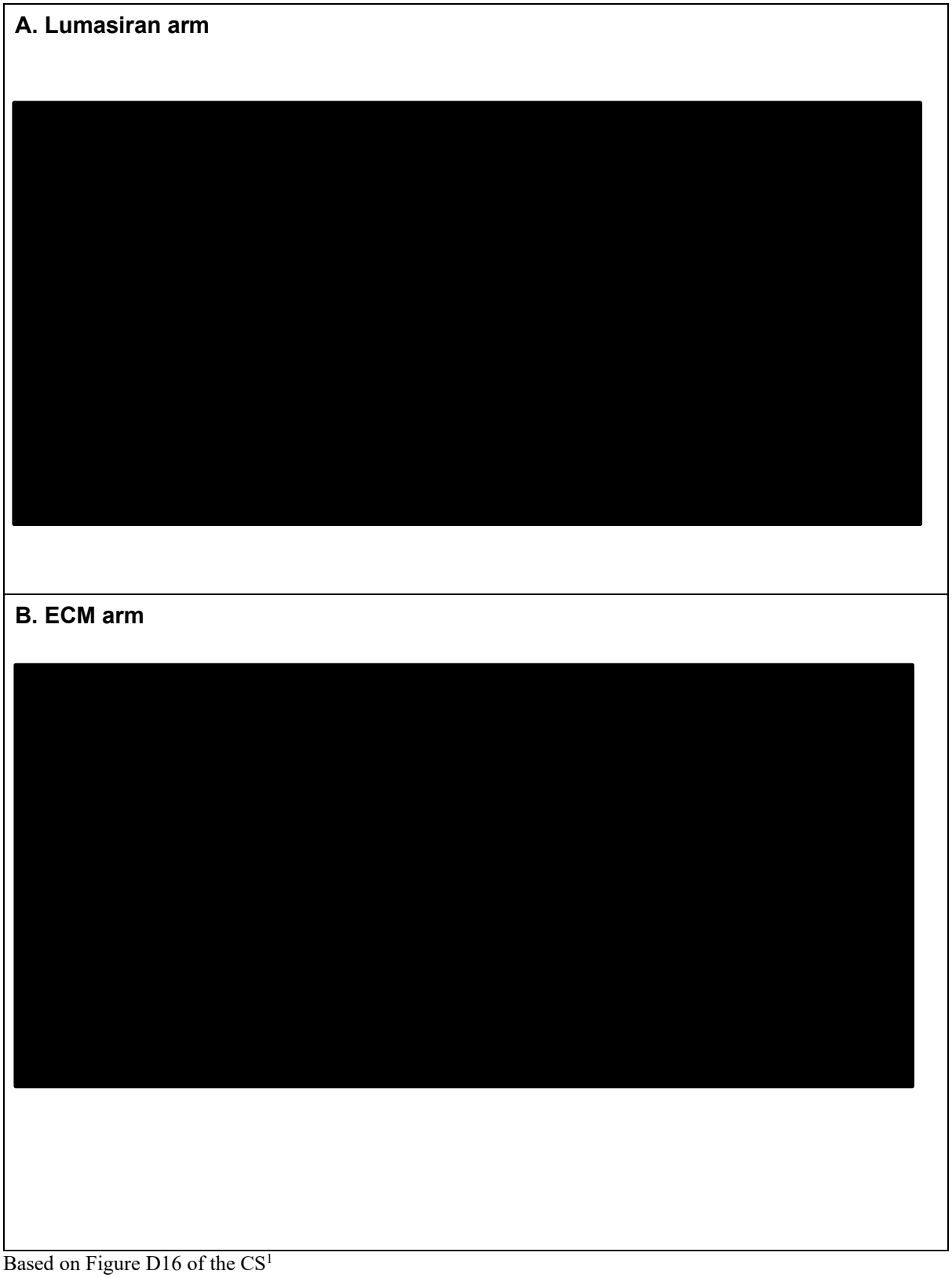
Table 5.44: Undiscounted QALYs per health state, infants with infantile onset of PH1

Technologies	CKD 1-2	CKD 3a	CKD 3b	CKD 4-Ox_C	CKD 4-Ox_U	ESKD-Ox_C	ESKD-Ox_U	cLKT-Ox_C	cLKT-Ox_U	Total
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table D56 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management; ESKD = end-stage kidney disease; LYG = life-years gained; PH1 = primary hyperoxaluria type 1; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate

Figure 5.13: Discounted QALYs over time – infants with infantile onset of PH1



Based on Figure D16 of the CS[1]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplantation; ECM = established clinical management; ESKD = end-stage kidney disease; PH1 = primary hyperoxaluria type 1; Ox_C = controlled oxalate; Ox_U = uncontrolled oxalate; QALY = quality-adjusted life-year

Disaggregated discounted costs per cost category are presented in Table 5.45. It can be seen that, as in the base-case, the majority of the additional costs associated to lumasiran are due to drug acquisition costs. Lumasiran also results in substantial cost savings compared to ECM in terms of dialysis avoided and, to a lower extent, in the reduced number of systemic oxalosis complications and monitoring. Disaggregated undiscounted costs per cost category are not presented here but can be found in Table D58 of the CS.[1]

Table 5.45: Discounted costs (£) per cost category, infants with infantile onset of PH1

Category	Lumasiran	ECM	Difference
Drug	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
Renal stone event	[redacted]	[redacted]	[redacted]
Systemic oxalosis complications	[redacted]	[redacted]	[redacted]
Post-cLKT	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Based on Table D59 of the CS[1]
AE = adverse event; cLKT = combined liver–kidney transplantation; CS = company submission; ECM = established clinical management

5.4.4 Validation

The company indicated in Section 12.7 of the CS that the model has been quality checked. The quality checklist used to assess the CE model of lumasiran in PH1 was based on the transparency and validation checklist in "Modeling Good Research Practices" by Caro et al. 2012.[144]

PH1 is a rare disease and published UK-specific HCRU data were not available. Structured interviews were used to elicit HCRU estimates from UK clinical experts. The key objective of this study was to elicit up to date and detailed HCRU estimates associated with the long-term management of PH1 for use as input data to a health economic model to assess the cost-effectiveness of lumasiran for HTA purposes, relevant to the UK.

Separately, the company solicited expert opinion to validate key model inputs and assumptions from a clinical perspective. Two UK-based clinical experts were approached to participate in web-based interviews. A consultant paediatric nephrologist was interviewed once, and a consultant nephrologist was interviewed twice. Those interviews covered key model inputs and assumptions.

ERG comment: The checklist used by the company in their model validation process is quite elaborate and it was filled in comprehensively. It should be remarked though that it only covers the technical validation of the model, it does not provide information on the conceptual validity and the operational (internal and external) validity.

The interviews covered some important aspects of conceptual validity, which is critical when modelling a disease for which no model yet exists. It was surprising though, to not see any report about a discussion how to conceptually map the surrogate outcome plasma oxalate to kidney functioning. The fact that the

model only sees increase in plasma oxalate as a cause for eGFR decrease, and does not incorporate length of exposure to above-normal plasma oxalate levels might point to a non-optimal approach to conceptual validation.

It is unfortunate that no attempts for internal validation were part of the validation process (or at least not reported as part of the validation process); that no extensive external validation took place is understandable given the very small patient population and only limited options for treatment for these patients.

5.5 Discussion of the available evidence relating to value for money for the NHS and PSS

In patients with PH1, there is a hepatic overproduction of oxalate that leads to toxic crystal deposits in the kidneys. This causes a progressive loss of renal function, kidney damage, increase in the occurrence of renal stones and systemic oxalosis complications. The subsequent loss of renal clearance of oxalate creates a feedback loop resulting in an acceleration of further kidney damage and oxalate accumulation. Through targeting a liver-specific enzyme to prevent the formation of a key substrate for oxalate synthesis, lumarisan reduces hepatic oxalate production and is therefore expected to halt the disease.

The key aspects of the CEA model pivot around the progressive nature of PH1 in absence of effective treatment, with patients transitioning over time to increasingly more severe health states defined as stages of CKD, and lumasiran being able to halt disease progression so that patients no longer transition to more severe health states.

An appropriate measure of kidney function is the eGFR, but to detect changes in eGFR that are representative of a clinical effect it would require an RCT with a relatively large sample size (approximately [redacted] patients) and [redacted] follow-up. Such a sample size is not feasible for an orphan disease, therefore an appropriate surrogate outcome is required. For this, plasma oxalate levels were used.

An important shortcoming of the company's approach in using plasma oxalate levels as a surrogate outcome for kidney function in PH1 is that it assumes that disease progression (in term of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on increased plasma oxalate levels that are steady yet sustained over time. The ERG considers it likely that disease progression also occurs in patients who sustain a steady, but increased, plasma oxalate level over time.

The progressive nature of the disease was modelled based on the changes in plasma oxalate levels as observed in patients receiving ECM in ILLUMINATE-A over 6 months of follow-up in combination with the relationship between plasma oxalate and eGFR as published by Shah et al. 2020.[34] This allowed the observed increase in plasma oxalate to be translated into an estimated reduction in eGFR per 6-months model cycle. From this it was calculated how many cycles would be needed to transition between CKD health states, the inverse of which provided the transition probabilities.

Since no increases, but rather decreases, in plasma oxalate were observed in patients who received lumasiran in ILLUMINATE-A and ILLUMINATE-B, also no decreases in eGFR were modelled for patients receiving lumasiran. As such, lumasiran is effectively modelled to halt disease progression. When patients discontinue treatment with lumasiran, they switch to the transition probabilities used for ECM. The model did not allow for increases in eGFR, which can be considered as conservative given observed reductions in plasma oxalate in patients receiving lumasiran in ILLUMINATE and the relationship between eGFR and plasma oxalate.

For patients receiving ECM, who have uncontrolled oxalate levels, the transition from CKD 4 to ESKD was modelled using a Gompertz parametric curve fitted to data derived from the ESKD-free KM survival curves published by Harambat et al. 2010.[16] Since the Harambat et al. study included patients who were in less severe CKD stages (i.e. further from progression to ESKD) than CKD 4, this likely represents a conservative approach. As described above, patients receiving lumasiran who have controlled oxalate levels, were assumed not to transition to ESKD.

Although patients receiving lumasiran could not transition to more severe CKD health states, patients starting treatment in late-stage disease (i.e. CKD 4 or ESKD) health states with plasma oxalate levels above 50 µmol/l (labelled uncontrolled oxalate) could transition to health states based on the same CKD stage but with plasma oxalate levels below 50 µmol/l (labelled uncontrolled oxalate). This transition probability was estimated using data from patients with CKD 4 and ESRD in ILLUMINATE-C on mean baseline plasma oxalate and mean reductions in plasma oxalate as observed over 6 months. This allowed an estimation of the number of cycles needed to transition that was converted into a transition probability. The ERG noted that an error appears to have been made in this calculation and corrected it. This resulted in a higher transition probability, favouring the intervention.

Patients in CKD 4 and ESKD may receive a cLKT to stop hepatic oxalate overproduction and restore kidney function. Since patients with controlled oxalate are likely to be considered better candidates for transplantation than patients with uncontrolled oxalate, the company assumed the same transplantation rate for patients with controlled oxalate as non-PH1 CKD patients. The cLKT transplantation rate was estimated by combining data on the 3-year rates of liver and kidney transplantations from NHS Blood and Transplant 2021.[113, 114] The company assumed that 100% of patients with controlled oxalate in CKD 4 and ESKD would be placed on a waiting list. For patients in CKD 4 and ESKD with uncontrolled oxalate, the cLKT transplantation rate was estimated based on a study by Compagnon et al. 2014.[115] This yielded a transplantation rate that was about 30 times smaller than for the controlled patients and translated in an average time until transplantation of around 80 years. The ERG found this very unrealistic, and hence choose to use the same approach as for controlled patients, but with the assumption that only 50% of patients would be deemed eligible for transplantation and put on the waiting list. A low probability of re-transplantation was modelled based on data from Compagnon et al. 2014.[115]

The model took also take the development of renal stones into account in the model, with event rates based on data from the pivotal clinical studies. In contrast, the occurrence of complications related to systemic oxalosis and the frequency and intensity of dialysis in the CKD 4 and ESKD health states were based on interviews with clinical experts.

Mortality was modelled by applying mortality multipliers reported by Go et al. to the general population mortality.[118] Mortality after cLKT was based on observational data as reported by Jamieson 2005.[104] It was assumed by the company that patients who had well controlled plasma oxalate before the transplantation would have a higher chance of survival than patients who has been uncontrolled. As Jamieson reported survival stratified by pre-transplantation condition, the survival of the patients in the best two strata were applied to controlled patients in the model, and of the worst two strata to uncontrolled patients. The ERG considers this incorrect since the whole patient population in the Jamieson 2005[104] study effectively represents ECM.

For the estimation of utility values for the health states and disutilities for events, complications and for dialysis, the company used various sources. For the utility of CKD 1-2, CKD 3a, and CKD 3b, EQ-5D data from the ILLUMINATE A study was used. For renal stone events and adverse events utility data were derived from the literature. For the estimation of the utility for CKD 4 and ESKD with

uncontrolled oxalate on high-intensity dialysis, a vignette study was done, where the general public filled out de EQ-5D for each health state (to which the UK tariff was subsequently applied), score the vignette on the VAS, and performed a TTO exercise to arrive at a utility value. For CKD 4 and ESKD with controlled oxalate utilities from the literature were used. Utilities for patients after transplantation were also obtained from the vignette study. Additionally, a one-off disutility was applied for the burden of the transplantation for a period of 91 days, based on literature.[122] The company also applied a disutility associated with graft failure which was derived from literature.[123] For patients in the CKD 4 and ESRD health states a disutility per caregiver of [redacted].[131]

The ERG had doubts regarding the choice of the EQ-5D based valuation of the vignettes instead of the TTO derived utilities. From a methodological point of view, it is not fully clear which option should be preferred, though the ERG would argue that in this instance the TTO valuation should be preferred. However, when comparing those health states that had both observed utilities through direct application of the EQ-5D and utilities values based on the vignette study, it was clear that the TTO valuations of the vignettes were much better aligned with those measured in the ILLUMINATE-A study.

Resource use for the various health states, events and complications were based on expert elicitation. However, it was for many items unclear how the company arrived at the preferred value for the resource use. As lumasiran is administered based on weight and only available in one vial size, the ERG asked the company how much of the drug would be wasted on average.[50] They explained that on average [redacted] mg and [redacted] mg of lumasiran is wasted for the paediatric and adult population, with corresponding costs due to wastage of [redacted] and [redacted] per administration, respectively.[51]

The discounted company base-case results using the proposed PAS discount of [redacted]% for lumasiran showed that lumasiran accrues [redacted] incremental QALYs compared to ECM at an additional cost of [redacted]. This corresponds to an ICER of £[redacted] per QALY gained.

The undiscounted gain in QALYs with lumasiran was [redacted] can be used to calculate a weighted threshold (of [redacted]).

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 New company analyses after the request for clarification

6.1.1 Revised company base-case

During the clarification phase, the ERG asked the company about the probability of transplantation for CKD 4 and ESKD patients. For the patients in the lumasiran group, for the CKD 4-Ox_C and ESKD-Ox_C patients a conditional probability was estimated, i.e. it gives the probability of a transplant given that patients are in CKD 4 or ESKD. However, for the uncontrolled patients in CKD 4 and ESKD, the estimated probability was unconditional, or simply conditional on being a PH1 patient. At the ERGs request, the company provided a conditional probability of transplantation for the uncontrolled group, together with an updated version of the model.

With this new transplantation probability, the revised company base-case are presented in Table 6.1.

Table 6.1: Company discounted base-case results after clarification

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	22.01	[redacted]				
Lumasiran	[redacted]	23.89	[redacted]	[redacted]	1.89	[redacted]	[redacted]

Based on v11.0 of the Excel model[110]
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

As a consequence of the increased probability of a transplantation, the ICER has increased from [redacted] per QALY gained to [redacted] per QALY gained.

6.1.2 Additional scenarios in response to clarification

6.1.2.1 Scenario definition

6.1.2.1.1 Scenario 1: Excluding early-stage disease adults

In response to a question from the ERG about the eligible population for lumasiran, the company added an option to the model to run the simulation excluding adult patients in CKD 1–2, which are defined as those with early-stage disease.[51, 52]

6.1.2.1.2 Scenario 2: Alternative initial distribution paediatric population

In response to the suggestion of an expert consultant paediatric nephrologist that for the specific subpopulation of patients with infantile onset of PH1 in the UK, the distribution of CKD stages is skewed more heavily toward later CKD stages, the company added the option to run the model based on 0% in CKD 1–3b, 10% in CKD 4, and 90% in ESKD at treatment initiation.

6.1.2.1.3 Scenario 3: High-intensity dialysis in lumasiran cohort

A scenario analysis was added where 100% of CKD 4 and ESKD patients in the lumasiran cohort would receive high-intensity dialysis, in line with the assumption in the ECM arm.

6.1.2.1.4 Scenario 4: TTO values for vignettes

A scenario was added with TTO utilities obtained from the vignette study instead of EQ-5D derived utilities.

6.1.2.1.5 Scenario 5: Additive approach to estimate disutility of multiple systemic oxalosis manifestations

A scenario was added to where the estimation of the disutilities of multiple systemic oxalosis manifestations was done using an additive approach instead of multiplicative approach.

6.1.2.1.6 Scenario 6: Vial sharing to reduce wastage

Lumasiran is only available in vials of 94.5 mg, with the consequence that on average large and costly quantities of lumasiran are wasted with each administration. In this scenario vial sharing was assumed, to assess the impact of vial wastage.

6.1.2.1.7 Scenario 7: Alternative dialysis schedule paediatric patients

The model assumes that [redacted] of the paediatric cohort receives daily haemodialysis alone based on the third-party survey with UK expert clinicians. A consultant paediatric nephrologist suggested however that 20% of the paediatric cohort would receive diurnal haemodialysis alone (six time a week), 60% diurnal haemodialysis (six times a week) plus nocturnal haemodialysis (six time a week) and 20% would receive diurnal haemodialysis (six times a week) plus nocturnal peritoneal dialysis (seven times a week). This pattern was explored in a scenario.

6.1.2.1.8 Exploratory alternative model structure

The ERG expressed concerns about the ability of the model structure used by the company to capture the full impact of PH1 on kidney functioning. In response, the company provided a purely exploratory model that partitions the CKD 1–3b cohort into two separate strata: (1) one corresponding to patients with normal or near-normal oxalate levels and (2) the other corresponding to patients with "above-normal" oxalate levels; the transition probabilities between CKD stages are differentiated for each stratum. In this way, decreases in eGFR with exposure to a constant high level of oxalate can be modelled specifically within the "above-normal" oxalate stratum.

6.1.2.2 Results scenarios

Table 6.2 presents the results of the scenario analyses described in the above section. From this we see that the alternative initial distribution for the paediatric population has a very large impact on the ICER, leading to a substantial decrease. Using the TTO values for the valuation of vignettes increased the ICER substantially. Furthermore, eliminating drug wastage would lead to a considerable decrease the ICER. The exploratory analysis with an alternative model shown an ICER that was only slightly smaller than the base-case ICER.

Table 6.2 Results of additional scenario analyses after clarification

Scenario	ICER (£)
Base-case	[redacted]
Base-case after clarification	[redacted]
Scenario 1: Excluding early-stage disease adults	[redacted]
Scenario 2: Alternative initial distribution paediatric population	[redacted]
Scenario 3: High-intensity dialysis in lumasiran cohort	[redacted]

Scenario	ICER (£)
Scenario 4: TTO values for vignettes	[redacted]
Scenario 5: Additive approach to estimate disutility of multiple systemic oxalosis manifestations	[redacted]
Scenario 6: Vial sharing to reduce wastage	[redacted]
Scenario 7: Alternative dialysis schedule paediatric patients	[redacted]
Alternative model structure	[redacted]
Based on the response to the request for clarification[51, 52] * The ERG was not able to reproduce the company ICER that was 88% lower than the company base-case ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life-year; TTO = time trade off	

6.2 Exploratory and sensitivity analyses undertaken by the ERG

6.2.1 Explanation of the ERG adjustments

The changes made by the ERG to the cost effectiveness model provided by the company are outlined. These changes were divided into the following three categories (as defined by Kaltenthaler 2016):[145]

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope, or best practice has not been adhered to)
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred)

These changes were implemented in the company's model to define the ERG base-case. Additionally, scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

6.2.1.1 Fixing errors

As outlined in Section 5.3.3.5.5, an error was made by considering the number of cycles as the number of years. To correct this, the ERG corrected the transition probability from uncontrolled oxalate to controlled oxalate CKD 4/ESKD health states to 0.89 rather than [redacted] in the first cycle.

6.2.1.2 Fixing violations

No violations that could be corrected by the ERG were identified in the economic model.

6.2.1.3 Matters of judgement

The ERG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

1. The probability of transplantation for the uncontrolled patients in CKD 4/ESKD lacks face validity. Instead of using a French study to derive the transplantation probability, the ERG prefers to assume that 50% of ECM patients in CKD 4/ESKD can be placed on the waiting list, compared to 100% in the lumasiran group.
2. The survival post-transplantation was shown to depend on pre-operative condition. The company assumed that survival for patients in very good and good condition would be reflective

of survival for oxalate-controlled patients, whereas survival for patients in fair and poor condition would be reflective of survival for oxalate uncontrolled patients. However, as the study by Jamieson 2005[104] was based on all ECM patients, it makes more sense to assume that the overall survival in Jamieson is representative of survival for the ECM group.

3. The vignettes used to elicit utility values for the CKD 4/ESKD health states were valued both by the general public filling out the EQ-5D for the vignette and by a TTO. The ERG is of the opinion that the EQ-5D utilities lack face validity and that the TTO values are more plausible. These are therefore adopted for the ERG base-case.
4. The price for a pack of 28 tablets pyridoxine 50 mg was updated from £21.93 (which the company sourced from MIMS in November 2021) to £12.60 (sourced from eMIT in September 2021, as provided by NICE).

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The results from the ERG deterministic base-case are shown in Table 6.3. It is clear that the three changes together have a very large impact on the ICER. In Table 6.4 we can see which of the changes had the largest impact i.e. the probability of transplantations for patients in the ECM group. Changing the valuation of the vignettes from EQ-5D to TTO also has a clear impact, whereas the error correction and the change in post-transplantation survival for ECM patients has little impact.

Table 6.3 ERG discounted base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	20.45	[redacted]				
Lumasiran	[redacted]	23.73	[redacted]	[redacted]	3.28	[redacted]	[redacted]

Based on v11.0 of the Excel model[110]
CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 6.4: Isolated impact of the ERGs preferred model assumptions

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company base-case	5.4.1	[redacted]	[redacted]	[redacted]
Company base-case after clarification	6.1.1	[redacted]	[redacted]	[redacted]
Company base-case after clarification and error correction	6.2.1.1	[redacted]	[redacted]	[redacted]
ERG change 1 – Probability of transplantation	5.3.3.5.6	[redacted]	[redacted]	[redacted]
ERG change 2 – Survival post-transplantation	5.3.3.5.12	[redacted]	[redacted]	[redacted]
ERG change 3 - TTO values vignettes	5.3.3.7.2	[redacted]	[redacted]	[redacted]
ERG change 4 – Pyridoxine price updated	6.2.1.3	[redacted]	[redacted]	[redacted]

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
ERG base-case – all 4 changes combined	-	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Ínc. = incremental; QALY = quality-adjusted life year

The ERG also conducted a PSA on their preferred base-case, with results shown in Table 6.5. The probabilistic ICER, averaged over 1,000 simulations, was [redacted], which is in line with the deterministic ICER shown in Table 6.3.

Table 6.5: ERG probabilistic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	NR	[redacted]				
Lumasiran	[redacted]	NR	[redacted]	[redacted]	NR	[redacted]	[redacted]

Based on electronic model with ERG preferred assumptions[110]
CS = company submission; ECM = established clinical management; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; NR = not reported; QALY = quality-adjusted life year

Figure 6.1 shows the scatterplot of the PSA outcomes on the CE-plane. [redacted].
Based on these, the CEAC was derived and shown in Figure 6.2. At the threshold ICER of £100,000 per QALY gained, the probability that lumasiran is cost effective compared to ECM was [redacted]%.

Figure 6.1: Probabilistic sensitivity analysis scatterplot ERG base-case

[redacted]

Based on electronic model with ERG preferred assumptions[110]
CE = cost effectiveness; ERG = Evidence Review Group; QALY = quality-adjusted life-year

Figure 6.2: Cost effectiveness acceptability curve ERG base-case

Based on electronic model with ERG preferred assumptions[110]
ERG = Evidence Review Group; QALY = quality-adjusted life-year; WTP = willingness-to-pay

6.4 Exploratory scenario analyses conducted by the ERG

The ERG conducted several additional scenario analyses to explore model uncertainties. The results of these scenarios are summarised in Table 6.6 and described below.

6.4.1 Scenario set 1: Initial distribution isolated CKD classes

In this scenario we explored the cost effectiveness of lumasiran per single CKD class. We found that .

6.4.2 Scenario set 2: Percentage ECM patients entering transplantation waiting list

In the ERG base-case, the percentage of ECM patients in CKD 4/ESKD that are placed on the waiting list was set to a rather arbitrary value of 50%. If the percentage is changed to 25%, we found that , whereas if the percentage is changed to 75% .

6.4.3 Scenario set 3: Vial sharing

When lumasiran vials can be shared to prevent drug wastage the incremental costs were more than lower than in the base-case, and the resulting ICER was .

6.4.4 Scenario set 4: Differential discounting

When differential discounting at 1.5% outcomes and 3.5% costs is applied, [redacted] incremental QALYs were estimated, thus approximately [redacted] more than in the base-case, and the resulting ICER was [redacted].

6.4.5 Scenario set 5: Proportion of patients receiving dialysis in CKD stage 4

When it was assumed that no patients receive dialysis in CKD 4 (i.e. instead of all patients in the ECM arm receiving dialysis in CKD 4), the resulting ICER was [redacted].

Table 6.6: ERG scenario analyses results

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£)
ERG base-case	Section 6.3 of this report	[redacted]	[redacted]	[redacted]
Initial distribution isolated CKD classes	CKD 1-2 100%, other 0%	[redacted]	[redacted]	[redacted]
	CKD 3a 100%, other 0%	[redacted]	[redacted]	[redacted]
	CKD 3b 100%, other 0%	[redacted]	[redacted]	[redacted]
	CKD 4 100%, other 0%	[redacted]	[redacted]	[redacted]
	ESKD 100%, other 0%	[redacted]	[redacted]	[redacted]
Percentage ECM patients entering transplantation waiting list	25%	[redacted]	[redacted]	[redacted]
	75%	[redacted]	[redacted]	[redacted]
Vial sharing	Optimal vial sharing	[redacted]	[redacted]	[redacted]
Differential discounting	1.5% outcomes and 3.5% costs	[redacted]	[redacted]	[redacted]
Proportion of patients receiving dialysis in CKD stage 4	0%	[redacted]	[redacted]	[redacted]

Based on electronic model with ERG preferred assumptions[110]
CKD = chronic kidney disease; ECM = established clinical management; ERG = Evidence Review Group; ESKD = end-stage kidney disease; ICER = incremental cost effectiveness ratio; Incr. = incremental QALY = quality-adjusted life year

7. COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

Based on data from the national RaDaR, the company estimated that there are approximately 120 patients with any type of hyperoxaluria in the UK, of which approximately [redacted] have PH1.[25-27] It was assumed, based on clinical expert opinion, that [redacted] of these patients have not already received a liver transplant or combined liver-kidney transplant. Considering that lumasiran would only be used in patients who have not already undergone a transplantation procedure, the company estimated that [redacted] prevalent patients with PH1 would currently be eligible for treatment with lumasiran in the UK. Based on an estimated incidence rate for PH1 in Europe of one per 100,000 live births and a number of 613,936 live births in England and Wales in 2020, it was assumed that there are [redacted] new patients with PH1 each year in the UK. Therefore, the estimated total number of patients with PH1 that are eligible for treatment with lumasiran is [redacted] in year 1 and increases by [redacted] in each subsequent year. In line with the base-case CEA, it is assumed that a proportion of [redacted] of the patient population consists of paediatric patients in year 1. The numbers of eligible patients, proportions paediatric patients and lumasiran market shares over the first five years after introduction are provided in Table 7.1.

Table 7.1: Eligible patients, proportions paediatric patients and lumasiran market shares over the first 5 years after introduction

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion paediatric patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share					
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated population					
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Tables D61 and D62 of the CS[1]
CS = company submission; ECM = established clinical management

The company estimated the undiscounted costs in each year, both for a world without lumasiran and a world with lumasiran, using the same base-case model as for the CEA over the 5-year time horizon. These cost estimates are provided in Tables D63 and D64 in the CS for each cost category separately.[1]

Based on these estimates, it is anticipated that the costs for dialysis and treatment of renal stone events and systemic oxalosis complications are reduced and the costs for treatment and transplantation are increased. The total costs in a world without lumasiran and a world with lumasiran are provided in Table 7.2, alongside the net budget impact for each year.

Table 7.2: Expected budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs					
World without lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
World with lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table D65 of the CS[1]					

Introducing lumasiran for the treatment of PH1 in England and Wales is projected to add [redacted] to the NHS budget in the first year of uptake and is anticipated to result in a net budget impact [redacted] in each of the first five years after introduction.

7.2 ERG critique of the company's budget impact analysis

The ERG considers the estimated number of eligible patients as a potential underestimate, since it is based on a subset of patients who registered voluntarily in RaDaR. Therefore, the real number of patients with PH1 in the UK could be much larger than the company estimated, see also Section 2.2.3.

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the CS

8.1.1 Proportion of costs or benefits which fall outside of the NHS and PSS

The company have not estimated the proportion of costs outside of the NHS and PSS that may be saved due to treatment with lumasiran, or of the additional benefits other than health. Only in Section 7.1.4 of the CS some narrative is presented to detail potential benefits outside of the NHS and PSS.[1]

8.1.2 Societal costs

In the CS it is mentioned that, while the impact of lumasiran on cost and cost savings to UK government bodies has not been quantified, lumasiran may be expected to bring cost savings to government bodies other than the NHS as a result of reduced patient disability especially in the young patients and the patients with late-stage disease.[1]

Caregivers are assumed to return to work and thus the company expects expenditures associated with the support for patients with PH1 and unemployed caregivers of PH1 patients may be reduced. [redacted][1]

8.1.3 Costs borne by patients

In the CS, it is indicated that costs borne by patients not reimbursed by the NHS include transportation to and from the hospital for dialysis treatment, renal stone treatment and consultation, parking and overnight accommodation and meals.[1] The company reported costs for transportation for dialysis of £14,000 per year assuming six sessions per week.[146] Costs may occur when home adaptations and aids are required. It is also indicated that carers often experience a loss of income due to time spent on caring for the patient. However, none of these costs were quantified in the CS.

8.1.4 Other carer costs

In the CS, the findings of caregiver surveys conducted at the start of the ILLUMINATE trials are discussed.[1]

[redacted].

8.1.5 Impact of the technology on research and innovation

According to the CS, the evidence base generated by the phase 3 ILLUMINATE trials of lumasiran in PH1 is a major advance considering that PH1 has a limited evidence base to inform clinicians on its management. The ILLUMINATE trials included patients with a range of ages and disease severity for whom lumasiran shows improved outcomes compared to ECM.

ERG comment: The CS only included some narrative about costs outside the NHS and PSS, without any quantification. The company reasoned that some of these costs may be saved when patients are treated with lumasiran, given that the treatment may reduce the need for certain time-intensive disease management and thus, frees up time of caregivers. However, there is currently no evidence to indicate to what extent improvements in the patients' condition will also lead to savings in societal, patient, and carer costs.

8.2 Staffing and infrastructure requirements associated with the use of the technology

Lumasiran therapy will be implemented through the Rare Disease Collaborative Network expert centres at the Birmingham Women's and Children's NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Great Ormond Street Hospital, and the Royal Free. The treatment should be initiated and supervised by a physician experienced in the management of hyperoxaluria.[147] The company stated that no additional infrastructure will be required to ensure the safe and effective use of the technology and equitable access for all eligible patients.[1]

9. DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

The company presented clinical efficacy results from four studies, two of which were placebo-controlled RCTs and two were non-comparative. Both RCTs included a double-blind comparative period followed by an open-label extension during which all patients received the active intervention.

The ILLUMINATE-A RCT (ALN-GOI-003) recruited adults and children (age range six to 60 years) with a diagnosis of PH1 and relatively preserved renal function (n=39 patients recruited from 16 study centres in France, Germany, Israel, the Netherlands, Switzerland, the United Arab Emirates, the UK and the USA). [redacted] patients were from the UK. The initial double-blind period entailed a randomisation ratio of lumasiran:placebo 2:1 and was of 6 months duration; the extension (involving the same participants) lasted up to 54 months.

The second RCT (ALN-GOI-001) recruited adults and children aged six to 64 years with a diagnosis of PH1 and eGFR >45 ml/min/1.73 m2 (n=20 patients recruited in France, Germany, Israel, the Netherlands and the UK). The number of study centres and the number of patients per country was not reported. Separate cohorts were recruited for the comparative and extensive phases. Participants were randomised in a 3:1 (lumasiran:placebo) ratio during the 3-month double-blind phase; this involved three different dosing schedules of lumasiran according to body weight. The duration of the extension was a further 3-months.

One of the single-arm studies (ALN-GOI-002) recruited the 20 participants who had participated in the second RCT described above and allocated them to three different dosing schedules of lumasiran as used in the RCT.

The second single-arm study (ILLUMINATE-B, ALN-GOI-004) recruited 18 children younger than six years of age from nine study centres in France, Germany, Israel, the UK and the USA (n = [redacted] UK patients) with a diagnosis of PH1 and relatively preserved renal function and administered lumasiran loading and maintenance doses based on body weight.

Below, there is a summary of results with a focus on the double-blind phase of the ILLUMINATE-A RCT (ALN-GOI-003). The results of all phases of all four studies are presented in detail in Section 4.2.

- Use of lumasiran was associated with relative and absolute reductions in 24-hour urinary oxalate excretion between baseline and 6 months versus placebo, with the respective estimates of treatment effect being: -53.5% (95% CI -62.3 to -44.8) and -0.98 mmol/24-hours/1.73 m^2 (95% CI -1.18 to -0.77).
- The results for change in 24-hour plasma oxalate between baseline and 6 months also suggested an effect in favour of lumasiran compared with placebo. The respective relative and absolute estimates of treatment effect were: -39.5% (95% CI -50.1 to -28.9) and -8.7 mmol/ 24 hours/ 1.73 m^2 (95% CI -11.5 to -6.0).
- The level of eGFR appeared to remain stable for both treatment groups during the 6-month follow-up period, however, estimates of treatment effect were not provided.
- In the group receiving lumasiran, the rate of renal stone events (per person year) was 3.19 (95% CI 2.57 to 3.96) in the 12 months prior to the trial and 1.09 (95% CI 0.63 to 1.87) during the 6-month double-blind period. The respective values in the placebo group were 0.54 (95% CI 0.26 to 1.13) and 0.66 (95% CI 0.25 to 1.76). A between-group estimate of effect was not provided.
- The number of patients needing a liver transplant without or without a kidney transplant was not reported.

- The mean ± standard deviation (SD) change from baseline to month 6 in the EuroQoL 5-dimension (EQ-5D) visual analogue scale (VAS) was [redacted] for the lumasiran group and [redacted] for the placebo group, with higher scores indicating better health status. However, comparability of baseline could not be assessed by the ERG, as relevant details were not provided.

AE data were available from the ILLUMINATE-A RCT, ILLUMINATE-B and an additional single-group study (ILLUMINATE-C). During the double-blind phase of ILLUMINATE-A, 85% of patients receiving lumasiran and 69% on placebo reported any type of AE. Injection site reactions were higher among patients in the lumasiran group compared with placebo (23% versus 0%). No SAEs or severe AEs were recorded in either group. All patients experienced at least one AE in the ILLUMINATE-B study whilst one SAE and no severe AEs were reported. In the ILLUMINATE-C study, 81% of patients experienced any type of AE, 29% experienced at least one SAE and 14% experienced at least one severe AE. No deaths were recorded in any study.

No pairwise meta-analyses, indirect treatment comparisons or multiple treatment comparisons were conducted.

9.2 Statement of principal findings – cost effectiveness

The discounted company base-case results using the proposed PAS discount of [redacted]% for lumasiran showed that lumasiran accrues [redacted] incremental QALYs compared to ECM at an additional cost of [redacted]. This corresponds to an ICER of [redacted] per QALY gained.

The undiscounted gain in QALYs with lumasiran was [redacted], indicating a weighting of [redacted] can be used to calculate a weighted threshold (of [redacted]).

In response to the request for clarification, the company submitted a revised model. The ICER has increased from [redacted] per QALY gained to [redacted] per QALY gained. Furthermore, the company explored various scenarios. One with an alternative initial distribution for the paediatric population (10% CKD 4, 90% ESKD) has a very large impact on the ICER, leading to a substantial decrease. Using the TTO values for the valuation of vignettes increased the ICER substantially. Furthermore, eliminating drug wastage would lead to a considerable decrease the ICER. The exploratory analysis with an alternative model structure showed an ICER that was only slightly smaller than the base-case ICER.

The ERG's preferences regarding alternative assumptions led to changes for the following input:

- The probability of transplantation for the uncontrolled patients in CKD4/ESKD
- The survival post-transplantation for ECM patients
- The utility values assigned to vignettes for the CKD 4/ESKD health states

Lumasiran accrued [redacted] incremental QALYs compared to ECM at an additional cost of [redacted]. This corresponds to an ICER of [redacted] per QALY gained. It is clear that the three changes together have a very large impact on the ICER. The largest impact had the probability of transplantations for patients in the ECM group. Changing the valuation of the vignettes from EQ-5D to TTO also has a clear impact, whereas the error correction and the change in post-transplantation survival for ECM patients has little impact.

The ERG also explored some other scenarios, i.e. changing the percentage of ECM patients entering the transplantation waiting list, assuming vial sharing (i.e. no drug wastage), applying differential

discount rates, and assuming that no patients receive dialysis in CKD stage 4. These all changed the ICER by more than 10%. The lowest ICER was attained when applying differential discounting ([redacted] per QALY gained), and the highest if the proportion of patients receiving dialysis in CKD stage 4 was set to 0 ([redacted] per QALY gained).

9.3 Strengths and limitations

9.3.1 Strengths of the CS

- The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify studies on lumasiran for primary hyperoxaluria.
- The CS provided comprehensive data concerning several of the outcomes that were in the agreed scope.
- The CS presented the first CEA for patients with PH1. The analysis aligns with the NICE reference case. The model reflects disease progression and its impact on HRQoL and costs.
- Availability of data from controlled studies to estimate model input.

9.3.2 Weaknesses of the CS

- Components of the DP addressed in the CS were in line with the NICE scope (population and intervention) but there are discrepancies with others (comparators, outcomes and subgroups).
- It should be noted that full CSRs were not available to the ERG, see Section 4.2.
- The approach used for data extraction was not in line with best practice.
- Potentially limited generalisability to population in England and Wales.
- The ERG has limited confidence that some of the observed effects in the non-randomised evidence truly reflect the treatment effects of lumasiran.
- The model assumes that disease progression in CKD 1–3b (in term of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on elevated plasma oxalate levels that are steady yet sustained over time.
- A lack of face validity with regards to the mortality after a transplantation and the probability of a transplantation for ECM patients.
- No data on the HRQoL measurements in the ILLUMINATE C was provided.
- No justification was provided why the same caregiver disutilities were applied in CKD 4 and ESKD, and independent of dialysis intensity.

9.4 Uncertainties

Three key issues were identified in the clinical effectiveness Section:

- The evidence base consists of two small RCTs, both with maximum follow-up period of 6-months for the double-blind phase. Both RCTs have non-comparative extension phases and two additional single-arm studies were identified, see Section 4.2 for details.
- The total eligible population in the UK may be larger than stated in the CS. The CS does not take account of new (incident) cases per year. This may result in a higher proportion of patients with PH1 being eligible for treatment with lumasiran, see Section 2.2.3 for details.
- Change in urinary or plasma oxalate levels is an intermediate, i.e. surrogate, outcome with unknown prediction of clinical endpoints such as renal stone events, renal failure, need for liver transplant with or without kidney transplant and survival. The maximum follow-up duration in the existing double-blind RCTs is 6 months which may not be long enough to detect the above

clinical endpoints. Related to this, the existing RCTs are likely to be statistically underpowered to detect clinical endpoints, see Section 4.1.2 for details.

A further five key issues were identified in the cost effectiveness Section:

- The model assumes that disease progression in CKD 1–3b (in terms of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on high plasma oxalate levels that are steady yet sustained over time. The ERG considers it likely that disease progression also occurs in patients who sustain a steady, but very high, plasma oxalate level over time. See Section 5.3.3.4 for details.
- The company assumed that 100% of patients with controlled oxalate in CKD 4 and ESKD would be placed on a waiting list for cLKT and then have the same chance as non-PH1 patients with ESKD. For patients in CKD 4 and ESKD with uncontrolled oxalate, the cLKT transplantation rate was estimated based on a study by Compagnon et al. 2014.[115] This yielded a transplantation rate that was about 30 times smaller than for the controlled patients and translated in an average time until transplantation of around 80 years, see Section 5. 3.3.5.6.
- For the estimation of the utility for CKD 4 and ESKD with uncontrolled oxalate on high-intensity dialysis, a vignette study was done, where the general public filled out the EQ-5D for each health state (to which the UK tariff was subsequently applied), scored the vignette on the visual analogue scale, and performed a time trade-off exercise to arrive at a utility value. The ERG had doubts regarding the choice of the EQ-5D based valuation of the vignettes instead of the TTO derived utilities, both from a methodological point of view as well as based on a lack of face validity, see Section 5.3.3.7.2 for details.
- The ERG considers the costs due to drug wastage for lumasiran high. On average [redacted] mg and [redacted] mg per administration of lumasiran is wasted for the paediatric and adult population, with corresponding costs due to wastage of [redacted] and [redacted] per administration, respectively. This raises the question if treatment administration can be optimised to reduce wastage, see Section 5.3.3.8.1 for details.
- The ERG noticed a disconnect between the dialysis schedules suggested by clinical experts and the schedules used for the model. Dialysis is expensive and more intensive schedules lead to a larger decrease of quality of life. No explanation or justification was provided. See Section 5.3.3.9.4 for details.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 30 March 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Preamble

Alnylam would like to express our sincere appreciation for the time and effort invested by the ERG in its careful review of our evidence submission for lumasiran for treating primary hyperoxaluria type 1 (PH1) and our follow-up clarifications. We are especially grateful for the ERG's timely review considering the additional challenges that the pandemic undoubtedly imposed on the reviewers.

In the following tables of this factual accuracy check form we have restricted our input to a limited number of suggested amendments to correct factual imprecision that could potentially result in misinterpretation by the Committee, and which we believe will therefore further improve the ERG Report overall. We will wait to raise issues related to the ERG's preferred assumptions and justifications at the next opportunity, in committee.

Please note that this is an interim draft of this check form, covering only the factual accuracy check and not Alnylam's check of the ACIC mark-up, which will follow.

Response to ERG Report

Issue 1 Characterisation of accounting for incident patients in the company submission (CS)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.4, Table 1.2, page 18, first row: "The total eligible population in the UK may be larger than stated in the CS. The CS does not take account of new (incident) cases per year. This may result in a higher proportion of patients with PH1 being eligible for treatment with lumasiran." Section 1.10.3, page 28, bullet 3: Identical sentences. This statement is not strictly speaking true since incident patients are explicitly accounted	Alnylam recommends deletion of the quoted sentences.	The recommended deletion would avoid incorrectly stating that incident cases were overlooked in the CS.	This is not a factual inaccuracy. However, we have amended the text in Section 1.4 (Table 1.2) and Section 1.10.3 of the ERG report to further clarify our concern. The statements made in Sections 6.2 and 13.1 of the CS in relation to the assumed number of new (incident) cases of PH1 per year are not substantiated by the cited references.

for in the budget impact analysis section of the CS, as described and tabulated in CS Section 13.1.			

Issue 2 Characterisation of data source supporting modelling of no decreases in eGFR for patients receiving lumasiran

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.5, page 20, paragraph 3: "Since no increases, but rather decreases, in plasma oxalate were observed in patients who received lumasiran in ILLUMINATE-A, also no decreases in eGFR were modelled for patients receiving lumasiran." Section 5.5, page 192, paragraph 6: Identical sentence. These two sentences omit one of the two studies demonstrating plasma oxalate (POx) decreases: ILLUMINATE-B.	Alnylam requests addition of "and ILLUMINATE-B" to both of these identical sentences as follows: "Since no increases, but rather decreases, in plasma oxalate were observed in patients who received lumasiran in ILLUMINATE-A and ILLUMINATE-B, also no decreases in eGFR were modelled for patients receiving lumasiran."	The recommended edit would clarify that the oxalate change in the lumasiran arm of the model was based on pooled data from ILLUMINATE-A and ILLUMINATE-B.	We have made the requested edit.

Issue 3 Characterization of the rules for model transitions from chronic kidney disease stage 4 (CKD 4) to end-stage kidney disease (ESKD)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.5, page 20, paragraph 4: "For patients receiving ECM,	Alnylam recommends that the quoted sentences be replaced along the following	The recommended revisions would clarify that the simulation of	Upon rereading the ERG understands how their text

the transition from CKD 4 to ESKD was modelled using ESKD-free Kaplan-Meier survival curves. As described above, patients receiving lumasiran could not transition to ESKD." The basis for not transitioning from CKD 4 to ESKD was controlled oxalate levels rather than a treatment-specific rule per se.	lines: "The transition from CKD 4 to ESKD for the cohort with uncontrolled oxalate levels was modelled using ESKD-free Kaplan-Meier survival curves. The cohort in CKD 4 with controlled oxalate levels was assumed not to transition to ESKD. A scenario analysis was included in which the CKD 4 controlled-oxalate cohort would transition to ESKD based on rates of progression in non-PH1 patients with CKD."	progression from CKD 4 to ESKD was not treatment-specific but instead specific to whether patients had controlled or uncontrolled levels of oxalate.	might be misinterpreted. We have therefore edited the text.
Section 5.5, page 192, paragraph 7: "For patients receiving ECM, the transition from the most severe CKD health state (i.e. CKD 4) to ESKD was modelled using a Gompertz parametric curve fitted to data derived from the ESKD-free KM survival curves published by Harambat et al. 2010.[16] Since the Harambat et al. study included patients who were in less severe CKD stages (i.e. further from progression to ESKD) than CKD 4, this likely represents a conservative approach. As described above, patients receiving lumasiran could not transition to ESKD." The basis for not transitioning from CKD 4 to ESKD was controlled oxalate levels rather than a treatment-specific rule per	Alnylam recommends that the quoted sentences be replaced along the following lines: "The transition from CKD 4 to ESKD for the cohort with uncontrolled oxalate levels was modelled using a Gompertz parametric curve fitted to data derived from the ESKD-free KM survival curves published by Harambat et al. 2010.[16] Since the Harambat et al. study included patients who were in less severe CKD stages (i.e. further from progression to ESKD) than CKD 4, this likely represents a conservative approach. The cohort in CKD 4 with controlled oxalate levels was assumed not to transition to ESKD. A scenario analysis was included in which the CKD 4 controlled-oxalate cohort would transition to ESKD based on rates of progression in non-PH1 patients with CKD."		See above

se.			

Issue 4 Characterization of the modelling of disease progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.10.2, page 28, bullet 6: "The model assumes that disease progression (in term of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on elevated plasma oxalate levels that are steady yet sustained over time." Section 9.3.2, page 208, bullet 6: Identical sentence. The quoted sentences do not specify the CKD stages to which this assumption applies in the model.	Alnylam recommends that the quoted sentences be amended as follows: "The model assumes that disease progression in CKD 1–3b (in term of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on elevated plasma oxalate levels that are steady yet sustained over time."	The recommended amendment would clarify that the relationship between POx level increase and reduction in eGFR is used to model progression in CKD 1–3b, whereas the progression in CKD 4 is based on whether the POx level is controlled or uncontrolled.	The ERG has made the recommended change.

Section 1.10.3, page 29, bullet 1: "The model assumes that disease progression (in terms of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on high plasma oxalate levels that are steady yet sustained over time." Section 9.4, page 209, bullet 1: Identical sentence. The quoted sentences do not specify the CKD stages to which this assumption applies in the model.	Alnylam recommends that the quoted sentences be amended as follows: "The model assumes that disease progression in CKD 1–3b (in terms of a decreasing eGFR) depends on changes in plasma oxalate levels over time, but not on high plasma oxalate levels that are steady yet sustained over time."		The ERG has made the recommended change.

Issue 5 Characterisation of accounting for baseline pyridoxine use

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Section 4.2.1.1.3, page 72, paragraph 4: "However, this argument demonstrates an incorrect interpretation of confidence intervals. For evaluating whether differences are statistically important, we should estimate the probability that the non-extreme parts of the sampling distribution around the point estimate of the mean difference between the pyridoxine groups (the spread of this distribution being informed by the	Alnylam suggests deletion of the quoted paragraph.	The suggested deletion would avoid leaving the implication that Alnylam adopted an approach without considering statistical rigour. We took careful note of the fact that the 95% CI for patients with baseline pyridoxine use encompasses the point estimate for patients without baseline pyridoxine use.	Not a factual inaccuracy. The statistical difference between groups can only be determined through hypothesis testing and this was not presented in the CS.

variance of the measure and the sample sizes) – which are represented by the 95% CI - includes the null value. Importantly, the 'overlap' method used by the developers does not do this; instead, the 'overlap method' might incorrectly conclude no difference when in fact one exists. Although the method of 'overlapping confidence intervals' can show a definite difference when there is no overlap it cannot directly confirm no difference when there is an overlap.[79] Therefore, the issue of whether pyridoxine use has been adjusted for has not been fully answered." Although Alnylam concedes the statistical point being made as a general principle, in this specific instance there is a very wide overlap between the 95% CI for patients with and without pyridoxine use, such that we contend it is not plausible that a statistically significant difference exists between the two groups (at a conventional alpha level).			

Issue 6 Characterization of the modelling of renal stone events and systemic oxalosis complications

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.6, page 135, paragraph 4: "Quality of life data were referred to briefly in the CS in relation to the ILLUMINATE-A RCT, but this demonstrated differences that would probably not be regarded as clinically meaningful.[1] This is a major drawback in the CS because if the treatment cannot be shown to affect quality of life it could be argued to have little clinical benefit." Alnylam is concerned that the first of these quoted statements appears to set up a conclusion that is unwarranted given the determinants of health-related quality of life (HRQoL) impairment in PH1. The second statement is not necessarily true and we consider it to be factually misleading in the present context.	Alnylam suggests deletion of the two quoted sentences.	Deletion of the first of these two statements is justified because the worst impairments of HRQoL for patients with PH1 appear in later disease stages (e.g., due to dialysis and systemic oxalosis complications; Lawrence, Wattenberg. *Clin J Am Soc Nephrol* 2020;15:909-11; Mujais et al. *Clin J Am Soc Nephrol* 2009;4:1293-301; Cruz et al. *Clinics (Sao Paulo)* 2011;66:991-5), whereas ILLUMINATE-A exclusively enrolled patients in early CKD stages. We note that the ERG accepted that lack of meaningful eGFR change in this trial is not indicative of lack of clinical benefit for lumasiran—e.g., ERG Report, page 75: "As expected, based on the natural course of the disease, eGFR remained relatively stable for both treatment groups during the 6-month double-blind treatment period." It follows that substantial HRQoL changes in ILLUMINATE-A should also not be expected, given that HRQoL impairment in PH1 is tied to declining kidney function. Therefore, the degree of HRQoL change observed within this trial	Not a factual inaccuracy. The ERG assessment was based on the very minimal details available from the CS. The available information included neither baseline scores nor estimation of the between-group difference for change in HRQoL between baseline and month 6.

		should not be misinterpreted to devalue the clinical benefit of lumasiran. Deletion of the second statement is justified on principle because there are numerous examples of therapies that do not improve HRQoL while nevertheless yielding important clinical benefits. For instance, androgen-deprivation therapy is the standard of care for advanced prostate cancer because it is life-saving even though it is associated with significant decreases in HRQoL (Tucci M *et al*. *Minerva Urol Nefrol* 2018;70:144-51).	

Issue 7 Characterization of the modelling of renal stone events and systemic oxalosis complications

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.3.2, page 141, paragraph 3: "Both of these are more likely to occur as patients transition to higher CKD classes." We suggest providing additional clarification around the modelling of these events.	Alnylam recommends that the quoted sentence be replaced along the following lines: "Treatment-specific rates of renal stone events were modelled in the CKD 1–3b health states based on data from ILLUMINATE-A and ILLUMINATE-B and in CKD 4 and ESKD based on data from ILLUMINATE-C (the baseline rate was assumed to be reflective of renal stone events in ECM since no data on ECM are available from the trial). Systemic oxalosis complications were modelled only in CKD 4 and ESKD, and a lower prevalence of systemic	Renal stone events and systemic oxalosis complications are not solely related to CKD progression—in fact, rates of renal stone events are lower at the worst CKD stages. The recommended revision would provide a more accurate description of how the model handles renal stone events and systemic oxalosis complications.	The ERG has edited the text and removed the erroneous sentence.

	oxalosis complications was assumed in CKD 4 and ESKD with controlled oxalate levels.”		

Issue 8 Characterization of the CKD stages in which utility decrements for adverse events (AEs) and renal stone events (RSEs) are applied

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.3.3.7.1, page 157, paragraph 1: [redacted]	Alnylam recommends that the quoted sentence be amended as follows: [redacted]	The recommended amendment would clarify that these utility decrements are also applied to the CKD 4 and ESKD health states.	The ERG has made the recommended edit.

Issue 9 Characterization of the company's budget impact analysis (BIA)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 7.2, page 203, paragraph 2: "It is not clear to the ERG how the proportions of paediatric patients were estimated and how these align with the estimated number of new (i.e. incident) patients per year. For example, [redacted] of [redacted] patients equals [redacted] paediatric patients in year 1 and [redacted] of [redacted] patients equals [redacted] paediatric patients in year 2. It is not clear how there can be [redacted] additional paediatric patients, given that there are only [redacted] new patients in year 2 and the assumption that there are no patients who no longer need treatment." It appears that the calculation of paediatric patient numbers has been misunderstood.	Alnylam recommends deletion of the quoted sentences.	The BIA calculations for the proportion of paediatric patients are discrete to each individual starting-year cohort modelled; i.e., we do not model this as 80% of 57 patients being paediatric in Year 2 but rather 70% of 51 patients in Year 1 were paediatric, added to whom are 80% of 6 new patients in Year 2 who were paediatric patients. Assuming this resolves the ERG's uncertainty, the quoted sentences can be deleted.	With this explanation from the company this issue is now resolved and we have deleted the quoted sentences plus the concluding sentences of the ERG critique.
Ibid., paragraph 3: "It is not clear how the company's cost estimates were arrived at using their base-case CEA model and the ERG could not reproduce the company's estimates using the CEA model. For example, the company estimated the treatment costs in a world without	Alnylam recommends deletion of the quoted sentences.	The ERG's calculation does not include VAT, and the apparent discrepancy is resolved if VAT is added: £8.35 +20% VAT = £10.	The ERG had indeed not included VAT in these calculations and has now deleted the suggested sentences.

lumasiran (i.e. only ECM) for [redacted] patients at [redacted] (i.e. see Table D63 in the CS) or [redacted] per patient in year 1.[1] However, the modelled treatment costs of ECM for adult and paediatric patients are £7.59 and £2.71 per 6 months, respectively. This gives an average annual cost of 2 x (70% x 2.71 plus 30% x 7.59) = £8.35 per patient, or £426 for [redacted] patients, i.e. without taking into account mortality, treatment discontinuation etc." These comparisons are mixing prices with and without VAT.			

Issue 10 Correction of minor typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.4, Table 1.1, page 18: "The ERG identified examples were groups were not comparable at baseline …" The first instance of "were" is a typographic error.	Alnylam recommends that the quoted sentence be corrected as follows: "The ERG identified examples where groups were not comparable at baseline …"	Correction of typographic error.	Changed accordingly
Section 4.2.1.1.3, Table 4.6, page 68: For five numbers in the P-value column the exponents are not superscripted. Section 4.2.1.5.3, Table 4.16,	Alnylam recommends superscripting of the exponents on these P values; e.g., 1.685×10-14 should be 1.685×10^{-14}.	Clarification of statistical reporting.	Changed accordingly

page 103: The exponent on the P value for percent change in POx in Cohort B is not superscripted.			
Section 4.2.1.8.1, Table 4.21, page 113: “Patients initiated dosing with SC lumasiran at the same dosing regimen as they received in ALN-GO1-001B (1 mg/kg monthly (n=8), 3 mg/kg monthly (n=7), or 3 mg/kg every 3 months (n=5)). 66,184 patients who received 1 mg/kg monthly were subsequently transitioned to 3 mg/kg every 3 months to align with the intended phase 3 maintenance dose” The reference numbers are not superscripted, are preceded by a space, and appear to relate to the numbering in the CS rather than the ERG Report. The last sentence should start with a capital letter.	Alnylam recommends that the quoted sentence be amended as follows: “Patients initiated dosing with SC lumasiran at the same dosing regimen as they received in ALN-GO1-001B (1 mg/kg monthly (n=8), 3 mg/kg monthly (n=7), or 3 mg/kg every 3 months (n=5)).[76,93] Patients who received 1 mg/kg monthly were subsequently transitioned to 3 mg/kg every 3 months to align with the intended phase 3 maintenance dose”	Correction of typographic and referencing errors.	Changed accordingly. The reference numbers were copied from the CS in error and have now been deleted.
There are multiple incorrect substitutions of “CKS” for “CKD” across the report, starting on page 138 and ending on page 189.	Alnylam recommends using Word’s Find and Replace to correct all instances of “CKS” with the standard abbreviation “CKD” [Find and Replace settings: Match case; Replace All].	Correction of typographic errors.	Changed accordingly
Section 5.3.1, Table 5.1, page 138: “For CKS 123b, observed EQ-5D utilities from the ILLUMINATA A study were used.”	Alnylam recommends that the quoted sentence be corrected as follows: “For CKD 1–3b, observed EQ-5D utilities from the ILLUMINATE-A study were used.”	Correction of typographic errors.	Changed accordingly

This sentence has three typographic errors.			
Section 5.3.3.5.9, Table 5.14, page 153, footnote: “Based on Table D16 of the CS[1]” The wrong table in the CS is cross-referenced.	Alnylam recommends that the quoted sentence be corrected as follows: “Based on Table D17 of the CS[1]”	Correction of typographic error.	Changed accordingly
Section 5.4.2, page 181, paragraph 1: “The results of these analyses are summarised in the remaining of this section.” “remaining” is a grammatical error.	Alnylam recommends that the quoted sentence be corrected as follows: “The results of these analyses are summarised in the remainder of this section.”	Correction of grammatical error.	Changed accordingly