National Institute for Health and Care Excellence

HIGHLY SPECIALISED TECHNOLOGIES EVALUATION PROGRAMME

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Lumasiran for treating primary hyperoxaluria type 1 ID3765

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Great Ormond Street Hospital NHS Foundation Trust	Absolutely	Thank you for your comment. No further action required.
	Renal Association	Yes, it is the second drug using this technology that is being introduced into practice. Suggest referring to the appraisal for patisiran.	Thank you for your comment. No further action required.
	Alnylam	Lumasiran was initially identified by NICE as being appropriate for potential HST guidance development. However, it has since been proposed to instead follow the Single Technology Appraisal process. Alnylam strongly believes STA will not be appropriate for evaluation of this highly novel therapy for the treatment of the ultra-orphan disease Primary Hyperoxaluria Type 1 (PH1). Specifically, lumasiran is a RNA interference therapeutic, based on gene silencing technology and is one of the first in a new class of medicines. Lumasiran received PRIME designation by the EMA and will shortly be	Thank you for your comments. After considering comments received from consultation and scoping workshop, it was agreed that the appropriate route for this topic is highly

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		available in the UK through the MHRA Early Access to Medicines Scheme due to the urgent need for an effective treatment in PH1. PH1 is an ultra-rare, severely debilitating, progressive, genetic disease that, in England, disproportionately affects children from specific ethnic minority groups. We understand that the HST process was designed to facilitate assessment of novel technologies in such rare disease populations where there is greater clinical uncertainty through the addition of broader evaluation criteria than under STA. We therefore believe that only the HST process would be appropriate to evaluate lumasiran for the treatment of PH1. Additionally, the extreme rarity of the disease and the highly innovative nature of this new gene silencing technology which can deliver benefits not adequately captured within the standard QALY measure, ensure it would be impossible to obtain an ICER within the range required for the STA process – and this could not reasonably be expected where the patient population eligible for lumasiran is smaller than that of the majority of HST evaluations. Further to this, we believe that lumasiran complies with the specific criteria required by NICE to qualify for HST evaluation, detailed as follows: **1) The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS** PH1 is an ultra-rare, autosomal recessive, inborn error of glyoxylate metabolism that predominantly affects children, with approximately 5-10 new patients diagnosed in England each year. We agree with the estimated prevalence of around 90 PH1 patients from the NICE scope. Of these however, only a subset would be treated with lumasiran as it would not be used in patients who have received a liver or combined liver and kidney transplant. Clinical experts estimate up to 10-15 patients would start treatment with lumasiran in the first year of availability in England, with no	specialised technologies (HST).

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		more than 5-10 new patients each year after this. It is expected that most of these patients would be children. The majority of patients are managed through the existing, national nephrology network in tertiary referral centres within 3 geographical areas (Birmingham, Leeds/Bradford and London). In the UK the incidence and prevalence of PH1 is disproportionately higher in ethnic minorities including those of Pakistani and other south Asian origin. The locations of the highly specialist treatment centres are therefore aligned with those of the most affected communities. This service is administered by the leading paediatric and adult nephrology centres in Birmingham, Leeds and London, where genetic confirmation of the diagnosis is performed and the majority of the most severely affected PH1 patients are currently managed. Initiating treatment with Lumasiran would be limited to these three paediatric centres plus the national renal reference centre for adult patients at the Royal Free Hospital in London. **2) The target patient group is distinct for clinical reasons** PH1 is an ultra-rare, autosomal recessive disease caused by mutations in *AGXT*, the gene that encodes AGT, a hepatic enzyme important for glyoxylate metabolism. PH1 is the most clinically severe form of primary hyperoxaluria and can be definitively diagnosed by gene sequencing to detect pathological mutations in the *AGXT*, or by evaluation of AGT enzymatic activity in liver tissue obtained by biopsy. A minority of patients are identified through familial testing, as full siblings of patients with PH1 each have a 25% risk of also having the disease. Thus, siblings are often screened to detect subclinical or early disease. **3) The condition is chronic and severely disabling** In PH1, progressive kidney damage leads to ESRD in 24% of patients by age 20 years, 57% by 40 years, and 88% by 60 years [Hopp 2015]. Patients with higher urinary oxalate are at higher risk of progression to ESRD. For the	

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		majority of patients, current clinical management approaches aim to slow disease progression but fail to prevent it. Without effective treatment, death occurs due to renal failure or complications of oxalosis. Deficiencies in AGT result in the excessive production of oxalate, the key toxic mediator of PH1. Oxalate cannot be metabolised and is excreted by the kidneys. Excessive urinary oxalate results in crystal formation in the renal parenchyma and urinary tract. This leads to recurrent urolithiasis and nephrocalcinosis and causes direct damage to renal tubular cells, causing progressive kidney damage and, ultimately, renal failure. As renal function declines, the capacity of the kidney to clear oxalate from the blood decreases so oxalate levels in the plasma increase. This leads to deposition of oxalate in tissues outside the kidney such as the bone, heart, skin and eye causing bone pain, pathologic fractures, refractory anaemia, cardiomyopathy, skin ulcerations, and vision impairment. [Hoppe 2009] Children with PH1 who are symptomatic during infancy (age <1 year) generally have the most severe disease course, characterised by rapid progression to renal failure. These infants are at high risk of ESRD and systemic oxalosis, which is particularly severe and problematic in children due to oxalate deposition in developing vital organs. Approximately one quarter of all PH1 cases present with this severe infantile form, which is associated with a 5-fold higher risk of death compared to older patients with PH1. [Harambat 2010] The severity of the clinical course of PH1 is however variable as some patients with a particular genotype experience a milder form of the disease that is responsive to vitamin B6 (where the enzyme AGT remains functional due to non-truncating mutations but is subject to mistargeting; in contrast to the other, more severe forms of PH1 where AGT is rendered non-functional, generally due to truncating mutations). [Hopp 2015] The small number of patients who are fully responsive to vitamin B6 would **not** be considered for lumasiran. Therefore, in the NHS lumasiran would be a treatment only for	

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		patients with the more severe forms of PH1 who are not responsive to vitamin B6. This is in line with the ILLUMINATE-A pivotal trial population where only patients with disease resistant to existing clinical management (as evidenced by elevated urinary oxalate levels) were eligible to participate – and is fully in line with the unmet clinical need for an effective treatment in PH1. **4) The technology is expected to be used exclusively in the context of a highly specialised service** Whilst no single Highly Specialised Service for PH1 is currently commissioned, PH1 patients are currently managed through the existing national nephrology networks and are concentrated in highly specialist, tertiary referral centres spread across 3 geographical regions (Birmingham, Leeds/Bradford and London), aligned with the locations of the ethnic communities most affected by the disease and the particular requirement for treatment of children at nearby specialist paediatric centres, as this disease disproportionately affects children. There is no current service specification for PH1 because there are no approved treatments beyond supportive care with subsequent dialysis and possible transplantation. Also, there are insufficient patients with only 5-10 new cases of PH1 diagnosed annually. These issues, together with the prevalent population demographics spanning neonatal, paediatric and adult patients mean that, prior to the availability of a specific and effective treatment for PH1, a highly specialised service dedicated to the care of primary hyperoxaluria patients has not been commissioned. 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 patients with PH1 near to the location of the affected communities - and this is especially important for the predominantly paediatric population that may require regular, highly specialist hospital care. Initiating treatment with	

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		lumasiran would be limited to these three paediatric centres, plus the national renal reference centre for adult patients at the Royal Free Hospital in London. These are expected to be the centres where patients will be enrolled into the forthcoming EAMS programme and are also aligned with the study sites in the lumasiran trial programme. **5) The technology is likely to have a very high acquisition cost** The price of lumasiran is not yet available. However, when considering both the severity and extreme rarity of PH1 together with the benefit that lumasiran brings to this patient population, as well as the highly innovative nature of this new gene silencing technology, it is anticipated that lumasiran will have a very high acquisition cost commensurate with other highly effective, innovative treatments for ultra-rare, life-threatening diseases evaluated through the HST pathway. **6) The technology and has the potential for lifelong use** Lumasiran is administered as a sub-cutaneous injection with either a monthly or 3-monthly schedule and is intended to be given chronically, with the potential for lifelong use. **7) The need for national commissioning of the technology is significant** Due to the rarity of PH1, an extremely limited number of clinicians have sufficient expertise to care appropriately for these patients. These clinical experts are therefore concentrated in specialist centres in the 3 geographical regions of highest disease incidence, in line with the affected ethnic communities (Birmingham, Leeds/Bradford and London). PH1 patients have a high risk of developing serious complications of the disease and may require care from different parts of the NHS, which is not routinely available outside specialist centres. National commissioning is essential to ensure the burden of health care resource use associated with this chronic and severely disabling condition does not fall disproportionately on the health services	

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		within these few regions of highest disease incidence. National commissioning will become increasingly important when considering the introduction of lumasiran, as the first ever approved treatment in PH1, because its administration would be limited to the four highly specialist centres described earlier. In summary, we strongly believe that STA would not be an appropriate methodology to assess this highly novel technology in such a rare genetic disease and therefore request that lumasiran be evaluated under the HST process, in line with the original proposal by NICE. Hoppe B. The Primary Hyperoxalurias. *Kidney Int*. 2009;75(12):1264–1271. Harambat J et al. Genotype-phenotype correlation in PH1: the p.Gly170Arg AGXT mutation is associated with a better outcome. *Kidney Int.* 2010;77(5):443-449. Hopp K et al. Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria. *J Am Soc Nephrol.* 2015;26(10):2559-2570.	
	NHS England and NHS Improvement	Selection of Lumasiran for treatment of Hyperoxaluria type 1 would be a step change in providing an effective drug in addition to dietary changes and vitamin B to reduce the severity of the disease and progression to end stage renal failure and the risk of requiring renal/liver transplantation.	Thank you for your comment. No further action required.
Wording	Great Ormond Street Hospital NHS Foundation Trust	Appropriate	Thank you for your comment. No further action required.

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	Renal Association	Yes	Thank you for your comment. No further action required.
	Alnylam	We agree that the wording in the draft remit appropriately reflects the issues NICE should consider.	Thank you for your comment. No further action required.
	NHS England and NHS Improvement	Largely the wording reflects the issues. Adding information on the cost saving impact of patients no longer progressing to transplantation surgery or this being delayed would be positive. Quality of life cost saving should also be emphasised	Thank you for your comment. The draft remit aims to give a brief description of the appraisal objective. These outcomes should be accounted for in the economic analysis. No further action required.
Timing Issues	Great Ormond Street Hospital NHS Foundation Trust	Urgent (Lumaisran has potential to significantly change prognosis for patients, in particular infants with severe PH1)).	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

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			No changes to the remit required.
	Renal Association	There are a number of patients who have worsening kidney function as a result of this disease who are not participating in clinical trials and who may potentially benefit before their kidney function deteriorates further.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No changes to the remit required.
	Alnylam	We believe there is a strong rationale for urgent HST evaluation of lumasiran for the following reasons: **Accelerated regulatory assessment** Lumasiran received Orphan Designation in 2016 and PRIME designation in 2018 in line with the EMA aim to bring therapeutic innovations of major public health interest to patients more quickly. Accelerated assessment was recently confirmed. The FDA also recently awarded lumasiran Priority Review following the earlier Breakthrough Designation in 2018. Applications for marketing authorisation were recently submitted to the EMA and the FDA. Lumasiran will also shortly be available in the UK through the MHRA Early Access to Medicines Scheme due to the urgent need for an effective treatment in PH1. A timely HST evaluation would be aligned with NICE's	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. After considering comments received

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		published procedural and methodological guidelines regarding the completion of appraisals as close to marketing authorisation as possible. **Urgent clinical need** Current limited clinical management options for the treatment of PH1 may benefit some patients, but in the majority, they merely delay disease progression and the inevitable onset of end stage renal disease (ESRD). Consequently, there is an urgent need for new therapies that can effectively target the causative factors of PH1 and reduce hepatic oxalate production. Such an approach has the potential to halt or reverse manifestations of disease progression in patients of all ages and stages of disease. **Children are most seriously affected** Although PH1 can affect patients of all ages, the most serious and life-threatening aspects of the disease often affect children. Children with PH1 who are symptomatic during infancy (aged <1 year) generally have the most severe disease course, characterised by very rapid progression to renal failure. Approximately one quarter of all PH1 cases present with this severe infantile form, which is associated with a 5-fold higher risk of death compared to older patients. [Harambat 2010] These infants are at high risk of ESRD and systemic oxalosis, which is particularly severe and problematic in children due to oxalate deposition in developing vital organs. In summary, we believe a prompt evaluation under the HST process would be appropriate to bring this highly novel technology to the patients in urgent need of an effective treatment in PH1. Harambat J et al. Genotype-phenotype correlation in PH1: the p.Gly170Arg AGXT mutation is associated with a better outcome. *Kidney Int.* 2010;77(5):443-449. Tang X et al. Acute and chronic kidney injury in nephrolithiasis. *Curr Opin Nephrol Hypertens.* 2014;23(4):385-390.	from consultation and scoping workshop, it was agreed that the appropriate route for this topic is highly specialised technologies (HST). No changes to the remit required.

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	NHS England and NHS Improvement	Urgent to reduce clinical risk and introduce a less invasive and improved treatment option.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No changes to the remit required.
Additional comments on the draft remit	Alnylam	We do not have additional comments.	Thank you for your comment. No further action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Great Ormond Street Hospital NHS Foundation Trust	1. Need to include effects of systemic oxalate deposition in the eyes, skin and bone marrow with associated mortality in severely affected patients (especially infants) with PH1 and reduced kidney function. 2. Vitamin B6 may reduce urinary oxalate levels in a subset of patients, but not all	Thank you for your comment. The scope is intended to provide a brief description of the disease area and epidemiology data. Some further detail

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			about oxalosis deposition and vitamin B6 have been added.
	Renal Association	No comment	Thank you for your comment. No further action required.
	Alnylam	We believe the background information is generally accurate. We agree with the estimated prevalence of around 90 patients with PH1. Of these however, only a subset would be treated with lumasiran as it would not be used in patients who have already received a liver or combined liver and kidney transplant. Experts estimate 10-15 patients would start treatment in the first year, with no more than 5-10 new patients per year.	Thank you for your comment. The scope is intended to provide a brief description of the disease area and epidemiology data. No further action required.
	NHS England and NHS Improvement	Yes	Thank you for your comment. No further action required.
The technology/ intervention	Great Ormond Street Hospital NHS Foundation Trust	Lumasiran is being studied in several international clinical trials, including - Double blind placebo controlled RCT in children >6years and adults with PH1 - Open label single arm study in infants and children < 6 years with PH1 with eGFR >45ml/min - Single arm study I patients (term infants to adults) with advanced PH1 and severely reduced kidney function (eGFR <45ml/min/1.73m2) on or off haemodialysis	Thank you for your comment. Some further detail about clinical trials have been added.

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	Renal Association	Yes	Thank you for your comment. No further action required.
	Alnylam	We believe the description of lumasiran is accurate but not complete so would add the following text: Lumasiran inhibits hydroxyacid oxidase 1 (HAO1) messenger RNA in the liver via the naturally occurring mechanism of RNA interference (RNAi), thereby reducing the production of the hepatic enzyme glycolate oxidase (GO) that is upstream of the defect that causes PH1. Reducing the level of GO enzyme results in a decrease in the production of oxalate in the liver and, consequently, lowers urinary and plasma oxalate in PH1 patients. Thus, lumasiran may eliminate excessive oxalate production by the liver, with the potential to halt or reverse the progression of PH1.	Thank you for your comment. The scope is intended to provide a brief description of the technology. Further details can be presented in the company submission. No changes required.
	NHS England and NHS Improvement	Yes	Thank you for your comment. No further action required.
Population	Great Ormond Street Hospital NHS Foundation Trust	Infants and young children should be considered separately - severely affected infants have a high risk of kidney failure and death. Currently, surviving adults are less severely affected.	Thank you for your comment. The population section of the scope is intended to cover the population that is likely to be the marketing authorisation of the technology. NICE acknowledges the differences in severity in potential subgroups and

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			a mention has been added in the 'other considerations' section of the scope.
	Renal Association	Yes, appropriate. It can affect any age so no need for subgroups.	Thank you for your comment. No further action required.
	Alnylam	We believe the population is defined appropriately in line with the proposed indication statement in the EMA application. However, patients who have already received a liver transplant or a combined kidney and liver transplant should be excluded from the scope. This is because patients with advanced 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. This substantially reduces the number of prevalent patients with PH1 as liver transplant is performed in the UK when there are no other remaining options to prevent the otherwise devastating effects of systemic oxalosis and where organs are available. As noted in the appropriateness section of the draft scope, the small number of patients who are fully responsive to vitamin B6 would not be considered for lumasiran. Therefore, in the NHS lumasiran would be a treatment only for patients with the more severe forms of PH1 who are not responsive to vitamin B6. This is in line with the pivotal ILLUMINATE-A trial population where only patients with disease resistant to existing clinical management (as evidenced by elevated urinary oxalate levels) were eligible to participate – and is fully in line with the unmet clinical need for an effective treatment in PH1. Clinical experts estimate 10-15 patients would start lumasiran in the first year, with no more than 5-10 new patients per year after this.	Thank you for your comment. The population section of the scope is intended to cover the population that is likely to be the marketing authorisation of the technology. NICE acknowledges the differences in severity in potential subgroups and a mention has been added in the 'other considerations' section of the scope.

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	NHS England and NHS Improvement	Patients who are newly diagnosed or at pre-end stage renal failure should be prioritised for treatment to prevent deterioration	Thank you for your comment. The population section of the scope is intended to cover the population that is likely to be the marketing authorisation of the technology. NICE acknowledges the differences in severity in potential subgroups and a mention has been added in the 'other considerations' section of the scope.
Comparators	Great Ormond Street Hospital NHS Foundation Trust	Comparators are appropriate	Thank you for your comment. No further action required.
	Renal Association	Yes. But "kidney transplant" alone is usually not appropriate management in this condition and should not be a comparator. If the AGXT mutation is vitamin B6 sensitive then the best comparator is B6+diet. If it is not B6 sensitive then combined liver-kidney transplant.	Thank you for your comment. Following the consultation and scoping workshop, the comparators section has been amended to reflect the current clinical practice. That is, haemodialysis and

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			hyperhydration have been added to the comparators and kidney transplant has been removed.
	Alnylam	We believe that established clinical management (ECM) without lumasiran is the appropriate comparator. The most important components of the ECM regimen are vitamin B6 – the only agent that may lower oxalate levels in some patients – plus crystallisation inhibitors and hyperhydration that do not reduce oxalate levels but may reduce crystallisation in the urinary tract. [Cochat 2012] In the pivotal studies, treatment with lumasiran was given in addition to a stable regimen of established clinical management. The aim of treatment with lumasiran will be to replace elements of ECM as clinically appropriate. **Vitamin B6 (pyridoxine)** This can be an important component of ECM as it has been shown to reduce oxalate levels in some patients with PH1, but responses are highly variable: • A minority of PH1 patients may experience normalisation of oxalate levels and subsequent arrest of disease progression. [Mandrile 2014] However, such favourable responses are limited to patients with specific genotypes, generally associated with a milder form of PH1. [Hopp 2015] • The majority of patients experience only a small reduction in oxalate levels that may delay but cannot halt the inexorable renal decline Although vitamin B6 is a key component of ECM, we do not believe that vitamin B6 alone should be a comparator for the following reasons:	Thank you for your comment. Following the consultation and scoping workshop, the comparators section has been amended to reflect the current clinical practice. That is, haemodialysis and hyperhydration have been added to the comparators and kidney transplant has been removed. We heard from clinical experts that sequential liver kidney transplant was part of the clinical management once patients progress to end stage renal failure and as a result, it has been retained as a comparator.

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		• The small number of patients who are fully responsive to vitamin B6 would **not** be considered for lumasiran • The ILLUMINATE-A trial showed that lumasiran was equally effective both in patients who were and who were not receiving vitamin B6 **Transplantation in PH1** Potential options for advanced PH1 include combined kidney-liver transplant (cKLT) and liver only transplant (LoT) according to the extent of renal impairment. However, both these transplant options would only be considered in the advanced stages of PH1 i.e. much later in the disease process than when lumasiran could be initiated. The great majority (82%) of patients enrolled into ILLUMINATE-A were in CKD stages 1-2 (eGFR ≥60 mL/min/1.73 m^2), so these patients would **not** be considered for transplantation. Details of the different forms of transplantation are discussed below. **Kidney only transplantation (KoT)** KoT should not be considered a comparator for the following reasons: • Kidney failure is a downstream consequence of PH1 and the use of renal transplantation to thereby return kidney function is in no way comparable with the action of lumasiran, which is targeted at the hepatic enzyme AGT to prevent oxalate production in the liver • There is generally no scientific rationale for this procedure in PH1 and it is not recommended in the great majority of circumstances. [Cochat 2012] • KoT no longer forms part of the management of PH1 patients in the UK due to the high failure rate (because the source of pathological oxalate production in the liver remains unchanged after this procedure) In summary therefore, KoT is not an appropriate comparator to lumasiran.	

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		Combined kidney-liver transplantation (cKLT) We do not believe that cKLT is an appropriate comparator for the following reasons: • cKLT is a high-risk procedure and is only employed as a treatment of last resort when patients with advanced renal disease have exhausted all other options and in order to prevent long-term, intensive renal dialysis. [Cochat 2012] • It would only ever be considered in the most advanced stage of renal insufficiency (CKD stage 5), which is much later in the disease process than when lumasiran would be initiated. ILLUMINATE-A enrolment was limited to CKD stages 1-3b (eGFR >30 mL/min/1.73 m^2) at screening • Transplantation is not an option for all patients, due to the limited availability of donors. Inequalities among ethnic groups in the UK may present serious challenges in the communities where PH1 mainly occurs • Some potential candidates may not find a match before progressing beyond the point where transplant is recommended • Related living donation of liver lobes, including parent to child donation, carries risks of morbidity and mortality to the donor. In a genetic condition such as PH1 with the highest incidence in specific families where more than one family member may be affected, there may be ethical complications and dilemmas around limited organ availability Considering all these factors together, neither KoT nor cKLT should be a comparator in the NICE evaluation of lumasiran.	

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		Cochat P et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. *Nephrol Dial Transplant.* 2012;27(5):1729-1736. Hoppe B. Evidence of true genotype – phenotype correlation in primary hyperoxaluria type 1. *Kidney International* 2010;77:383–385. Hopp K et al. Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria. *J Am Soc Nephrol.* 2015;26(10):2559-2570. Mandrile G et al. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. *Kidney International.* 2014;86:1197-1204. Cochat P, Groothoff J. Primary hyperoxaluria type 1: practical and ethical issues. *Pediatr Nephrol.* 2013;28(12):2273-2281.	
	NHS England and NHS Improvement	Standard treatments are dietary modification and ingesting vitamin B to reduce oxalate levels. End stage renal disease progresses to kidney/liver transplant, sequential kidney/liver transplants or stand alone kidney or liver transplant. Of these, dietary modification with or without vitamin B are considered the best alternative care	Thank you for your comment. Following the consultation and scoping workshop, the comparators section has been amended to reflect the current clinical practice. That is, haemodialysis and hyperhydration have been added to the comparators and kidney transplant has been removed.

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Outcomes	Great Ormond Street Hospital NHS Foundation Trust	Urinary oxalate levels are the most appropriate outcome measure as this is the most sensitive measure of efficacy. The other measures should also be included.	Thank you for your comment. No further action required.
	Renal Association	Yes. For many patients, the primary clinical problem is frequent stone disease, and this is not mentioned. However, changes in stone formation are well known to be very difficult to measure in clinical trials, hence recognition by regulators of urine oxalate as a surrogate measure. In longer term trials, measuring stone outcomes would be important from a patient perspective.	Thank you for your comment. No further action required.
	Alnylam	We believe that the outcomes listed in the draft scope are generally appropriate for patients with PH1 and many were selected as endpoints in the pivotal lumasiran trials. However, some of these should be considered in the wider context of the natural history of the disease and the highly variable rates of disease progression. Oxalate levels are well established as the most immediate predictors of morbidity in PH1, followed by changes in eGFR. Therefore, long term outcomes can be predicted from changes in these early markers of disease progression. **Oxalate levels in urine** • Urinary oxalate (UOx) excretion is regarded as the most sensitive and clinically relevant marker that directly relates to the disease pathophysiology and is widely used clinically for diagnosis and management of PH1 patients with preserved renal function. [Milliner 2020] • Regulatory agencies have approved oxalate related outcomes as primary endpoints in all the pivotal lumasiran trials based on their ability to predict long-term outcomes • We believe that the UOx related outcomes discussed above are the most relevant for consideration in PH1 but would be appropriate for	Thank you for your comment. The outcomes listed are not intended to be exhaustive. The outcomes have been amended to include oxalate levels in plasma.

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		evaluation only under the HST pathway due to the rare and complex nature of the disease and the associated, inevitable clinical uncertainty Although UOx is regarded as the most appropriate indicator in patients with preserved renal function, plasma oxalate (POx) is most appropriate when renal function has begun to decline significantly and then in advanced PH1 where it is an important indicator of the systemic manifestations of the disease. Therefore, when considering the overall impact of oxalate on declining renal function, it is helpful to consider both UOx and POx related outcomes. [Milliner 2020] For this reason, changes in both UOx and POx were selected as endpoints in the pivotal ILLUMINATE trials. Milliner D et al. Endpoints for Clinical Trials in Primary Hyperoxaluria. *Clin J Am Soc Nephrol.* 2020 Mar 12; doi: 10.2215/CJN.13821119. Published online ahead of print.	
	NHS England and NHS Improvement	Yes Add in any adverse incidents relating to the treatment.	Thank you for your comment. Adverse effects of treatment are included in the outcomes. No further action required.
Economic analysis	Great Ormond Street Hospital NHS Foundation Trust	Appropriate	Thank you for your comment. No further action required.
	Renal Association	Many outcome measures (e.g. change in eGFR, need for transplant, quality of life (which is often dictated by stone frequency) are long-term and would need to be ascertained over at least 2 years and preferably longer. Economic	Thank you for your comment. The NICE reference case

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		costs due to changes in need for stone procedures and time off work/school should be included in the analysis.	specifies that the time horizon should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared (please see sections 5.1.15–5.1.17 of the Guide to the methods of technology appraisal 2013). The NICE reference case specifies that the perspective on costs is NHS and PSS in which time off work/school would not be included (Please see section 5.1.7 of the Guide of the methods of technology appraisal 2013).
	Alnylam	Lumasiran is **not appropriate** for consideration under STA as this methodology is in no way suited to a treatment for a tiny number of patients in a disease with single figure annual incidence rates, where the clinical uncertainty is inevitably greater than in larger populations. The entire patient population with PH1 is estimated at 90 patients in the UK and a significant number of these would not be considered for treatment with lumasiran. Clinical experts estimate up to 10-15 patients would start treatment with lumasiran in the first year of availability in England, with no more than 5-10	Thank you for your comment. After considering comments received from consultation and scoping workshop, it was agreed that the appropriate route for

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		new patients each year after this. The great majority of HSTs concluded to date have evaluated treatments for total patient populations larger than this. We request that lumasiran be scheduled for evaluation as a highly specialised technology for these reasons, together with those cited in the appropriateness section of the scope.	this topic is highly specialised technologies (HST).
	NHS England and NHS Improvement	Yes	Thank you for your comment. No further action required.
Equality and Diversity	Great Ormond Street Hospital NHS Foundation Trust	PH1 is an autosomal recessive disorder, therefore cultures in which consanguineous marriage is common are disproportionately affected. The proposed remit and scope do not need to be changed to address this, however it may be helpful to note.	Thank you for your comment. Equalities considerations will be addressed in the Equalities Impact Assessment form in detail.
	Renal Association	Ease of access for patients from all areas of the country to attend specialist centres for metabolic kidney stone disease. Possibly the greatest inequality risk would be those that have symptoms of primary hyperoxaluria but are not referred for assessment to a specialist centre because of distance or inadequate referral pathways. Nowadays, some of this can be done by telemedicine.	Thank you for your comment. Equalities considerations will be addressed in the Equalities Impact Assessment form in detail.
	Alnylam	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. Many of these patients are located in three distinct geographic regions.	Thank you for your comment. Equalities considerations will be addressed in the Equalities Impact

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		This treatment represents a paradigm shift for the very small group of patients with PH1, a total population of around 90 people in the UK with only 15-20 patients anticipated to require lumasiran in the first year and with no more than 5-10 new patients per year. Assessment of lumasiran under the standard Single Technology Appraisal process, which is acknowledged to have significant difficulties in assessing very small groups of patients, would be discriminatory to patients with this debilitating genetic disease where the numbers are small, but the need is nevertheless extremely urgent. A more appropriate technology evaluation route available to other patients with comparable ultra-rare conditions would therefore eliminate such discrimination.	Assessment form in detail.
	NHS England and NHS Improvement	No issues identified	Thank you for your comment. No further action required.
Other considerations	Renal Association	Does the company have any plans to assist in diagnosis of new patients? This is the case with manufacturers of high cost drugs in rare diseases such as Fabry disease.	Thank you for your comment. This may be something the company will refer to in their submission. No further action required.
	Alnylam	We do not have additional comments.	Thank you for your comment. No further action required.
	NHS England and NHS Improvement	N/A	Thank you for your comment. No further action required.

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Innovation	Great Ormond Street Hospital NHS Foundation Trust	Yes – Small interfering RNA therapies are highly innovative. Initial clinical trial data indicate that this will be a pivotal treatment with potential to transform outcomes for severely affected children with PH1.	Thank you for your comment. The innovative nature of lumasiran will be considered by the NICE appraisal committee during the appraisal. No action required.
	Renal Association	Yes, without doubt this will be a step-change. The published data show a very profound and impressive 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. Published abstract at ERA-EDTA conference in 2020 of the manufacturer's trial data. Outcomes of transplantation in patients with hyperoxaluria from NHSBT.	Thank you for your comment. The innovative nature of lumasiran will be considered by the NICE appraisal committee during the appraisal. No action required.
	Alnylam	Lumasiran represents a paradigm shift in the management of PH1 by offering a pharmacological option that can normalise endogenous oxalate levels and reduce or remove the need for dialysis and organ transplantation. It will be the first approved treatment for PH1 and addresses urgent unmet clinical needs, as demonstrated by the accelerated regulatory assessments and, in the UK, the PIM designation and forthcoming EAMS programme. There are currently no approved treatments for PH1. Most current clinical management approaches aim to slow disease progression but fail to prevent it. In contrast, lumasiran targets the disease at its source by reducing the production of oxalate, the toxic metabolite produced by the liver, and directly mediates the pathology observed in organs including those of the urinary system, thereby slowing the progression of the disease. The natural history of	Thank you for your comment. The innovative nature of lumasiran will be considered by the NICE appraisal committee during the appraisal. No action required. After considering comments received from consultation and scoping workshop, it

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		untreated PH1 is one of progressive decline in renal function with eventual progression to oxalosis and death either from ESRD or complications of oxalosis. Lumasiran is only the third medicine to work through RNA interference (RNAi) – gene silencing – a highly novel 'break through' class. The prompt commencement of HST evaluation would allow the timely development of NICE guidance in order to bring this treatment to the patients urgently in need. The economic analyses performed under Single Technology Appraisal do not permit in-depth consideration of the impact beyond direct health benefits, but these may be included in HST evaluation. Specifically, the burden of PH1 on the day to day life of patient families and caregivers may be acute and this will not otherwise be captured in the economic analyses. For example, an average-sized 10-year-old with PH1 is instructed to consume approximately 3.5 litres of fluid per day, distributed throughout the day and night to maintain dilute urine. The impact on caregivers, especially of young children, of continuously maintaining this regimen over many years can be considerable. Infants and younger children who are unable to comply may require a naso-gastric or percutaneous endoscopic gastrostomy tube passed into the stomach through the abdominal wall, to provide a means of delivering continuous, day and night hyperhydration. [Cochat 2012] The psychological trauma associated with hyperhydration in adolescents and teenagers can also be so burdensome as to negatively impact health. [Leflot 2018]. In addition, the requirement for almost daily travel to long dialysis sessions following the onset of advanced disease can become all-consuming for patients and for caregivers. [Lawrence & Wattenberg 2020] Together these procedures are associated with a huge burden on families and caregivers. The impact of lumasiran could drastically reduce this burden over the long term and offer considerable benefits in these patient populations at highest risk of rapid disease progression. It is essential that	was agreed that the appropriate route for this topic is highly specialised technologies (HST).

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		lumasiran undergoes HST evaluation so that due consideration may be given to all of the substantial benefits that lumasiran may offer to these patients, which otherwise would not be considered under the STA process. Cochat P et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. 2012;27(5):1729-1736. Leflot M et al. Type I primary hyperoxaluria: From childhood to adult, how to manage adequately medical therapy compliance? Nephrol Ther. 2018;14(3):148-152. Lawrence & Wattenberg Primary Hyperoxaluria - The Patient and Caregiver Perspective. CJASN April 2020. DOI: https://doi.org/10.2215/CJN Published online ahead of print.	
	NHS England and NHS Improvement	Yes, this treatment would be a step change in improving the treatment options available for this cohort of patients to prevent or delay development or deterioration of end stage renal failure.	Thank you for your comment. The innovative nature of lumasiran will be considered by the NICE appraisal committee during the appraisal. No action required.
Questions for consultation	Great Ormond Street Hospital NHS Foundation Trust	1. Liver only transplant, and combined liver kidney transplant should be considered as comparator therapies. Lumasiran would replace transplant 2. Absence of long term follow up data for patients on Lumasiran may impact QUALY calculations. Extrapolation of anticipated benefit based on biochemical results will be necessary.	Thank you for your comments. The comparator section has been amended following consultation and workshop.

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		3. Lumaisran clinical trial data are currently available in abstract form rather than published manuscripts at the present time.	The anticipated benefits will be considered by the NICE appraisal committee along with extrapolation.
	Renal Association	*Would lumasiran be given in addition to established clinical management or replace current established clinical management?* Possibly in addition to vitamin B6 and diet; would aim to replace liver transplantation. Data on the number of liver transplants performed in the UK for the indication of hyperoxaluria are available from NHSBT. *Are there any other subgroups of people in whom lumasiran is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?* One could argue that those with CKD stage 2 or 3 due to primary hyperoxaluria are likely to benefit disproportionately, as they have evidence of low eGFR due to hyperoxaluria with potential scope to reduce the rate of progression with the drug. *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* It would need to be managed and co-ordinated via specialist centres, perhaps along the lines of the National Amyloid Centre or National Complement Therapeutics Centre. This will prevent appropriate use of the technology	Thank you for your comments. The comparator section has been amended following consultation and workshop. NICE acknowledges the differences in severity in potential subgroups and a mention has been added in the 'other considerations' section of the scope.
	Alnylam	1) *Have all relevant comparators for lumasiran been included in the scope? Is transplant considered a comparator to this technology?*	Thank you for your comments. The comparator section has

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		A1. Yes. All relevant comparators are discussed in the comparator section of *"Comment 2: the draft scope"*. A2. No. Transplant should not be considered as a comparator because it would be regarded as a potential option only in advanced PH1 i.e. where renal function has already deteriorated. Lumasiran has been studied in patients with relatively preserved renal function. 2) *Which treatments are considered to be established clinical practice in the NHS for primary hyperoxaluria type 1?* A. The most important components of the established clinical management regimen in the NHS are vitamin B6 – the only agent that may lower oxalate levels in some patients – plus crystallisation inhibitors and hyperhydration that do not reduce oxalate levels but may reduce crystallisation in the urinary tract. For more details please refer to the comparator section of *"Comment 2: the draft scope".* 3) *Would lumasiran be given in addition to established clinical management or replace current established clinical management?* A. In the pivotal studies, treatment with lumasiran was given in addition to a stable regimen of established clinical management. The aim of treatment with lumasiran will be to replace elements of ECM as clinically appropriate. For more details please refer to the comparator section of *"Comment 2: the draft scope".* 4) Please refer to the outcome section of *"Comment 2: the draft scope"* for answers to the questions regarding outcomes. 5) *Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?*	been amended following consultation and workshop. The innovative nature of lumasiran will be considered by the NICE appraisal committee during the appraisal.

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		A. Lumasiran demonstrated a consistent treatment effect across all subgroups. 6) Please refer to the equality section of *"Comment 2: the draft scope"* for answers to the questions regarding equality. 7*) Do you consider lumasiran to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* A. Lumasiran represents a paradigm shift in the management of PH1 by offering a pharmacological option that can normalise endogenous oxalate levels and reduce or remove the need for dialysis and organ transplantation. It will be the first approved treatment for PH1 and addresses urgent unmet clinical needs, as evidenced by the accelerated regulatory assessments and, in the UK, the PIM designation and forthcoming EAMS scheme. 8) *Do you consider that the use of lumasiran can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* A. Please refer to the innovation section of *"Comment 2: the draft scope"* for answers to the questions regarding health-related benefits that are unlikely to be included in the QALY calculation.	
	Metabolic Support UK	We'd like to ask why this technology is considered under single topic appraisal and not as a Highly-Specialized Technology?	Thank you for your comment. After considering comments received from consultation and scoping workshop, it was agreed that the

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			appropriate route for this topic is highly specialised technologies (HST).
	NHS England and NHS Improvement	The treatment can be introduced using current clinical pathways and services.	Thank you for your comment. No further action required.
Additional comments on the draft scope	Alnylam	We do not have additional comments.	Thank you for your comment. No further action required.