NICE National Institute for Health and Care Excellence

Highly Specialised Technology Appraisal

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY APPRAISAL

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Contents:

The following documents are made available to consultees and commentators:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Comments on the Evaluation Consultation Document from Alnylam**

2. **Consultee and commentator comments on the Evaluation Consultation Document from**:
   a. Metabolic Support UK and Jess Doyle, Head of Insight – patient expert nominated by Metabolic Support UK:
      i. Response form
      ii. Member responses
   b. UK Kidney Association

3. **Comments on the Evaluation Consultation Document from experts**
   a. Dr Wesley Hayes, Consultant Paediatric Nephrologist – clinical expert, nominated by British Association for Paediatric Nephrology
   b. Dr Sally-Anne Hulton, Consultant Paediatric Nephrologist – clinical expert, nominated by Alnylam (company)

4. **Comments on the Evaluation Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the Evaluation Consultation Document**

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 (HST)

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Company resubmission post-ECD

September 2022

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1 Introduction

Alnylam wishes to express our gratitude to the HST Evaluation Committee and the Evidence Review Group (ERG) for their careful consideration of our company submission (CS) for lumasiran for treating primary hyperoxaluria type 1 (PH1). In the draft Evaluation Consultation Document (ECD),[1] the Committee expressed uncertainty about certain topics incorporated in our original submission. In our company comments on the ECD (submitted on 13 June 2022), we resolved to undertake a number of approaches to address these uncertainties, including additional analyses, an updated literature search, and consultation with clinical experts. These steps have now been completed, and we have made substantive changes to our cost-effectiveness analysis (CEA) informed by the findings, to enable a more robust interpretation of the clinical and economic evidence for lumasiran.

In this resubmission document we describe only the revised methods and results arising from the changes we have implemented. Please refer to our original CS for an overview of the pathophysiology and disease burden of PH1, description of current clinical practice, details of relevant evidence sources, and documentation of aspects of the CEA that did not need to be modified for this resubmission. Other model revisions to address questions from the ERG prior to the Committee meeting are described in our previous responses to the ERG questions.

We addressed the following topics in our research and revision of the CEA:

- **Transplant probability:** following an updated literature search for relevant data on liver transplant rates for patients with PH1 in clinical practice, as well as consultation with UK clinical experts ([redacted] a [redacted] and an [redacted] and [redacted] also a [redacted] and a [redacted]), we have updated the source for transplant rates from the French study by Compagnon et al. (2014)[3] to a recently published study by Metry et al. (2022) reporting data from eight countries in the European Hyperoxaluria Consortium (OxalEurope) Registry.[4] In addition, we have identified an error in the ERG's calculation of transplant probability, which had prompted the ERG's conclusion that this parameter lacked face validity in our submitted model (ECD Section 3.20).
- **Health-state utilities:** we have reviewed the NICE methods guidance and individual-patient-level EQ-5D data from the ILLUMINATE-C trial to answer concerns raised by the ERG about the face validity of certain health-state utilities and their overall appropriateness for use in the CEA (ECD Sections 3.21 and 3.22[1]).
- **Dialysis rates:** to address concerns raised by the ERG and Committee (ECD Section 3.24),[1] we have incorporated different dialysis rates (i.e., percentages of patients receiving dialysis) for paediatric and adult patients in chronic kidney disease (CKD) stage 4 in the base-case analysis. In the absence of rigorous sources for these percentages, we have performed a range of scenario analyses to assess the impact of alternative rates of dialysis. (Please note that we addressed the separate issue of dialysis

intensity [i.e., number of sessions per week among patients receiving dialysis] in our response to the ERG report.)

- **Survival after transplant:** we have adopted the ERG's preferred assumption to base survival post-transplantation in patients receiving established clinical management (ECM) on the data for all patients in the study by Jamieson et al. (2005),[5] rather than only for those patients in *Fair* and *Poor* pre-operative condition as in our original submission.
- **CKD stage-specific progression:** to address the uncertainty of the ERG regarding different rates of disease progression in patients in different CKD stages (ECD Section 3.18),[1] the revised CEA incorporates rates of disease progression in CKD3b and CKD4 in the ECM arm as reported in a recently published study by Singh et al. (2022).[6] The appropriateness of using this approach was confirmed in consultation with the UK clinical experts [redacted].
- **Subpopulations of PH1 patients treated with lumasiran:** in response to insights shared by the clinical experts at the first Committee meeting regarding their intended use of lumasiran in different patient subpopulations (ECD Section 3.8),[1] we have refined which patients are modelled to receive lumasiran.

All cost results of the revised CEA incorporate the updated Patient Access Scheme (PAS) for lumasiran, communicated on 22 September 2022. In addition, the revised model incorporates the updated price for pyridoxine as shared by the ERG. This price is used in the base case and all scenario analyses.

Alnylam has also taken note of the issue of drug wastage related to fixed vial sizes, which was raised by the ERG (see ECD Section 3.27).[1] Given the constraints on a company the size of Alnylam, it was not feasible to create multiple vial sizes for lumasiran upon market entry. Although Alnylam is investigating other vial sizes as part of the life cycle of lumasiran, we hope that NICE and the ERG will understand that we are currently unable to account for this possibility in the revised CEA. However, we consider that in real-world clinical practice in the UK, it is likely that vial wastage could be mitigated by dose rounding to the nearest vial, a common practice in other therapeutic areas like oncology, where rounding down of a patient's calculated weight-based dose by up to 10%–15% if needed to avoid administration of an additional fractional vial is considered to be a rational strategy to help control drug costs.[7] This practice could not be accounted for in the revised CEA, which still uses the single-use vial size specified in the SmPC,[8] in accordance with the principle noted in the ECD that the Committee can only recommend the use of lumasiran within its marketing authorisation.[1] Because not accounting for potential dose rounding is conservative, we anticipate that the actual cost-effectiveness of lumasiran in real-world practice will be better than implied by the results of the revised CEA.

We believe that this resubmission with the revised model adequately addresses the uncertainties identified by the Committee. We wish to note that this resubmission document contains confidential information that has been marked accordingly.

2 Revised CEA Methods

2.1 Transplant probability

2.1.1 Revised evidence search

To ensure that the revised CEA incorporates liver transplant probabilities relevant to current UK practice based on the most current data available, a new targeted literature search was performed on 8 July 2022. Searches were conducted in MEDLINE, Embase, Transplant Library, Cochrane CENTRAL, Cochrane CDSR, and Epistemonikos using the combinations of terms related to PH1 and transplant shown in Table 1.

Table 1. Search strategy to identify sources for transplant rates in PH1

Search strategy
1 Hyperoxaluria, Primary/ (937) 2 ((primar$ or "type 1" or "type one") adj5 (hyperoxaluri$ or oxaloses or oxalosis or oxaluria or oxalurias)).ti,ab,ot,kw,hw. (1649) 3 ("congenital oxaluria" or "D-glycerate dehydrogenase deficien$" or PHGDH or "glyceric aciduria" or "glycolic aciduria" or "hepatic AGT deficiency" or "mckusick 25990" or "Alanine-glyoxylate aminotransferase deficiency" or "Peroxisomal alanine glyoxylate aminotransferase deficiency" or "Serine pyruvate aminotransferase deficiency").ti,ab,ot,kw,hw. (355) 4 1 or 2 or 3 (1974)
5 exp Transplants/ (30267) 6 (Transplant* or graft* or allograft*).ti,ab,kw,kf. (793493) 7 5 or 6 (804279)
8 4 and 7 (510)

PH1 = primary hyperoxaluria type 1

To increase sensitivity, the search was not limited by date of publication, publication type, study design, or language.

Results of this targeted literature search have been submitted to NICE. The most relevant publication on transplant rate resulting from this search, in terms of large sample size, rigorously defined PH1 population, and applicability to current clinical practice, was a study by Metry et al. (2022) based on data from the OxalEurope Registry.[4] This study was published online on 28 November 2021, so was not captured in the original CS, for which the last search update was performed on 4 August 2021. Given its larger size and geographic scope, we judged the study by Metry et al. to be a more relevant source for this NICE appraisal than the French study by Compagnon et al. (2014)[3] used in the CS.

2.1.2 Metry et al. (2022)

This was a retrospective cohort study that identified all patients with PH1 in the OxalEurope registry (one of the largest PH registries worldwide) who underwent liver or kidney transplantation.[4] Patients were from eight countries in Europe. Out of >1100 patients with PH, data were retrieved and analysed for 993 patients with PH1, of whom 159 underwent combined liver–kidney transplantation (cLKT) between 1978 and 2019.

2.1.3 Estimation of the probability of liver transplant

We updated the probability of liver transplant in patients with uncontrolled oxalate levels in the revised CEA based on Metry et al. (2022). Over the 41-year period covered by Metry et al. (2022), we calculated an average of 3.9 transplants per year (i.e., 159 transplants ÷ 41 years = 3.9 transplants per year).

Considering, in alignment with European PH1 clinical guidelines,[9] that cLKT for patients with PH1 would be performed only in those who have progressed to later-stage kidney disease, patients in the CEA may only transit to cLKT from CKD4 or end-stage kidney disease (ESKD). Therefore, to ensure direct applicability to the model health states in which transit to cLKT is possible, the transplant rate per patient per cycle should be calculated using a denominator that considers only those patients in CKD4 or ESKD. Residing in one of these two states is a precondition for transit to cLKT, such that patients in earlier CKD stages can be excluded from the denominator representing the pool of patients in which cLKT has some probability of occurring. Based on Singh et al. (2021),[10] the study from which CKD stage distribution was derived for the CS, 37.6% of prevalent PH1 patients are in CKD4 or ESKD. With 993 patients in the total OxalEurope PH1 cohort, the estimated number in CKD4 or ESKD would thus be 373 (i.e., 993 total patients × 37.6% of patients in CKD4 or ESRD = 373 CKD4 and ESKD patients).

The estimate of 3.9 transplants per year divided by 373 patients in CKD4 or ESKD yields an annual probability of transplant of 0.010, or a probability per 6-month cycle in the Markov model of 0.005 (i.e, $1-[1-0.010]^{0.5}$, where 0.5 is model cycle length in years).

This per-cycle transplant probability of 0.005 was used in the revised CEA base case and all scenario analyses for patients with uncontrolled oxalate in CKD4 or ESKD.

2.1.4 Clinical expert validation

Alnylam asked the two clinical experts whether they considered the study by Metry et al. (2022) to be an appropriate source for the liver transplant rate for patients with PH1 receiving ECM in the UK. Both experts indicated that OxalEurope is recognised as being comprehensive of historical outcomes for patients with PH1 and that it is representative of UK patients with PH1. They noted that it is one of the best sources of PH1 data available. They were supportive of using this dataset to estimate transplant rates in the model.

When the calculation used to model cLKT in PH1 patients (as outlined in the preceding section) was described to the experts, they agreed that the steps were logical/appropriate.

2.1.5 Error in ERG estimate of time on transplant waiting list

In Section 3.20 of the ECD, the Committee repeated the ERG's estimates of how long patients would have to wait for a transplant in our model depending on their age and whether or not their oxalate levels were controlled, and reiterated the ERG's opinion that face validity was lacking for the difference in implied mean time to transplant between people with controlled and uncontrolled plasma oxalate, namely:[1]

- 2.5 years for children and 4 years for adults with controlled oxalate
- 83 years for children and adults with uncontrolled oxalate

Alnylam notes that the ERG's calculations incorporate a methodological flaw leading to significant differences in the modelling of transplant. Specifically, the ERG calculated mean time to transplant by inverting the overall, cohort-level per-cycle transplant probabilities used in the model. Based on our review of the slides for the Committee meeting, this approach was also reflected in the wording used to obtain expert clinician input on this topic during the meeting. However, the per-cycle probability of receiving a transplant at the cohort level in the model is not within patients on the transplant waiting list, but instead within the aggregate group of patients on the waiting list and patients not on the list (i.e., patients who are not in suitable condition for a transplant). As a result, it is methodologically incorrect to invert this aggregated per-cycle probability to estimate a mean time to transplant as the ERG has done, because the resulting waiting time would not be representative of the subgroup of patients who are suitable candidates for transplant and actually on the waiting list, but rather would be confounded by the (essentially infinite) waiting time of patients who are not suitable candidates for transplantation and thus not on the waiting list. Consequently, the ERG's estimates are misleading as they substantially overestimate the waiting time for patients suitable for a transplant, and the clinician input on this question during the Committee meeting also reflected this misunderstanding.

Subsequently, we have consulted with the two clinical experts mentioned in Section 1 above, and reframed the question about transplant rate in language aligned with how this parameter is actually implemented in the CEA. Both clinical experts confirmed that our approach is logical. Supporting the face validity of our modelling of transplant probabilities, one of the clinical experts we consulted indicated that the implied rate of cLKT based on our calculated per-cycle probability—i.e., 1 cLKT every 2–3 years in the United Kingdom—seemed reasonable based on experience. The per-cycle probability of 0.007 based on Compagnon et al. (2014)[3] in our original model accompanying the CS was similar to the value of 0.005 obtained using cLKT data observed in the OxalEurope Registry as reported by Metry et al. (2022).[4] We note that these revised assumptions and corrected calculations based on these updated data yield very different values from the assumptions utilised by the ERG, as shown in Table 2.

Table 2. Transplant probabilities for patients on ECM

Approach	Transplants, N	Time period (years)	Patient cohort, N	Proportion of patients in CKD4/ESKD	Transplant probability	
					Per year	Per model cycle
Model in CS based on Compagnon et al. (2014)[3]	33	31	250	0.376	0.014	0.007
Revised model based on OxalEurope Registry[4]	159	41	993	0.376	0.010	0.005
ERG assumption – adults						0.06
ERG assumption – paediatric						0.1

CKD = chronic kidney disease; CS = company submission; ECM = established clinical management; ERG = Evidence Review Group; ESKD = end-stage kidney disease

2.2 Health-state utilities

2.2.1 Necessity of using vignette study instead of EQ-5D measures from ILLUMINATE-C for advanced disease state utilities

In Section 3.22 of the ECD, the Committee concluded, "it would have been helpful for the company to have provided the EQ-5D data measured in the ILLUMINATE-C study and complete an analysis to derive more accurate estimates of utility values for the late CKD and post-transplant health states."[1] In order to base these health-state utilities on data from ILLUMINATE-C, we would have needed to have robust EQ-5D data from ILLUMINATE-C for each subgroup included in the model. Unfortunately, due to the low total number of patients in ILLUMINATE-C and the number of model states over which these patients are distributed, it is not feasible to derive representative utility values for the different advanced-disease health states from this study. The extent of the problem is revealed in Table 3, which shows that many subgroups by CKD stage, age, and dialysis status had no patients with any EQ-5D assessments, while most other subgroups had EQ-5D scores from only 1 or 2 patients. This limitation precludes using ILLUMINATE-C as a source of accurate or meaningful utility values for the CEA.

Table 3. Number of patients in ILLUMINATE-C with an EQ-5D Index score

	eGFR			
	30–44 (CKD3b)	15–29 (CKD4)	<15 (ESKD)	Not Applicable*
Age <18 y				
Cohort A	[redacted]	[redacted]	[redacted]	[redacted]
Cohort B	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥18 y				
Cohort A	[redacted]	[redacted]	[redacted]	[redacted]
Cohort B	[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, ILLUMINATE-C data on file
Cohort A = patients who do not yet require dialysis; Cohort B = patients on dialysis; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol-5 Dimension; ESKD = end-stage kidney disease
*eGFR was calculated for patients in Cohort A only.

2.2.2 NICE methods guidance

In the first Committee meeting, the ERG and Committee questioned our position that EQ-5D valuation of vignettes is the preferred method for estimating health state utilities in advanced disease states in the CEA. Section 3.22 of the ECD states, "The committee agreed that the EQ-5D-5L utility values used in the company's base-case analysis were inconsistent with the values seen in the ILLUMINATE-A study. The committee agreed that it preferred the ERG's approach of using the time-trade-off valuations of the vignettes to estimate utilities for the late CKD and post-transplant health states."[1] To assess this suggestion, we have reviewed the relevant NICE methods guidance.

The relevant Decision Support Unit (DSU) guidance on this topic states explicitly that the DSU prefers EQ-5D over time-trade-off (TTO) for vignette valuation. The NICE Centre for Health Technology Evaluation (CHTE) methods review on health-related quality of life (HRQoL) notes that when utilities are to be derived from vignette studies:[11]

"The DSU recommend the following methods, in order of preference:

a) General population, clinical experts or patients complete the EQ-5D for each vignette and this is then valued using the relevant value set for EQ-5D, provided EQ5D is appropriate.

b) Preference elicitation techniques such as time trade-off with a sample of the general population.

c) Preference elicitation techniques such as time trade-off with patients.

d) Utility values elicited directly for each vignette from clinical experts, for example, using Delphi panels or preference elicitation methods including time trade-off."

Similarly, the DSU's 2020 report on best practices for measuring and valuing HRQoL when sufficient EQ-5D data are unavailable specifies, "Utility values for vignettes are generated using an appropriate sample of patients completing the EQ-5D for each vignette, and this is then scored using the appropriate and relevant value set for EQ-5D".[12]

These recommendations are reflected in the 2022 NICE health technology evaluation manual, which presents a hierarchy of preferred HRQoL valuation methods.[13] This hierarchy states that if EQ-5D data are not available from a relevant study, the literature, or mapping from another measure, then vignettes should be:[13]

- Developed using the DSU's best practice recommendations (see 2020 report)
- A sample of the general population, or people with the condition, should complete the EQ-5D based on the vignette; utilities should be calculated using the relevant EQ-5D value set

Therefore, Alnylam's use of EQ-5D valuations rather than TTO valuations from the vignette study aligns with best practices as identified by the DSU[12] and codified in the current NICE methods guidance.[13] Conversely, the use of TTO valuations by the ERG in preference over the EQ-5D valuations is not in accordance with NICE recommendations, and thus was not incorporated in our revised CEA.

2.2.3 Face validity of EQ-5D valuations of vignettes

Section 3.22 of the ECD suggests that the EQ-5D valuations of the vignettes had lower face validity than the TTO valuations.[1] However, EQ-5D Index scores at initial evaluation for the only subgroup in ILLUMINATE-C with more than 5 patients with available measures, namely paediatric patients on dialysis (n=[redacted]), show closer agreement with the low utilities yielded by EQ-5D valuation ([redacted] and [redacted] for CKD4 and ESKD, respectively) than with the utility values derived via TTO ([redacted] and [redacted], respectively). Notably, of these [redacted] patients, 3 had negative utility values at their first assessment in ILLUMINATE-C (see Table 4), and indeed these three scores were all substantially lower than the negative mean values yielded by the EQ-5D valuation of patient vignettes. These direct observations are not consistent with the assertion by the ERG that the TTO-derived health state utility values have greater face validity than the corresponding EQ-5D-derived values, thus further supporting the use of the EQ-5D valuations of the health-state vignettes.

Table 4. Individual-patient-level EQ-5D Index scores at first assessment for paediatric patients on dialysis in ILLUMINATE-C

Patient*	Index score
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: Alnylam, ILLUMINATE-C data on file
EQ-5D = EuroQol-5 Dimension
*Anonymised

2.2.4 Interpretation of differences between EQ-5D and TTO valuations of PH1 health-state vignettes for CKD4 and ESKD

Although it is not possible to ascertain precisely the reasons for the differences in vignette valuations using the EQ-5D vs. TTO methods, there are several possible contributing factors, including the following:

- Some participants may have held attitudes reducing their willingness to trade off years of life, such as certain religious beliefs, negative opinions about euthanasia, fear of death, and optimistic expectations about mental ageing and life expectancy,[14] which may in part explain the differences in outcomes between the TTO and EQ-5D approach to valuing the vignettes, as the EQ-5D approach does not require people to explicitly trade off years of life and therefore is not subject to upward bias of results due to respondents' potential aversion to trading life years in exchange for improved health.
- The EQ-5D items map more directly to the health issues included in the detailed PH1 health states described in the vignettes, and can therefore more systematically capture the impacts of these issues than the TTO method (which is less structured in its approach to capturing specific impacts of disease), potentially yielding a more objective valuation with greater sensitivity to the impacts of PH1.

2.2.5 Conclusion regarding valuation of PH1 health-state vignettes for CKD4 and ESKD

In summary, the use of utility values derived from EQ-5D valuation of PH1 health-state vignettes for CKD4 and ESKD is in agreement with best practices as identified by the NICE DSU and codified in the current NICE methods guidance. In addition, to the extent that the vignette-based utility values can be validated against data collected directly from ILLUMINATE-C, the EQ-5D valuations derived from the vignette study appear to have greater face validity than do the TTO-based vignette valuations. We believe the TTO valuation may not be as well-suited to capturing the complexity and specific impacts of PH1 health states as the EQ-5D method, which may provide a more sensitive and objective valuation of the vignettes. Therefore, we consider it to be appropriate to retain EQ-5D valuation of the vignettes for utilities in late-stage disease (CKD4/ESKD) in the revised CEA.

2.3 Dialysis rates in CKD4

In Section 3.24 of the ECD, the Committee expressed that they would have preferred for the company to have provided scenario analyses that varied the proportion of people undergoing dialysis among those receiving standard care (i.e., ECM) in the CKD4 health state.[1] Based on the clinical expert feedback received during the first Committee meeting, it is unclear whether all adult patients in CKD4 receiving ECM will be on dialysis. In the absence of rigorous evidence for the proportion of adult patients on ECM in CKD4 who were receiving dialysis, we addressed this uncertainty by selecting scenarios with intermediate proportions ranging from 0% to 50% and tested the sensitivity of model results to this parameter across such scenarios, as shown in Table 5.

Table 5. Dialysis rates in CKD4 in the revised CEA: base-case and scenario analyses

	Base case		Scenario analysis 1		Scenario analysis 2	
Age	Lumasiran	ECM	Lumasiran	ECM	Lumasiran	ECM
Adults	0%	25%	0%	50%	0%	0%
Paediatric	50%	100%	50%	100%	50%	100%

CKD = chronic kidney disease; ECM = established clinical management

2.4 Survival after transplant

Section 3.25 of the ECD notes that the ERG preferred to assume that estimates of overall survival from the full population of the study by Jamieson et al. (2005)[5] were representative of survival for all people in the standard care group.[1] The Committee agreed with the ERG's approach.

Accordingly, we have adopted the ERG's preferred assumption to base survival post-transplantation in patients with uncontrolled oxalate levels on the data for all patients in the study by Jamieson et al. (2005),[5] rather than only for those patients in *Fair* and *Poor* pre-operative condition as in our CS.

2.5 Rate of disease progression

In the revised base-case CEA, as in the original submission, the rate of disease progression in the ECM arm for paediatric patients in CKD1–3a was set to the change in estimated glomerular filtration rate (eGFR) calculated from the plasma oxalate–eGFR relationship reported by Shah et al. (2020)[15] multiplied by the change over time in plasma oxalate observed in the placebo arm of the ILLUMINATE-A trial, namely a per-cycle decline of 2.83 mL/min/1.73 m^2. This method has the advantage of using oxalate data from the ILLUMINATE-A trial to inform disease progression in the ECM arm of the model, and we thus deemed it appropriate to retain in the revised CEA for patients in less severe health states.

However, this method cannot be applied to more severe health states, because few patients in ILLUMINATE-A were in these health states, and because trials of lumasiran in such health states did not include a placebo arm in which to observe decline in eGFR in patients receiving only ECM. To fill this evidence gap, the original model accompanying the CS based the transition probability for CKD4 to ESKD on the ESKD-free survival curves reported by Harambat et al. (2010).[16] This represented a qualitatively different (and more limited) approach compared with the calculations of eGFR loss per cycle that are used

to estimate transitions in the less severe health states. Addressing this inconsistency, the revised CEA bases transitions for both paediatric and adult patients from CKD3b to CKD4 and from CKD4 to ESKD on a recently published study by Singh et al. (2022), which reported the rate of eGFR decline as a function of CKD stage in patients with PH1 enrolled in the Rare Kidney Stone Consortium (RKSC) registry.[6]

The clinical experts noted that the differential rates of annual eGFR decline in PH1 patients by CKD stage seen in clinical practice were generally consistent with those in the Singh et al. (2022) publication, and suggested that these rates in the publication by Singh et al. (2022) were appropriate to use in the model. Therefore, we used the rates of eGFR change reported by Singh et al. to fill the evidence gap where we did not have placebo-arm data from the lumasiran studies. This approach replicates the recognised phenomenon in which rates of eGFR decline increase with higher CKD stage.

As explained in Section 2.6.1, in the revised CEA we assumed that only those adult patients in CKD1–3a who showed signs of rapid progression (considered similar to CKD3b) would be initiated on lumasiran. Therefore, the rate of eGFR change in adults in CKD1–3a was assumed to be the same as the rate of progression in CKD3b, to model the fast rate of progression that would prompt treatment with lumasiran.

The resulting rates of eGFR decline by CKD stage in the ECM arm of the revised model are shown in Table 6.

Table 6. Per-cycle changes in eGFR in the ECM arm, by health state.

Model health state	Paediatric	Adult
CKD1-2	-2.83*	-7.35‡
CKD3a	-2.83*	-7.35‡
CKD3b	-7.35†	-7.35†
CKD4	-8.30†	-8.30†

CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate
*Calculated as the rate of change in plasma oxalate in ILLUMINATE-A multiplied by the rate of change in eGFR per unit change in plasma oxalate reported by Shah et al. (2020),[15] as in the original model.
†Calculated from the annual change reported by Singh et al. (2022)[6] divided by 2 to obtain change per cycle.
‡For adults in CKD1–3a, only those who are fast progressors are considered eligible for treatment, and therefore the eGFR progression of CKD3b per Singh et al. (2022) is applied to the CKD1–2 and CKD3a health states.

2.6 Subpopulations of PH1 patients treated with lumasiran

2.6.1 Patients initiating lumasiran

Alnylam acknowledges that the cost-effectiveness of lumasiran varies by patient subpopulation according to age group and CKD stage. At the first Committee meeting, the clinical experts provided insights into their intended use of lumasiran in different patient subpopulations, which would have clear impact on CEA results. Alnylam heard that whereas all paediatric patients would receive lumasiran, the therapy would be initiated in all adult patients in CKD3b or higher, and only those adults in earlier stages (i.e., CKD1–3a) experiencing rapid progression. This change was implemented in the revised CEA by adjusting the distribution of the cohort at model start to assume (arbitrarily) that 50% of all prevalent adult patients in

CKD1–3a are fast progressors. The resulting health-state distribution (after rescaling the overall distribution to account for exclusion of patients in CKD1-3a who are not fast progressors) for adults at model start following this change is shown in Table 7.

Table 7. Health-state distribution among adults at model start in revised base case with 50% of prevalent adult patients in CKD1–3a as fast progressors.

Health state	Proportion (%)
CKD1–2	26
CKD3a	8
CKD3b	16
CKD4	13
ESKD	37

CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease

To test the sensitivity of model results to the assumed proportion of adults in CKD1–3a who are fast progressors, we also performed a series of scenario analyses in which this parameter was varied: 10%, 25%, 75%, and 100%. The health-state distributions for adults at model start in these scenarios are presented in Table 8.

Table 8. Health-state distribution among adults at model start in scenario analyses with different proportions of fast progressors among prevalent adult patients in CKD1–3a.

	Percentage of fast progressors among prevalent adult patients in CKD1–3a			
	10%	25%	75%	100%
Proportion (%) of adult cohort in:				
CKD1–2	7	15	33	38
CKD3a	2	5	10	12
CKD3b	22	19	14	12
CKD4	18	16	11	10
ESKD	51	45	32	28

CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease

2.6.2 Lumasiran continuation rule

During consultation with the clinical experts, both considered it to be a plausible hypothesis that, upon maturity, a patient with paediatric-onset PH1 with mature kidneys could potentially sustain clearance of a higher background rate of oxalate production than they were able to sustain as a child with immature kidneys, and that as a result, even oxalate production rates that were above normal to some extent during maturity might not lead to increased morbidity or mortality in such patients. Thus, we considered that in the absence of severe renal impairment, it could be appropriate to pause lumasiran treatment at maturity to assess whether a patient with PH1 is able to remain stable without lumasiran intervention, with criteria for re-initiation of treatment with lumasiran in the event that the patient showed signs of progression.

One of the experts informed us that similar continuation rules are already used with therapies for other indications where a patient initiates treatment in childhood, giving the example of burosumab for X-linked hypophosphataemia in children and young people.[17]

In the absence of any data to inform the proportion of patients that would remain stable following lumasiran treatment interruption, we have not incorporated a continuation rule in the revised base-case analysis, but instead performed scenario analyses in which lumasiran therapy is discontinued in patients with paediatric-onset PH1 in the lumasiran arm of the model who are in CKD1–3b upon onset of adulthood (i.e., at age 18 years). We explored five scenarios in which treatment is discontinued for all such patients and re-initiation of treatment is modelled by returning different proportions of these discontinued patients to lumasiran therapy over time. The curves for patients remaining off treatment in these scenarios are shown in Figure 1; these curves yield the following proportions of patients resuming treatment within 10 years: 10%, 30%, 50%, 70%, and 90%.

Figure 1. Proportion of patients with paediatric-onset PH1 remaining off lumasiran treatment over time following discontinuation upon adulthood.

KM = Kaplan–Meier

2.6.3 Infantile-onset patients

Our original CS noted that infantile onset of PH1 is characterised by rapid progression to ESKD and significantly reduced survival.[9,16,18] As did the CS, the revised CEA presents a base-case analysis for the total population, and scenario analyses for patients of all ages with infantile onset of PH1 and for infants with infantile onset of PH1.

2.7 Summary of revisions

Changes in the revised CEA compared with the model submitted in response to ERG questions are tabulated in Appendix Section 6.1.

3 Results

3.1 Base-case analysis

Results of the revised base-case analysis are presented in Table 9. Lumasiran is estimated to yield an additional [redacted] QALYs at an additional cost of £[redacted]. Given the large gain in undiscounted QALYs, a weighting factor of 3.0 would apply, implying a willingness-to-pay threshold of £300,000/QALY.

Table 9. Base-case effectiveness and cost results

Technology	LYs	Disc LYs	QALYs	Disc QALYs	Costs (£)	Disc Costs (£)
Lumasiran	56.82	23.74	[redacted]	[redacted]	[redacted]	[redacted]
ECM	48.84	22.38	[redacted]	[redacted]	[redacted]	[redacted]
Difference, lumasiran vs. ECM	7.99	1.36	[redacted]	[redacted]	[redacted]	[redacted]

ECM = established clinical management; Disc = discounted; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year

Table 10 presents the resulting incremental cost-effectiveness ratios (ICERs) in terms of cost per life-year gained and per QALY gained for lumasiran compared with ECM. The discounted ICER for lumasiran vs ECM was £[redacted]/QALY.

Table 10. Base-case cost-effectiveness results

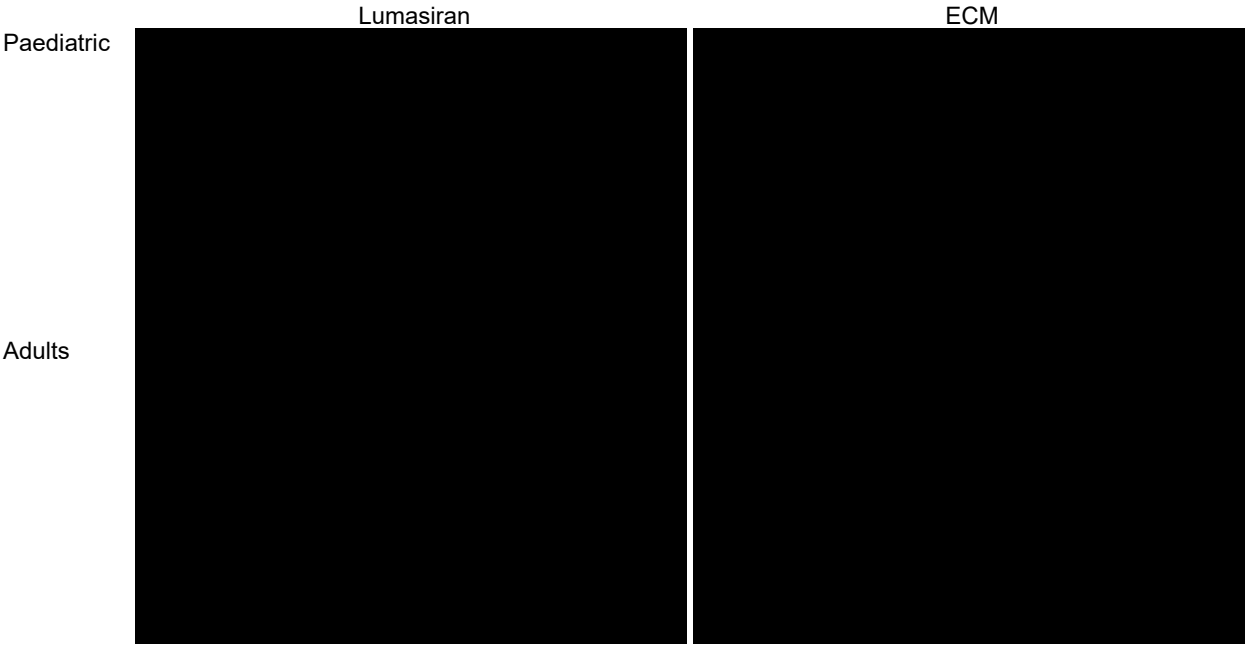
	Undiscounted		Discounted	
ICER	Cost/LY	Cost/QALY	Cost/LY	Cost/QALY
Lumasiran vs. ECM	[redacted]	[redacted]	[redacted]	[redacted]

ECM = established clinical management; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year

Proportion of the model cohorts in each health state over time

Figure 2 presents the health-state distributions of the model cohorts over time in the lumasiran and ECM arms. The model predicts that most patients receiving lumasiran either remain in their starting health state until death if they were in a less-severe health state at model start or transition to cLKT if they were in a more-severe health state at model start. In contrast, patients on ECM progress steadily to worse health states across the model time horizon.

Figure 2. Health-state distributions of the patient cohorts over time (Markov traces)



CKD = chronic kidney disease; cLKT = combined liver–kidney transplant; ECM = established clinical management; ESKD = end-stage kidney disease; OXc = controlled oxalate; OXu = uncontrolled oxalate

Disaggregated QALYs by health state

The QALYs accrued in the different health states are summarised in Table 11. The majority of QALYs for lumasiran were accrued in CKD1–3b (with an approximately [redacted]-fold higher accrual of QALYs in CKD1–2 compared with ECM) and post-cLKT. Patients on ECM lost QALYs mainly in the ESKD health state.

Table 11. Distribution of QALYs in the patient cohorts across health states

	Undiscounted QALYs			Discounted QALYs		
Health state	Lumasiran	ECM	Lumasiran vs. ECM	Lumasiran	ECM	Lumasiran vs. ECM
CKD1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD4-OXc	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD4-OXu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESKD-OXc	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESKD-OXu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-cLKT–OXc	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-cLKT–OXu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CKD = chronic kidney disease; cLKT = combined liver–kidney transplant; ECM = established clinical management; ESKD = end-stage kidney disease; OXc = controlled oxalate; OXu = uncontrolled oxalate

Disaggregated costs by category of cost

Overall costs per patient in the lumasiran and ECM arms disaggregated by category of cost are shown in Table 12. The majority of costs for lumasiran were attributable to drug acquisition; in contrast, the main cost

component for ECM was dialysis. Systemic oxalosis costs were [redacted] higher for ECM than for lumasiran.

Table 12. Summary of costs per patient by category of cost

	Undiscounted costs (£)			Discounted costs (£)		
Cost category	Lumasiran	ECM	Lumasiran vs. ECM	Lumasiran	ECM	Lumasiran vs. ECM
Drug	[redacted]					
Administration	[redacted]					
Monitoring	[redacted]					
Dialysis	[redacted]					
RSE	[redacted]					
SO	[redacted]					
Post-cLKT	[redacted]					
AEs	[redacted]					
EOL	[redacted]					
Total	[redacted]					

AE = adverse event; cLKT = combined liver–kidney transplant; ECM = established clinical management; EOL = end of life; RSE = renal stone events; SO = systemic oxalosis

Disaggregated costs by health state

Costs disaggregated by health state are presented in Table 13. Costs were primarily accrued in CKD1–2 for lumasiran, but in ESKD for ECM.

Table 13. Summary of costs per patient by health state

	Undiscounted costs (£)			Discounted costs (£)		
Health state	Lumasiran	ECM	Lumasiran vs. ECM	Lumasiran	ECM	Lumasiran vs. ECM
CKD1-2	[redacted]					
CKD3a	[redacted]					
CKD3b	[redacted]					
CKD4-OXc	[redacted]					
CKD4-OXu	[redacted]					
ESKD-OXc	[redacted]					
ESKD-OXu	[redacted]					
Post-cLKT–OXc	[redacted]					
Post-cLKT–OXu	[redacted]					
Total	[redacted]					

CKD = chronic kidney disease; cLKT = combined liver–kidney transplant; ECM = established clinical management; ESKD = end-stage kidney disease; OXc = controlled oxalate; OXu = uncontrolled oxalate

3.2 Scenario analyses

As shown in Table 14, most of the variation in ICER results among the scenario analyses performed for this resubmission was accounted for by differences in incremental costs rather than incremental QALYs. Due to the relative consistency in QALY gain, the QALY weight of 3.0 was maintained for all of these scenarios. The ICERs varied from dominant to [redacted].

Table 14. Results of scenario analyses

Scenario	#	Parameter settings	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	QALY weight
Base case	0		[redacted]	[redacted]	[redacted]	[redacted]
ECM cohort on dialysis in CKD4	1	Adults: 50% Paediatric: 100%	[redacted]	[redacted]	[redacted]	[redacted]
	2	Adults: 0% Paediatric: 100%	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of fast-progressors among adults in CKD1–3a	3	10%	[redacted]	[redacted]	[redacted]	[redacted]
	4	25%	[redacted]	[redacted]	[redacted]	[redacted]
	5	75%	[redacted]	[redacted]	[redacted]	[redacted]
	6	100%	[redacted]	[redacted]	[redacted]	[redacted]
Paediatric-onset cohort in CKD1–3b at adulthood onset discontinues lumasiran treatment: proportion restarting treatment at 10 y	7	10%	[redacted]	[redacted]	[redacted]	[redacted]
	8	30%	[redacted]	[redacted]	[redacted]	[redacted]
	9	50%	[redacted]	[redacted]	[redacted]	[redacted]
	10	70%	[redacted]	[redacted]	[redacted]	[redacted]
	11	90%	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup with infantile onset of PH1	12	Infants only	[redacted]	[redacted]	Dominant	[redacted]
	13	Patients of all ages	[redacted]	[redacted]	[redacted]	[redacted]

CKD = chronic kidney disease; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life-year

The largest change in the ICER compared with the base-case scenario was seen in the subgroup analysis comprising only infants with infantile onset of PH1, which resulted in lumasiran being dominant over ECM. Large differences compared with the results of the base-case analysis were also seen with the scenarios in which patients with paediatric-onset disease who are in CKD1–3b at the onset of adulthood discontinue lumasiran treatment. The magnitude of the reduction in the ICER for these patients was highly sensitive to the proportion of these patients requiring resumption of lumasiran therapy in future.

In contrast, the ICER was relatively insensitive to variation in the proportion of adult patients in CKD1–3a who were fast progressors and thus eligible for lumasiran treatment, varying by only £[redacted]/QALY when this proportion was changed from 10% to 100%.

3.3 Sensitivity analyses

3.3.1 One-way sensitivity analysis

In the one-way sensitivity analysis (OWSA) performed as described in the CS, the percentage change in results from the base-case analysis following lower and upper variation in the 10 most influential model parameters is shown in Table 12 and Figure 3. The most influential variables in the OWSA were the discount rates on costs and outcomes, and patient adherence to lumasiran therapy.

Table 15. Percentage change in base-case results following lower and upper variation in the 10 most influential model parameters

Parameter	Lower value	Upper value
Discount rate costs	[redacted]	[redacted]
Discount rate outcomes	[redacted]	[redacted]
Lumasiran drug adherence	[redacted]	[redacted]
Distribution of CKD at baseline, CKD1–2	[redacted]	[redacted]
Distribution of CKD at baseline, ESKD	[redacted]	[redacted]
Constant parameter in general population utility equation	[redacted]	[redacted]
Initial age (years), paediatric	[redacted]	[redacted]
High-intensity dialysis cost (£), per cycle, adults	[redacted]	[redacted]
High-intensity dialysis cost (£), per cycle, paediatric	[redacted]	[redacted]
High-intensity dialysis add-on to ECM in ESKD	[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; POx = plasma oxalate

Figure 3. Tornado diagram of the change from base-case ICER 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

3.3.2 Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis (PSA) performed as described in the CS are summarised in Table 16. Figure 4 and Figure 5 show the individual PSA simulation results and cost-effectiveness acceptability curve, respectively.

Table 16. 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]

CI = confidence interval; ECM = estimated clinical management; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 4. Results of the 1000 simulations in the PSA for the ICER of lumasiran vs. ECM

ECM = estimated clinical management; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 5. Cost-effectiveness acceptability curve for the PSA

PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; WTP = willingness-to-pay

4 Conclusions

The revised analyses presented here represent Alnylam's effort to address the uncertainties raised by the Committee and ERG, as well as to incorporate the intended use of lumasiran as stated by the clinical experts. The revisions to the CEA resulted in a lower ICER compared with the results of the company base-case model submitted to address the original round of ERG questions prior to the Committee meeting: £[redacted]/QALY vs. £[redacted]/QALY, respectively. Due to the large QALY gain, the maximum QALY weighting of 3.0 would apply.

It should be noted that a number of conservative assumptions from the original model, as described in the CS, are retained in the revised CEA, including the following:

- Duration of disutility due to a renal stone event is limited to only 6 months
- No recovery of lost eGFR with lumasiran treatment
- No increased mortality due to systemic oxalosis or infantile onset of PH1

We hope that the revisions we have made to the CEA have provided the Committee with the basis to render an informed decision on lumasiran.

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6 Appendices

6.1 Log of changes since model submitted in response to ERG comments

To facilitate the review by the ERG, we applied all changes in the version of the model shared by ERG and titled “ID3765 Lumasiran PH1 CKD1-5 CEM UK_v11.0_ERG base case v2 220322 (ACIC)”.

Model aspect	Description of changes
Transplant rate in uncontrolled-POx health states	• “Clinical Data” sheet: added updated calculation of transplant rate based on new evidence in rows 152–159
Proportion on dialysis in CKD4	• “Clinical” sheet: the proportion of cohort on dialysis in CKD4 was split between adult and paediatric patients. • “Markov LUMA” sheet: the proportion on dialysis in CKD4 was adjusted in formulas in columns HH, IF and IG. • “Markov ECM” sheet: the proportion on dialysis in CKD4 was adjusted in formulas in columns GT, HR and HS. • “QoL Data” sheet: formulas were adjusted in rows 23–26
Probability of death post-transplant in uncontrolled-POx health states	• “Survival Post-LKT” sheet, cell IJ1=1, to reflect ERG-preferred scenario
CKD stage-specific progression	• “Clinical” sheet rows 41–43: added the eGFR change by health state. For CKD1–2 and CKD3a, the rate was calculated based on ILLUMINATE-A data and the POx-eGFR relationship reported by Shah et al. 2020. For CKD3b and CKD4 the rate of eGFR change per cycle (6 month) was set equal to half the annual rate of change reported in the publication by Singh et al. (2022). Rows 47–50: we reported the rates used by health state in the paediatric and adult cohorts at model start. In the adult cohort, the rate of eGFR change in CKD1–2 and CKD3a was set equal to that in CKD3b since only adults who are fast progressors are included in the analysis. • “TransMx” sheet rows 17–20: formulas were added so that the appropriate rates from “Clinical” sheet are selected depending on whether the analysis is running for paediatric or adult patients at model start. Rows 23-26: the formulas to calculate the probability per cycle were updated to refer to the appropriate eGFR change per cycle. The probability of transition from CKD4 to ESKD was added. • “Time to ESRD” sheet: the probability per cycle of transition to ESKD from CKD4 was updated based on eGFR change reported by Singh et al. (2022). The time-to-ESKD curve from Harambat et al. (2010) was removed.
Among adults in CKD1–3a, only those with signs of fast progression are included in the analysis	• “LookUps sheet” sheet: rows 74–71, column C, the alternative proportions of fast progressors among all CKD1–3a PH1 adults were added. Cell E79: a choose function was included to model the selected proportion. • “Clinical Data” sheet: the formulas in cells C52 and C53 were adjusted to estimate the corrected health-state distribution of adult patients at model start based on the proportion of CKD1–3a fast progressors • “Clinical” sheet: cells E47 and E48, the rate of eGFR change in CKD1–2 and CKD3a was set equal to that in CKD3b.

Model aspect	Description of changes
Lumasiran continuation rule	• "LookUps sheet" sheet: cells H73–77, all alternative options to define the probability of the CKD1–3b cohort going back on treatment after discontinuing at start of adulthood were listed. • "Clinical Data" sheet: from row 191, the KM functions of time to return to treatment for the different alternatives were estimated. The annual rate was reported in cells B196–F196 and the probability per cycle for the selected option was calculated in cell B193. • "Markov LUMA" sheet: the Markov trace was adjusted to allow for substates by treatment status (i.e., on vs. off lumasiran) within the CKD1–2, CKD3a and CKD3b health states (columns AF–AK, BT–BY and CH–CO). Allowing for such substates will only have an impact if the treatment-discontinuation rule is activated in cell T9 of the Results sheet. The transitions from "on tx" to "off tx" occur only at the start of adulthood, and the transitions from "off tx" to "on tx" occur at every cycle thereafter based on the probability of going back to treatment. Column AB includes the index of the cycle at which discontinuation occurs. The proportion of the cohort on treatment in column EA was adjusted to consider patients in CKD1–3b only if they are in "on tx" substates. The formulas to estimate LYs (columns EX–EZ), QALYs (columns GF–GH) and costs (columns HG, IC–IE) were adjusted to consider the appropriate proportion of the cohort on and off treatment.
PAS	• All results incorporate updated PAS

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; KM = Kaplan–Meier; LY = life=year; PAS = Patient Access Scheme; POx = plasma oxalate; QALY = quality-adjusted life-year; tx = treatment

NICE National Institute for Health and Care Excellence

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Consultation on the evaluation consultation document – deadline for comments 5pm on Monday 13 June. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Patient Expert, Metabolic Support UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]
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Comment number	**Comments** Insert each comment in a new row.

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Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Consultation on the evaluation consultation document – deadline for comments 5pm on Monday 13 June. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The decision not to recommend Lumasiran for people living with PH1 appears to be solely based on the economic model and therefore is for the company to address.
2	It is disappointing that Lumasiran has not been deemed cost-effective. Lumasiran offers many benefits to the recipient including overall quality of life and a reduction in usage of other NHS resources, therefore offers the potential to reduce NHS expenditure longer term.
3	The ECD effectively summarises the symptomology of Ph1 and highlights some of the issues people living with PH1 experience. However, it fails to emphasise the severity of the condition and the overall impact on the patient and caregiver quality of life. Metabolic Support UK have recently released a PH1 insight report, which can be found via the following link: https://www.youtube.com/watch?v=6PGlOBXhS1w
4	We are concerned that this recommendation may imply that Lumasiran is not an effective treatment for people living with PH1. It is important to note that in comparison, there are no current effective treatments available for people living with PH1.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

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METABOLIC SUPPORT UK
Your rare condition. Our common fight.

Responses to NICE public consultation regarding Lumasiran

Following the release of the public committee papers, we received feedback from members of our PH1 community that the process to take part in the public consultation was challenging. Therefore, we designed a simple survey and collated responses to the NICE public consultation regarding Lumasiran. The results can be found below.

Total Responses: 6

1. Demographics

- Status: 3 parent/caregivers, 1 sibling, 1 patient and 1 consultant
- 50% of respondents in receipt of Lumasiran

2. Do you agree with NICE's recommendation which is that Lumasiran is not recommended for any age groups for treating primary hyperoxaluria type 1 (PH1)?

- I agree with this recommendation – 0%
- I do not agree with this recommendation – 100%

3. Please share, in as much detail as possible, the reasons for your answer to the previous question.

There are limited treatment options for PH1. In recommending that Lumasiran not be used as treatment, NICE recommends patients to find the other non-existent drugs necessary to mitigate kidney damage and adverse health effects of the disease. Lumasiran is an effective drug, but more importantly, it is the lone drug with such efficacy for patients with PH1, who deserve to have treatment that greatly improves their condition—or may save their life—when it exists.
Lumasiran is the only drug available that can significantly reduce urine oxalate levels in patients with PH1. Without a drug like Lumasiran, which prevents calcium oxalate deposition in the kidneys, the only other treatment option (which NICE calls "standard care") for patients with this disease is a kidney/liver transplant, a procedure which is both incredibly expensive and is accompanied by a great deal of risk and a reduction in quality of life for patients–this is not an ideal treatment option for anyone but is often an inevitable outcome for patients with PH1. The great benefit of Lumasiran is that it can prevent the need for such a major intervention as a double kidney and liver transplant by slowing down the disease course. My younger brother, who was diagnosed with PH1 at 8 years old after having had 10 kidney stones which had to be surgically removed, drinks 4 litres of water daily in addition to several medications to efforts to reduce his oxalate levels. He is fortunate that one of his alleles for PH1 makes him responsive to the vitamin B6, which is one of the medications he takes daily, but many other PH1 patients are not as fortunate. While taking these medications and drinking so much water is somewhat helpful, these treatment methods alone are unsuccessful in preventing

the need for transplantation. As a result of his disease, my brother's kidney function has already been significantly and irrevocably reduced. Without Lumasiran, it is almost certain that his kidney function would continue to decline, requiring dialysis and eventual liver/kidney transplantation. As just a 17-year-old who is already incredibly accomplished and who will begin his studies at an Ivy League school this fall with plans to eventually attend medical school, these outcomes would hamper his ability to participate in the activities he loves and would likely impede his ability to receive an education and pursue his dreams. Lumasiran makes it possible for my brother to maintain his quality of life and will delay, and perhaps even prevent altogether, the need for a transplant, a "treatment" option with a very low success rate, as multiple transplants throughout a patient's life are typically required, if they work at all. If NICE does not recommend Lumasiran for use, patients like my brother will have no viable treatment options for this disease, and their bright futures will be cut short by the realities of PH1. The lives of patients, like my brother's, are at stake if NICE does not recommend Lumasiran—the only available drug that can treat this disease for which there is no cure. There are no alternative options. "Standard care" for this disease i.e., liver and kidney transplant are an extremely invasive and ultimately ineffective outcome—it cannot be considered a solution for this disease. Lumasiran, on the other hand, is a proven, effective treatment option for patients with PH1 and must be recommended for use.

My daughter is currently receiving lumasiran. It has been life changing for her and for our family. She was previously the 0.1/ 1 percentile for height and weight and is now the 75/50 th respectively. Her plasma oxalate and urine oxalate levels are now normal and her kidney function and nephrocalcinosis remain stable. Although the biggest difference is in function. Our daughter is now able to attend day-care and social activities allowing for full growth and activity, her older 4-year-old brother no longer worries for her and my husband who had taken 2 years of work to care for her can return to full time work. We can reconsider moving rurally that was on hold for 2 years and finally take a vacation. We no longer have the daily life altering stress and fear of kidney transplant.

The findings of the illuminate study speak positively for the use of Lumasiran in primary oxaluria type 1. Reductions of urinary oxalate were significant (~>50%) . In the patient I know ,he has not had a kidney stone since being on that medicine (~3 years)whereas before Lumisarin he had a number of painful passages of calcium oxalate stones requiring surgical intervention. His kidney function has been stabling which is quite desirable since chronic kidney disease is an unfortunate costly complication seen with this disorder.

1. Except for the fortunate few that have a b6 responsive allele, there is no other way to lower oxalate levels in people with PH1.
2. There is a high rate of renal failure in people with PH1. Not only is this a horrible medical outcome with the attendant effects of renal failure as well as the damaging effects of oxalosis, but this outcome is very expensive: must dialyze for longer time periods and more frequent days per week as oxalate is poorly dialyzed. Even with this these patients suffer from the accumulation oxalate throughout their bodies.
3. Currently, without a medicine like lumasiran, the only viable approach is then a liver -kidney transplant- risky, not readily available, requires a lifetime of immunosuppression and is unbelievably expensive. No reasonable person would be satisfied with this approach if there is any reasonable chance that another approach may prevent this outcome.
4. We know that the clinical consequences of PH1 result from high oxalate levels, and we also know that lumasiran significantly lowers oxalate levels and oxalate excretion. My son has been in a clinical trial of lumasiran and is now on this medicine as part of an extension study. For the first time since his diagnosis was made, he now has normal a 24-hour urine for oxalate. This was entirely unachievable before he had access to this medication.
5. The data is clear that 24-hour urine oxalate levels correlate with the risk of renal failure, so oxalate levels are a reasonable surrogate measure.
6. It seems cruel to withhold the only effective treatment currently available to substantially lower oxalate levels just on the basis of cost. Those affected by PH1 cannot control the cost of this medicine. Imagine having a child who already has some renal impairment and who has responded well to this medicine and then being told your child cannot get this medicine. I have seen what renal failure in people with PH1 looks like and I can't imagine not doing everything possible to prevent this outcome.

4. **NICE summarised that in PH1, "the liver produces excess oxalate which combines with calcium in the tissues to form toxic crystals. These crystals can cause recurrent kidney stones, kidney damage and in severe cases kidney failure and multiorgan damage. Standard care includes supportive measures, dialysis and a liver–kidney transplant depending on a person's kidney function". Here, NICE are highlighting key symptoms and how they are treated. Do you agree with this summary, or do you have any additional comments? Do you have experiences about other health problems associated with PH1?**

Common treatment also includes drinking copious amounts of water and medications such as Vitamin B6 (only if patients are responsive to this, and many are not) or citric acid.
Our daughter was failure to thrive in infancy. She was the 0.1/1 percentile for weight and height. After lumasiran treatment she is a thriving 75 and 50 th percentile for weight and height two-year-old. She still has some ongoing fatigue and requires a long afternoon nap, but this has significantly improved with Lumasiran.
I agree that if this disease is treated without Lumisarin the clinical outcome is very guarded. It is potentially painful to the patient in terms of passage of kidney stones, (without the aid of Lumisarin) and undergoing both renal and hepatic transplantation , which requires medications for providing anti-rejection of the transplants. In the only patient I have experience with (PH1 is a rare disorder) his urinary oxalate values were never near normal and were ~ 90 mg /day (normal < 40 mg/day) despite 4 liters of water every day and oral vitamin B6.
That assessment is accurate but glosses over the human suffering caused by kidney stones, renal failure and oxalosis. Anyone who has ever had a kidney stone knows how painful they are. But few are aware of how painful systemic oxalosis is: severe bone and joint pain; dental problems; heart failure in some. The availability of a liver kidney transplant is far from certain for those who need one. It is almost impossible to have a life while requiring nearly continuous dialysis while waiting and praying for a transplant.
I agree that these are key symptoms of the disease, but this statement leaves out other severe, yet very possible, symptoms of oxalosis. Oxalosis leads to systemic depositions of calcium oxalate—all blood vessels, bones, and organs are affected, which has severe and often fatal implications. Oxalate deposition in the eyes can lead to blindness; oxalate deposition in the joints leads to arthritis, synovitis, tenosynovitis, spinal stenosis, and chondrocalcinosis; oxalate deposits in the heart cause arrhythmias and diastolic dysfunction; oxalate in the nerve and muscle can cause axon loss and demyelination which, in turn, causes symptoms like vision loss and loss of movement; oxalate deposition in the bones leads to fractures and sclerosis, to name only a few symptoms. The effects of oxalosis are far-ranging and life-threatening.

5. **NICE summarised that "the cost-effectiveness estimates are uncertain, and the most likely estimates are significantly higher than what NICE normally considers an acceptable use of NHS resources". Do you agree with this or do you have any additional comments?**

While the cost is high, this drug offers incredible value for any price, because no other treatment option reduces risk/prevalence of renal failure to the degree Lumasiran has been able to. The treatment options other than Lumasiran (including vitamin B6, water-drinking, etc) have been proven ineffective in decrease oxalate levels when standalone.
I do not agree. Without Lumasiran my daughter would still be unwell and need a high level of acute and chronic medical care yearly in addition to the possibility of dialysis or kidney transplant in the future. The quality-of-life component is essential and also needs to be considered. My daughter can now attend regular day-care and social activities which wasn't possible before. Her quality of life today is excellent, and I anticipate in the years to come this will remain excellent which without lumasiran would likely to have been poor. There is also the financial implications of caring for a sick child. My husband took a two year leave from his work and I reduced my hours in the first year In

order to care for her and manage her medical appointments, and the stress associated with PH1. Now, I'm back to full time hours and my husband will be returning to full time work contributing to the workforce.
I do not agree with above statement . Aside from the moral issue denying life saving medication on a monetary basis seems cruel. In addition the costs of treating chronic kidney disease (usual care including treating hypertension, metabolic acidosis, bone disease)/ +/-renal dialysis and or chronic care from either kidney or both kidney and liver transplantation can be enormous on a chronic basis .
I do not agree. 1. Fortunately, PH1 is rare so the number of people requiring this medication is small. So even though the cost per person is high, the total burden to society is lessened by the small number who will need the medicine 2. The "estimate" considers current cost if lumasiran is used but does not take into account the high cost to taxpayers when people with PH1 cannot work and then require dialysis, kidney-liver transplant, etc. And it certainly does not consider the human suffering associated with the progression of the disease in people with PH1. It is nothing short of a tragedy to finally have an effective treatment available but yet not be able to use it to help those with PH1
I do not agree with this statement. Lumasiran offers taxpayer value for money because it is a life-saving drug and is the only drug available that is effective in mitigating symptoms of disease, which makes it highly valuable.

6. Are there any aspects of the recommendations that need consideration to ensure that NICE avoid unfairness against any group of people (e.g. gender, religion etc.)?

The PH 1 gene can be found in all people and is not limited to a single ethnic group. Lumisarin should be available to anyone in need of this medication.

7. Lastly, please use this box to input any additional comments relevant to the draft recommendation

It should be noted that patients with PH1 have access to no other drug that is as effective as Lumasiran in decreasing oxalate and improving renal function, and the other treatment options which exist currently do not adequately achieve either of the above.
This is a lifesaving and life altering treatment for both the patient and their family. This decision needs to be reconsidered.
I have met many people from many counties with PH1. Some of these people are unbelievably talented and have the potential to do great things in this world. The research continues and the hope is that lumasiran is just the beginning of new treatments for PH1, as well as other forms of PH. I think that lumasiran can be a bridge to a future where just as effective but less expensive options become available. And there is a reasonable chance this may occur sooner than one may expect given the advances in techniques and the collective effort globally. Providing the best treatment currently available to people with PH1 is not only humane but is a wise investment so that they can lead productive lives until more affordable treatments are available.
Patients with PH1 have access to no other drug that is as effective as Lumasiran in decreasing oxalate and improving renal function, and the other treatment options which exist currently do not adequately achieve either of the above.

NICE National Institute for Health and Care Excellence

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Kidney Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to the tobacco industry
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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1	**Positioning:** We agree with the positioning statements for adults. The ILLUMINATE-C trial showed a beneficial effect on plasma oxalate in both CKD stage 5 and dialysis patients. But it is unknown if this translates into clinical benefit, particularly post-transplantation. This is because the benefit of reduced new oxalate creation (by lumasiran) might be small compared to the effect of existing body oxalate stores (oxalosis) and/or to the release of the massive body stores of oxalate (which is not treated by lumasiran) after kidney transplantation
2	**NHSE&I perspective:** We partially agree that the Hyperoxaluria Rare Disease Collaborative Network may provide a structure for distribution of the technology. This can only happen if there is provision of infrastructure and funding for clinician time. Currently the RDCN exists in name only (https://ukkidney.org/rare-renal/patient/hyperoxaluria-0) with no resources available to action any potential NICE recommendations. A structure for distribution should include constant evaluation and reporting back to NICE or NHSE about clinical effectiveness, outcomes data, addition/removal of clinical indications, etc. We would strongly recommend that a framework for providing and funding a suitable outcomes infrastructure is mandated in the final guidance. This is the approach adopted by the National Renal Complement Therapeutics Centre, with excellent outcomes despite very high cost drugs (https://www.atypicalhus.co.uk/wp-content/uploads/2018/10/NRCTC-Annual-report-2017_18.pdf) and improved efficacy and cost-effectiveness (e.g. SETS-aHUS: trial of withdrawal of eculizumab in aHUS) to the NHS.
3	**Should isolated liver transplant be included as a comparator?** Data from the European registry (Metry et al 2021, DOI: https://doi.org/10.1016/j.ekir.2021.11.006) showed that up to 2021 there were 159 combined liver-kidney transplants, compared to 37 sequential liver-kidney transplants (most of whom had already completed their kidney transplantation) and only 12 isolated liver transplants. All 12 were in B6-unresponsive patients (as would be expected), and all were paediatric. Outcomes: 2 died of liver graft failure, 2 went on to have end-stage renal disease, 8 had a functioning liver graft at 5.7 years median follow-up. Therefore, 33% of the cohort either died or went on to need a kidney transplant. This represents a poorer outcome than for combined liver kidney transplantation, and in addition isolated liver transplant is much less commonly performed than other forms of transplantation and is therefore not standard practice.
4	**Would lumasiran be used in people who continue to have high oxalate levels post transplantation?** If high oxalate levels occur after surgically/immunologically-successful liver-kidney transplantation, this would most likely indicate mobilisation of body oxalate stores. There is no known effect of lumasiran on modifying oxalate outside the liver, but equally the risk of high oxalate levels to the renal graft is very severe. There is no evidence and so this would need to be the subject of a clinical trial. If high oxalate levels occur after kidney alone transplant (rarely performed unless in the case of B6-responsive patients) then there may be a case for short-term lumasiran treatment to attempt to further flatten the oxalate excretion curve to allow renal excretion.
5	**Is plasma oxalate 50uM appropriate for determining systemic oxalosis?** Systemic oxalosis is a clinical diagnosis, made by assessing end-organ damage over time in organs such as kidneys, eyes, skin, heart, bone, and marrow. It does not rely on

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	biochemistry. The 50 µmol/L figure was originally expert opinion in Cochat and Rumsby 2013, and was suggested as part of PH diagnosis, not for systemic oxalosis diagnosis. Ogawa et al 2006 (doi:10.1007/s00240-005-0004-6 (2006)) showed that non-PH dialysis patients have oxalate of about 50 umol/L (and they suggest that oxalosis might start >100 umol/L). In addition plasma oxalate levels vary between laboratories. So our feeling is that this threshold is not appropriate.
6	**How robust is the clinical evidence for lumasiran in terms of decision making?** The main issue is the lack of clinical outcome data (eGFR, stones, oxalosis). But even the best designed trial could not expect to show convincing effects in anything shorter than 2-3 years. There is ample evidence, and general acceptance of the validity of urine oxalate as a surrogate measure (less so for plasma oxalate). Thus, there is an argument for waiting for this longterm clinical evidence for some of the clinical indications, but there are other urgent indications where the potential for benefit is so high that it makes clinical sense to allow usage without full evidence. We therefore suggest stratification of clinical indications, supervised by a national clinical body. This would not only take into account this uncertainty, but a national clinical decision making body could monitor and re-stratify the indications as clinical evidence is obtained.
7	**Will more people be eligible for lumasiran than the company estimates?** This depends on the approved clinical indications. Stratification of indications might allow clinical prioritisation if more patients are eligible than first thought. For example, the highest priority might be given to patients with infantile oxalosis, adults with PH1 presenting as primary non function of renal transplant, or with end-stage renal disease with a strong clinical suspicion but before genetic confirmation. Other indications would be ranked in priority order. Guidance from OxalEurope is expected to be published later in 2022. The vast majority of known UK patients with PH1 are already included either in RADAR or OxalEurope or both, so we do not expect high numbers meeting criteria for lumasiran outside these, unless there are many new diagnoses made. New patients notified to RDCN clinician members are offered participation in these registries, and none have so far refused.
8	**Use of oxalate levels to predict outcomes and effect of uncontrolled plasma oxalate levels on waitlisted patients?** As stated, there is reasonable evidence for urine oxalate to predict outcomes, but not for plasma oxalate. My feeling from my clinical cohort is that the predictive power of urine oxalate is greater in adult patients when measured over longer periods of time. The role of plasma oxalate is predicting outcomes is controversial. Clinically, workup for transplantation would not rely on plasma oxalate levels. Indeed, very high plasma oxalate levels in a patient with PH1 may herald more rapid progression or development of systemic complications, meaning that transplantation should happen sooner rather than later. We already do this in other areas of renal transplantation where the index disease is not controlled e.g. we do not automatically exclude patients with uncontrolled diabetes, or ongoing immunological kidney disease risk, from kidney transplantation.
9	**Dialysis regimes plausibility** We might commence dialysis in CKD 4 if, for example, there was evidence of rapid renal function deterioration, or development of systemic oxalosis. But even in dialysis-dependent patients, 7 days/week dialysis is not performed for anything more than a very short time period, e.g. post transplantation. In reality, decisions on dialysis regimes are very individualised and depend strongly on the patient's or their family's viewpoint. It can also vary depending on clinical state and transplantation plan.

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Insert extra rows as needed

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Lumasiran for treating primary hyperoxaluria type 1 [ID3765]: Comments on Evaluation Consultation Document 13 May 2022

Has all of the relevant evidence been taken into account?

At the time of writing the relevant evidence has been considered. Further long term follow up data will likely be available in due course.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summary of clinical effectiveness is a reasonable interpretation of the evidence available. I do not have health economic expertise to comment on cost effectiveness.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

As a clinician who has seen significant benefit to NHS patients treated with Lumasiran via clinical trials, EAMS and compassionate use, the initial recommendation is disappointing. We hope that a revised submission will represent value to the NHS and allow treatment of severely affected patients such as infants with a severe phenotype of Primary Hyperoxaluria type 1 in NHS care.

In addition, I suggest the following corrections to clinical expert input to the first committee review meeting:

ECD Section 3.8

a. Lumasiran would be offered to all infants with evidence of a severe infantile phenotype (e.g. early nephrocalcinosis) - not just a family history of infantile phenotype

b. Children with normal kidney function do not have high plasma oxalate levels - Lumasiran would be offered to all children with reduced kidney function

ECD Section 3.12

a. Lumasiran is not solely provided at the 4 centres contributing to the Rare Disease Collaborative Network for PH1 (RDCN). This network advises and supports clinicians in use of Lumasiran in their own centres, closer to patients' home (13 specialist Childrens kidney units for children with PH1, plus further adult centres).

ECD Section 3.17

a. Urinary oxalate is a widely accepted marker of the risk of *future* decline in kidney function and progression to end-stage kidney disease (it is not a marker of kidney function at the time of the sample).

b. Urinary oxalate levels are used as a marker of prognosis in children who pass urine, and are used for clinical decision making

c. Plasma oxalate levels are a useful marker of prognosis in children with end stage kidney disease

ECD Section 3.18

a. Disease progression (kidney function decline) will likely happen in people who sustain a steady but high URINE oxalate level over time, not just high plasma oxalate level.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Chief Investigator for the ALN GO and Lumasiran trials in the UK Expert advisor to Alnylam Previous Chair of OxalEurope (the research and scientific network of European Primary Hyperoxaluria experts) - received grant funding from Alnylam No connection with the tobacco industry
Name of commentator person completing form:	Dr Sally-Anne Hulton

Comment number	**Comments**

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Section 3.7 – 3.8	Appropriately summarises the priority use groups in which the unmet need is most acute and presumably, in which cost effectiveness may be better compared to the broader licensed indication for lumasiran. Although all patients with primary hyperoxaluria type 1 (PH1) eventually develop renal failure, the rate of progression and the development of systemic oxalosis and resulting complications can vary significantly. The urgency to address the unmet need for a treatment to lower endogenous oxalate production varies with patient phenotype. It is acknowledged that cost effectiveness will be significantly different for patients whom without effective oxalate lowering therapy rapidly develop renal failure and severe complications of systemic oxalosis in early childhood compared to patients who demonstrate a modest decrease in renal function throughout adult life. Whilst a NICE recommendation allowing some physician and patient discretion in treatment decisions would be welcomed, it would be appropriate for initiation of lumasiran therapy to be limited to the rare disease collaborative network centres with thoughtful development of the Blueteq form to secure availability of this important treatment for the most acutely affected patients.
3.11	As is often the case during the clinical development of treatments for ultra-orphan diseases with highly variable rates of disease progression, in which there is a high unmet need for a disease modifying therapy, only a relatively short placebo-controlled period was possible in the ILLUMINATE-A study. It was anticipated when the study was designed that the placebo-controlled period may be too short to capture the full range of treatment benefits. I agree with the committee's conclusion that a significant component of the decrease in quality of life for people with PH1 is due to worsening CKD stage and the associated anxiety. The 6-month double blind period was too short for the ILLUMINATE-A population to demonstrate a significant difference in progression of CKD stage in the placebo arm. Similarly, it was too short to address years of psychosocial conditioning in a chronic progressive disease.
3.12	I wish to reiterate larger trials or trials with significantly longer placebo-controlled follow-up are not feasible in this disease, especially in the paediatric population. The population and the best supportive care in the trials are likely to be broadly representative of NHS practice throughout the international trials. Also ILLUMINATE-A and B includes 3 of 4 rare disease collaborative network centres. The fourth rare disease collaborative network centre included a patient in the phase I/II OLE study.
3.13	The infantile onset population doesn't go undiagnosed for long so the estimate of 3-4 new patients per year will not be a significant underestimate. It is of particular importance to establish availability of lumasiran for this population as soon as possible due to the rapid disease progression with current treatments."
3.19-3.20	It is not possible to calculate this from existing publications on liver transplant in PH1, hence the ERG and Company estimates which are very different. In UK clinical practice is there a difference in the probability of Liver transplant based on the Pox in different centres. It would be important to get consensus from the RDCN group for the different proportions of controlled vs. uncontrolled as it is important for modelling cost effectiveness in the later CKD stages. The model requires values for % patients with CKD4 and 5 with controlled oxalate POx<50 that will be listed for LT and % patients with CKD4 and 5 with uncontrolled oxalate POx>50 that will be listed for LT. The ERG suggested values of 100% for controlled oxalate group and 50% for uncontrolled group but a consensus from the expert RDCN consultants would be necessary here.
3.21 – 3.22	The health-related quality of life impact of later stage disease with systemic oxalosis can be amongst the most severe encountered in paediatric nephrology practice and must not be underestimated. Unfortunately, there is no established HRQoL measures for Cystinosis with which to compare

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3.23 – 3.24	A high intensity haemodialysis regime is the most efficient currently available at temporarily reducing plasma oxalate by ~60% following a dialysis session, but this will return to 80% of the pre-dialysis level with 24 hours [Yamauchi et al 2001]. There is individual variability in frequency of dialysis due to both NHS capacity and the high patient and caregiver burden of such intensive dialysis regimes. The summary in 3.24 may underestimate the "average" dialysis frequency currently achieved for paediatrics in the NHS. This information can be obtained easily through the BAPN and Renal Registry. There are children and adults on both nocturnal peritoneal and in centre haemodialysis – probably the only disease in which both forms of dialysis are utilised simultaneously. Thus these costs are high. The "average" should be used as the starting point for the updated model, and the company should provide scenarios with this in mind.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Comments on the ECD Received from the Public through the NICE Website

Name	[redacted]
Conflict	N/A
Has all of the relevant evidence been taken into account?	
No	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	
No	
Are the recommendations sound and a suitable basis for guidance to the NHS?	
No (see below)	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	
Yes (see below)	
Comments on individual sections of the ECD:	
Section 1 (Evaluation Committee's preliminary recommendations)	*Under section 1.2: 'Clinical trial evidence suggests that, after 6 months of treatment, lumasiran plus standard care reduces a person's oxalate levels compared with standard care alone. The cost-effectiveness estimates are uncertain, and the most likely estimates are significantly higher than what NICE normally considers an acceptable use of NHS resources. So, lumasiran is not recommended for use':* Patients with primary hyperoxaluria experience painful kidney stones from a young age and can develop progressive oxalate nephropathy. Progression to kidney failure often develops over a number of years, and is associated with systemic oxalosis, intensive dialysis, and often combined kidney and liver transplantation in addition to interruptions in life, in school, in work, and psychological stresses. Not only is there a burden to the patient suffering with this disease, but there is a tremendous burden to the family. Clin J Am Soc Nephrol. 2020 Jul 1;15(7):1056-1065. doi: 10.2215/CJN.13821119. Epub 2020 Mar 12.and CJASN March 2020, CJN.13831119; DOI: https://doi.org/10.2215/CJN.13831119 As published April 1, 2021 in the New England Journal of Medicine, the use of Lumasiran in a phase 3 trial was shown to successfully reduce oxalate levels in 39 patients with PH1 already taking their home therapy. Patients were randomly assigned to receive subcutaneous Lumasiran or placebo for 6 months. The primary end point was the percent change in 24-hour urinary oxalate excretion from baseline to month 6. The least-squares mean difference in the change in 24-hour urinary oxalate excretion (lumasiran minus placebo) was −53.5 percentage points (P<0.001) N Engl J Med 2021;384:1216-26. DOI: 10.1056/NEJMoa2021712. My son was a participant in this trial. His urinary oxalate levels had been markedly elevated despite standard therapy of

	Pyridoxine, a low oxalate diet in addition to potassium citrate and hyper-hydration. He had several procedures for kidney stones and had progression of renal dysfunction with standard therapy. During the blinded aspect of the trial, we were unaware of his urinary oxalate levels. However, after the treatment period, during the extension period, we were allowed to evaluate his urinary oxalate levels clinically and his urinary oxalate levels have been near normal and also normal on Lumasiran. The cost of repeated procedures for kidney stone treatment, the cost of dialysis and kidney transplantation or combined kidney-liver transplantation well exceeds the cost of Lumasiran. But, more importantly, as we know that there is progression of renal disease and oxalate deposition and suffering with standard therapy alone, it seems immoral to deprive children and adults of a successful and available novel therapy.
Name	[redacted]
Conflict	N/A
Comments on individual sections of the ECD:	
Section 1 (Evaluation Committee's preliminary recommendations)	PH1 can be a devastating disease and Lumasiran is the ONLY really effective treatment. It takes away the need for organ transplant, for surgical interventions to remove kidney stones and it totally changes quality of life for patients. I appreciate that NHS funds are not infinite, but there must be a way to make this possible, to make it affordable? It's available in USA, how do they make it happen?
Name	[redacted] and [redacted]
Conflict	N/A
Comments the ECD:	

We are writing in response to the recently published draft decision by NICE not to approve Lumasiran for use as treatment for Hyperoxaluria Type 1 (PH1).

We feel that this decision does not take fully into account the truly life-changing results that this medicine can have for those afflicted with this terrible condition. It also seems to have been made on economic grounds which, while we understand, we also feel is less relevant given the extremely limited prevalence of PH1 within the population and thus the overall impact on NHS budgets.

We would like to focus on the life-changing impact of this medicine and how it has transformed the fortunes for our [redacted].

[redacted], who is now [redacted], was diagnosed in 2016 at age [redacted] following multiple urinary tract infections which finally led to him being admitted to our local General Hospital in Buckinghamshire. After two weeks he was then transferred to the [redacted] in London where he was diagnosed with PH1. This was the start of our nightmare. His kidney function had already deteriorated to stage 4 (1-5 being the stages of End Stage Kidney Disease) and we were told he needed to be put onto a liver/kidney transplant list immediately. At the same time, other treatments were started including Pyridoxine and hyper-hydration.

[redacted] was passing kidney stones on a regular basis and in immense pain during these episodes. Seeing this happen to our child, watching him in agony but being

unable to help or do anything to stop it is one of most heart-wrenching memories of this period. [redacted] was in and out of hospital on a bi-weekly basis for ongoing assessment, discussion and planning for the upcoming transplants and for laser treatment on his kidney stones.

While [redacted] was stabilised and luckily for us, we were made aware by staff at the [redacted] of a potential drug trial at Great Ormond Street Hospital (GOSH) involving a revolutionary new drug (Lumasiran) that would potentially mean that [redacted] would not need a liver transplant. We were introduced to the team at GOSH and discussed at length the pros and cons of [redacted] participating in the drug trial. This process continued for 12 months or so while preparations were made for the start of the trial.

During this 12-month period [redacted] remained on the transplant lists and we were offered a liver transplant for him. We had to make the agonising decision whether to proceed with the liver transplant or wait in the hope of the drug's successful trial. This is a decision that I hope no other parent needs to make. We were put in a very difficult situation whereby we had to decide within 15 minutes whether to accept the organ as is the nature of time-pressure when an organ becomes available. We decided to wait and hope that the drug trial would work but knowing [redacted] was steadily deteriorating and that transplant was then the inevitable outcome.

Fortunately, [redacted] was accepted onto the Lumasiran trial and commenced treatment in 2019. The results have been amazing and his experience is consistent with those published. [redacted]'s life has genuinely been transformed. He has had no further kidney stone events, imaging shows that there is no new build-up of oxalate in his kidneys. Both his blood and urine oxalate levels are close to normal and most importantly he can lead a normal life. His hospital visit frequency is down to once every three months, he has more than doubled in body weight in since diagnosis and is now a strapping 6ft teenager with hardly a thought about his illness. We can't tell you how wonderful this is to see and how it has transformed our lives too; from worrying about when his next kidney stone event would be, constantly ensuring he hydrates and takes his medicine and then thinking about the then inevitable transplants….it has been such a relief…...

We are very lucky that timing of the Lumasiran drug trial worked out for [redacted] and we can't imagine a life where he could not receive this treatment and a life then burdened by the need for liver and kidney transplants. It just doesn't seem fair for a boy who has experienced such pain to then be thrown back into a world of major operations, hospital admission and life-long follow-up and all at a time when he should be focussing on GCSEs, A Levels and his future.

We hope that you will consider this letter and we remain available to provide more information or comment as needed.

Name	[redacted]
Conflict	N/A

Comments the ECD:

Dear Members of the NICE panel,

My name is [redacted]. I am [redacted] years old and I have been receiving my life changing medicine, Lumasiran, from Great Ormond Street Hospital for three years.

I was diagnosed with hyperoxaluria in 2016 following several kidney stone events.

Thinking about it now brings back painful memories, even six years later. I distinctly remember the agony that came with every stone, sitting on the toilet hoping that the stone would pass. Eventually it did but not before intense and seemingly never ending torment. I remember saying to my mother “I want to die” as the pain was so intolerable.

I was treated at the [redacted] and had to stay there for many weeks while my consultant found the diagnosis. I was told that I required a kidney and liver transplant and I was placed on a waiting list. Regular visits to the hospital ensued and I missed out on a lot of vital learning during that period. In January of 2019 I underwent an operation to laser some of the larger stones in my kidneys.

In February of 2019 I was offered the opportunity to become part of the Lumasiran clinical trial to see if we could stop the excess oxalate from being produced in my liver. I received the medicine monthly until December of 2020 when it switched to a three month phase. This medicine has turned my life around. Not only has it stopped any future stones from forming, it has meant that I can live a normal life and go to school and just have fun. It has also meant that I no longer require the transplants which would have been wholly detrimental to my quality of life. It is hard to put into words how bad the time around my diagnosis was and now it seems like a distant memory. I haven’t had to experience a truly horrible kidney stone in four years (touch wood) and now I feel absolutely fine. I visit the hospital every six months for blood tests and an injection of the drug. I receive the drug via home visit for the in between period.

I often hear that some of the two most painful things a human can endure are giving birth and passing a kidney stone. It is with absolute gratefulness to the [redacted] and this medicine at GOSH that I can say that I will hopefully never have to go through this phase of torture ever again and I am so glad that I was able to have my life turned around by this medicine.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

ADDENDUM: Critique of the company's response to ECD including updated PAS price for lumasiran

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 4/10/2022

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.

Company's response to ECD

The purpose of this addendum is to provide a critique of the company's response to the evaluation consultation document (ECD), including the updated patient access scheme (PAS) discount of [redacted] per 1 x 94.5mg/0.5mL solution for injection vial.

1 Introduction

The company's response to the ECD focuses on a revised cost-effectiveness analysis (CEA).[1] The revisions involve changes in relation to: estimation of transplant probability; face validity of health-state utility measurement; dialysis rates; estimation of post-transplant survival; rates of chronic kidney disease (CKD) stage-specific progression; reconsideration of patient subgroups; and updated price for pyridoxine. The company also provided details of a new literature search and related study selection process and consultation of clinical experts.[1, 2] The new literature search, study selection details, clinical expert consultation process and revised CEA have been critiqued by the Evidence Review Group (ERG), whose summaries and comments are provided below.

2 Revised search strategy, study selection and clinical expert consultation

2.1 Search strategy

The company conducted additional searches focusing on transplantation in people with primary hyperoxaluria (PH).[1]

The original search only searched for terms on PH and was limited by study design, using filters for randomised and controlled trials, observational studies, adverse events, systematic reviews, economics, and health-related quality of life. The new strategy combines PH terms and transplantation terms using the Boolean operator AND. As it does not contain study design filters it is not a subset of what was retrieved by the original searches and should retrieve additional unique references.[1]

In Table 1 of the post-ECD submission,[1] the company appears to have provided a MEDLINE search (based on the subject indexing terms used). The ERG noted that some details of the search strategy were lacking (e.g., database name/date range/host) as well as full details of the searches conducted on the other resources listed. The example strategy (Table 1) however, appears likely to have identified relevant records, and a good range of resources has been accessed.

ERG comment

In summary, the ERG is satisfied with the searches that appear to have been undertaken.

2.2 Study selection

Some details of the study selection criteria were outlined in the post-ECD submission[1] and other details were provided later at the request of the ERG.[2] An overall summary of this information is tabulated below (Table 1).

Table 1: Study selection criteria

Inclusion criteria	Exclusion criteria
Data reported for patients with PH1[a]	Studies reported data for other or unspecified types of PH[a]
Rigorously defined PH1 population[b]	No information

Inclusion criteria	Exclusion criteria
Transplant rate reported or can be calculated from information in record (i.e., total N with PH1 and n with transplant)[a]	Studies reporting data only for transplanted patients without indicating the sample size of the source cohort (i.e., not allowing the rate to be calculated)[a]
Large sample size[b]	No information
Applicable to current clinical practice[b]	No information
[a]Based on information in the document listing the study selection criteria.[2] [b]Based on information in the post-ECD submission (Section 2.1.1).[1] Abbreviations: n = number (numerator); N = number (denominator); PH = primary hyperoxaluria; PH1 = primary hyperoxaluria type 1; UK = United Kingdom.	

An Excel workbook was provided that contained details of records retrieved from the literature searches. Of 50 records listed, one was identified as being relevant to inform transplant probability[3] and the company considered that the data from this study superseded those from an earlier evaluation,[4] cited in the original company submission (CS).[5]

ERG comment

Details of the study selection criteria were provided in two different documents: the main post-ECD submission document;[1] and a separate document provided later and on request from the ERG.[2] The ERG noted that the two sources of information differed[1, 2] and that some details from the post-ECD submission were lacking. For example: it was not clear what "*Rigorously defined*" meant for the definition of the population with PH1; "*Large sample size*" was not defined; and "*applicability to current clinical practice*" was not explained further.[1] Regarding the information across both documents, it was also not clear to the ERG whether the study selection criteria had been formulated *pre-* or *post-hoc* (or whether a combination of both applied). Therefore, the ERG remains uncertain as to the exact set of criteria used to select studies as well as the rigour of the underlying process. Considering this, the ERG cannot discount the risk of study selection bias in this instance.

The Excel workbook included two worksheets (lists) showing bibliographic details relating to the retrieved records. It is possible that one list represented all retrieved hits (n=50 records) whilst the other showed those considered as full-text reports (n=33), but this was not explained. The one included study included data from patients across eight European countries in the European Hyperoxaluria Consortium (OxalEurope) Registry; this appeared to be a relevant evaluation.[3] However, it is possible that additional records could also have been eligible, for example Bergstralh et al. (2010),[6] Hoppe and Langman (2003),[7] Mandrile et al. (2022)[8] and Wang et al. (2020).[9] It was unclear why these other studies were not considered further and therefore uncertain whether the derived estimates for transplantation rates are the optimum and least biased available.

2.3 Consultation of clinical experts

In the post-ECD submission, the company referred to consultation with two UK-based clinical experts to validate model inputs and assumptions. Details of the clinical experts are as follows:

"[redacted] *and an* [redacted], *also a* [redacted] *and a* [redacted]"[1]

The company went on to mention that the two clinical experts agreed with using the dataset from Metry et al. (2022)[3] to estimate transplant rates in the cost-effectiveness model.[1] Furthermore, the company stated that the two experts were supportive of the methods used to calculate transplant rates in the CEA and that they endorsed the use of rates of disease progression in CKD stages 3b and 4 in the established clinical management (ECM) arm reported by Singh et al. (2022).[1, 11]

ERG comment

The ERG requested details of the methods used to select and elicit support from the two clinical experts. The company replied as follows:

"*Alnylam Pharmaceuticals solicited expert opinion to validate key model inputs and assumptions from a clinical perspective. The criteria for selecting experts was based on them having been* [redacted]

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

The information provided by Alnylam and verbalised during interviews as background for discussion consisted of Metry et al. (2022)[3] and Singh et al. (2022).[11]"[12]

The ERG remains unclear as to the exact methods used in the interviews as no details of questions or interview schedules were provided. The independence of the experts' views is also uncertain given that they were [redacted]

3 Revised cost-effectiveness model

In their resubmission post-ECD, the company addressed the following topics:

- **Transplant probability:** following an updated literature search for relevant data on liver transplant rates for patients with PH1 in clinical practice, as well as consultation with two UK clinical experts (both involved in the [redacted], the company has updated the source for transplant rates from the French study by Compagnon et al. (2014)[4] to a recently published study by Metry et al. (2022)[3] reporting data from eight countries in the European Hyperoxaluria Consortium (OxalEurope) Registry. In addition, the company identified an error in the ERG's calculation of transplant probability, which had prompted the ERG's conclusion that this parameter lacked face validity in our submitted model (ECD Section 3.20).
- **Health-state utilities:** The company has reviewed the NICE methods guidance and individual-patient-level EQ-5D data from the ILLUMINATE-C trial to answer concerns raised by the ERG about the face validity of certain health-state utilities and their overall appropriateness for use in the CEA (ECD Sections 3.21 and 3.22).
- **Dialysis rates:** to address concerns raised by the ERG and Committee (ECD Section 3.24), the company has incorporated different dialysis rates (i.e., percentages of patients receiving dialysis) for paediatric and adult patients in CKD stage 4 in the base-case analysis, and performed scenario analyses to assess the impact of alternative rates of dialysis.
- **Survival after transplant:** The company has adopted the ERG's preferred assumption to base survival post-transplantation in patients receiving ECM on the data for all patients in the study by Jamieson et al. (2005),[13] rather than only for those patients in *Fair* and *Poor* pre-operative condition as in our original submission.
- **CKD stage-specific progression:** to address the uncertainty of the ERG regarding different rates of disease progression in patients in different CKD stages (ECD Section 3.18), the revised CEA incorporates rates of disease progression in CKD3b and CKD4 in the ECM arm as reported in a recently published study by Singh et al. (2022).[11] The appropriateness of using this approach was confirmed in consultation with the UK clinical experts [redacted].
- **Subpopulations of PH1 patients treated with lumasiran:** in response to insights shared by the clinical experts at the first Committee meeting regarding their intended use of lumasiran in different patient subpopulations (ECD Section 3.8), the company has refined which patients are modelled to receive lumasiran.

For each of these issues, a short summary of the company's response in their resubmission post-ECD is presented, followed by ERG comments, if relevant.

3.1 Transplant probability

3.1.1 Parameter estimation

The company performed a new systematic literature review to facilitate the estimation of the probability of transplantation in the ECM population (see also Section 2 above). The company stated that the most relevant publication on transplant rate resulting from this search, in terms of large sample size, rigorously defined PH1 population, and applicability to current clinical practice, was a study by Metry et al. (2022) based on data from the OxalEurope Registry.[3] This study was published online on 28 November 2021, so was not captured in the original CS, for which the last search update was performed on 4 August 2021. Given its larger size and geographic scope, the company judged the study by Metry et al.[3] to be a more relevant source for this NICE appraisal than the French study by Compagnon et al. (2014)[4] used in the CS.

Metry et al. (2022)[3] was a retrospective cohort study that identified all patients with PH1 in the OxalEurope registry (described by the company as one of the largest PH registries worldwide) who underwent liver and/or kidney transplantation. Patients were from eight countries in Europe. Data retrieved from the OxalEurope registry, including information on >1100 patients, of whom 993 patients had PH1, were analysed. In total, 159 underwent combined liver–kidney transplantation (cLKT) between 1978 and 2019.

Over the 41-year period covered by Metry et al. (2022),[3] the company calculated an average of 3.9 transplants per year (i.e., 159 transplants ÷ 41 years = 3.9 transplants per year).

Based on Singh et al. (2021),[14] the study from which CKD stage distribution was derived for the CS, 37.6% of prevalent PH1 patients are in CKD4 or end-stage kidney disease (ESKD). With 993 patients in the total OxalEurope PH1 cohort, the estimated number in CKD4 or ESKD would thus be 373 (i.e., 993 total patients × 37.6% of patients in CKD4 or ESKD = 373 CKD4 and ESKD patients).

The estimate of 3.9 transplants per year divided by 373 patients in CKD4 or ESKD yields an annual probability of transplant of 0.010, or a probability per 6-month cycle in the Markov model of 0.005 (i.e, $1-[1-0.010]^{0.5}$, where 0.5 is model cycle length in years).

This per-cycle transplant probability of 0.005 was used in the revised CEA base case and all scenario analyses for patients with uncontrolled oxalate in CKD4 or ESKD.

The company asked the two clinical experts whether they considered the study by Metry et al. (2022)[3] to be an appropriate source for the liver transplant rate for patients with PH1 receiving ECM in the UK. Both experts indicated that OxalEurope is recognised as being comprehensive of historical outcomes for patients with PH1 and that it is representative of UK patients with PH1. They noted that it is one of the best sources of PH1 data available. They were supportive of using this dataset to estimate transplant rates in the model. When the calculation used to model cLKT in PH1 patients (as outlined in the preceding section) was described to the experts, they agreed that the steps were logical/appropriate. (Please note the ERG critique of the process of consulting the clinical experts in Section 2 above).

3.1.2 Error in ERG estimate of time on transplant waiting list

The company also addressed the ERG estimate of the expected wait time for a transplant (83 years for uncontrolled oxalate), when using the transplantation probability estimated in the CS of 0.007 per cycle based on Compagnon et al. (2014).[4]

They explained that the ERG's calculations incorporate a methodological flaw leading to significant differences in the modelling of transplant. Specifically, the ERG calculated mean time to transplant by inverting the overall, cohort-level per-cycle transplant probabilities used in the model. However, the per-cycle probability of receiving a transplant at the cohort level in the model is not within patients on the transplant waiting list, but instead within the aggregate group of patients on the waiting list and patients not on the list (i.e., patients who are not in suitable condition for a transplant). As a result, it is methodologically incorrect to invert this aggregated per-cycle probability to estimate a mean time to transplant as the ERG has done, because the resulting waiting time would not be representative of the subgroup of patients who are suitable candidates for transplant and actually on the waiting list, but rather would be confounded by the (essentially infinite) waiting time of patients who are not suitable candidates for transplantation and thus not on the waiting list.

ERG comment:

The ERG thanks the company for explaining the major flaw in the estimation of the expected waiting time. It is now clear that this approach of the ERG is unsuitable to validate the per cycle transition probabilities.

The ERG concurs with the company that the Metry study[3] may a suitable source to use for the estimation of the probability of transplantation (but please see the ERG critique of the study selection process in Section 2 above). However, using that study, the ERG comes to a different outcome.

First, the company uses for the number of transplants only the 159 cLKTs between 1978 and 2019, whilst also 37 sequential cLKTs were observed. Since both are viable options for PH1 patients, the ERG has used the total of 196 cLKTs as the numerator of the estimate.

For the denominator, the ERG also made adjustments. The company assumes implicitly in their calculations that all 993 patients were observed for the full 41 years that the registry covers. This appears very unlikely. Personal communication between the ERG and [redacted] found that the average age of patients in the registry [redacted] and that these patients have been in the registry since birth. Furthermore, [redacted] explained that of the 993 PH1 patients in the registry, follow-up data since birth is only available in [redacted]. Using the same approach as the company to calculate the per cycle probability of transplantation we come to an estimate of 0.0123.

It should also be noted that [redacted] further explained that estimating and using an overall probability of transplantation for PH1 patients should not be attempted, as this probability fluctuates with age groups. For example, in patients with infantile oxalosis (i.e. reaching ESKD before the age of 1), this probability is much higher. A recent study, also based on the OxalEurope registry, showed that out of 87 patients, 66 (76%) underwent liver transplantation (either combined or as first step in sequential).[15]

Thus, the ERG considers that the current approach in the model of one overall probability of transplantation for PH1 patients represents an extreme simplification of clinical reality.

3.2 Health-state utilities

As quoted in the ECD, the Committee concluded that "*it would have been helpful for the company to have provided the EQ-5D data measured in the ILLUMINATE-C study and complete an analysis to derive more accurate estimates of utility values for the late CKD and post-transplant health states.*"[1] The company has now presented an overview of the number of patients in ILLUMINATE-C with an EQ-5D Index score (Table 2) showing the lack of robust EQ-5D data from ILLUMINATE-C for each subgroup included in the model. Thus, the company considered it not feasible to derive representative utility values for the different advanced-disease health states from this study.

Table 2. Number of patients in ILLUMINATE-C with an EQ-5D Index score

	eGFR			
	30–44 (CKD3b)	**15–29 (CKD4)**	**<15 (ESKD)**	**Not Applicable***
Age <18 y				
Cohort A	[redacted]	[redacted]	[redacted]	[redacted]
Cohort B	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥18 y				
Cohort A	[redacted]	[redacted]	[redacted]	[redacted]
Cohort B	[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, ILLUMINATE-C data on file
Cohort A = patients who do not yet require dialysis; Cohort B = patients on dialysis; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol-5 Dimension; ESKD = end-stage kidney disease
*eGFR was calculated for patients in Cohort A only.

The company points out that section 3.22 of the ECD suggests that the EQ-5D valuations of the vignettes had lower face validity than the time-trade-off (TTO) valuations. However, EQ-5D Index scores at initial evaluation for the only subgroup in ILLUMINATE-C with more than 5 patients with available measures, namely paediatric patients on dialysis (n=[redacted]), show closer agreement with the EQ-5D utilities ([redacted] and [redacted] for CKD4 and ESKD, respectively) than the TTO utilities ([redacted] and [redacted], respectively). Notably, of these [redacted] patients, 3 had negative utility values at their first assessment in ILLUMINATE-C (see Table 2), and these three scores were all substantially lower than the negative mean values yielded by the EQ-5D valuation of patient vignettes. Based on this, the company states that these direct observations are not consistent with the ERG opinion that the TTO utilities have greater face validity than the corresponding EQ-5D utilities, and that this is further support for the use of the EQ-5D valuations of the health-state vignettes.

Table 3. Individual-patient-level EQ-5D Index scores at first assessment for paediatric patients on dialysis in ILLUMINATE-C

Patient*	Index score
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: Alnylam, ILLUMINATE-C data on file. Average added by ERG
EQ-5D = EuroQol-5 Dimension
*Anonymised

The company tried to account for the large differences in vignette valuations using the EQ-5D vs. TTO methods and suggested that there might be several possible contributing factors, including the following:

- Some participants may have been unwilling to trade off years of life,[16] which might partially explain the differences in outcomes between the TTO and EQ-5D approach to valuing the vignettes. In the TTO, the more a patient is willing to trade life years for health, the lower the resulting utility. The EQ-5D approach does not require people to explicitly trade off years of life and therefore is not subject to upward bias of results due to respondents' potential aversion to trading life years in exchange for improved health.
- The EQ-5D items map more directly to the health issues included in the detailed PH1 health states described in the vignettes and can therefore more systematically capture the impacts of these issues than the TTO method (which is less structured in its approach to capturing specific impacts of disease), potentially yielding a more objective valuation with greater sensitivity to the impacts of PH1.

Finally, the company sets out to explain that using the EQ-5D valuations of the vignettes in the model is in line with the NICE guidance.

The DSU's 2020 report on best practices for measuring and valuing HRQoL when sufficient EQ-5D data are unavailable specifies, "*Utility values for vignettes are generated using an appropriate sample of patients completing the EQ-5D for each vignette, and this is then scored using the appropriate and relevant value set for EQ-5D*".[17]

These recommendations are reflected in the 2022 NICE health technology evaluation manual, which presents a hierarchy of preferred HRQoL valuation methods.[18] This hierarchy states that if EQ-5D data are not available from a relevant study, the literature, or mapping from another measure, then vignettes should be:

- Developed using the DSU's best practice recommendations (see 2020 report)
- A sample of the general population, or people with the condition, should complete the EQ-5D based on the vignette; utilities should be calculated using the relevant EQ-5D value set

Therefore, the company considers that the use of EQ-5D valuations rather than TTO valuations from the vignette study aligns with best practices as identified by the DSU[17] and codified in the current NICE methods guidance.[18]

ERG comment

The ERG agrees with the company that using the EQ-5D valuations of the vignettes is the preferred choice to adhere to current NICE methods guidance.

The main reason why the ERG still considered it acceptable to deviate from this guidance was the lack of face validity when comparing the EQ-5D valuations of vignettes for CKD1-3b to the observed EQ-5D values from the ILLUMINATE-A trial. As can be seen in Table 3, the utilities as measured in the ILLUMINATE-A study are more aligned with the TTO-derived utilities than the EQ-5D-derived utilities from the vignette study.

Table 4 HRQoL utilities derived from the health-state vignettes and ILLUMINATE-A

	Adult			Child		
	Vignette study		ILLUMINATE-A	Vignette study		ILLUMINATE-A
	EQ-5D-5L	TTO	EQ-5D-3L	EQ-5D-5L	TTO	EQ-5D-3L
CKS 1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKS 3a	[redacted]	[redacted]				
CKS 3b	[redacted]	[redacted]				
CKS 4	[redacted]	[redacted]		[redacted]	[redacted]	
ESKD	[redacted]	[redacted]		[redacted]	[redacted]	
Post-cLKT	[redacted]	[redacted]		[redacted]	[redacted]	

Based on Table C17 of the CS[5]
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

The company showed the EQ-5D utility values from [redacted] patients in the ILLUMINATE-C study, to explain that the TTO values for children in CKS4 and ESKD lacked face validity. The ERG agrees with the company that indeed a large variation in utilities can be seen (Table 2), with 3 values much lower than the EQ-5D values derived from the vignettes but at the same time also three values above [redacted]. Note that the average of these [redacted] values is [redacted], which sits between the EQ-5D-derived utility and the TTO-derived utility, though slightly closer to the EQ-5D utilities.

Taken all together, the above-mentioned issues make it difficult to come to a definitive conclusion. NICE guidance clearly points to the EQ-5D-derived utilities, whereas comparison of the different utility estimates in CKS 1-3 clearly leads to the TTO-derived utilities. Exploring the observed EQ-5D values from ILLUMINATE-C also provides little support for one option over the other.

Given that the Committee followed the ERG preference for the TTO values in the ECD, the ERG will use the TTO values in an ERG preferred analysis. The average of the [redacted] observed utilities ([redacted]) will be used in a further scenario analysis.

3.3 Dialysis rates

In the ECD, the Committee expressed that they would have preferred for the company to have provided scenario analyses that varied the proportion of people undergoing dialysis among those receiving standard care (i.e., ECM) in the CKD4 health state. To test the sensitivity of model results to this parameter, the company has provided a range of values for the proportion of adult patients on dialysis in CKD4 in the ECM arm, as shown in Table 4.

Table 5. Dialysis rates in CKD4 in the revised CEA: base-case and scenario analyses

Age	Base case		Scenario analysis 1		Scenario analysis 2	
	Lumasiran	ECM	Lumasiran	ECM	Lumasiran	ECM
Adults	0%	25%	0%	50%	0%	0%
Paediatric	50%	100%	50%	100%	50%	100%

CKD = chronic kidney disease; ECM = established clinical management

3.4 Survival after transplant

In line with the ERG and Committee preferred approach, the company has now based survival post-transplantation in patients with uncontrolled oxalate levels on the data for all patients in the study by Jamieson et al. (2005),[13] rather than only for those patients in *Fair* and *Poor* pre-operative condition as was in the original CS.

3.5 CKD stage-specific progression

In the revised base-case CEA, as in the original submission, the rate of disease progression in the ECM arm for paediatric patients in CKD1–3a was set to the change in estimated glomerular filtration rate (eGFR) calculated from the plasma oxalate–eGFR relationship reported by Shah et al. (2020)[19] multiplied by the change over time in plasma oxalate observed in the placebo arm of the ILLUMINATE-A trial, resulting in a per-cycle decline of 2.83 mL/min/1.73 m^2. Thus, this method uses oxalate data from the ILLUMINATE-A trial to inform disease progression in the ECM arm of the model for patients in less severe health states.

However, this method cannot be applied to more severe health states because few patients in ILLUMINATE-A were in these health states, and because trials of lumasiran in such health states did not include a placebo arm in which to observe decline in eGFR in patients receiving only ECM. To fill this evidence gap, the original model accompanying the CS based the transition probability for CKD4 to ESKD on the ESKD-free survival curves reported by Harambat et al. (2010).[20] This is clearly a different approach compared to that used to estimate transitions in the less severe health states. Addressing this inconsistency, the revised CEA bases transitions for both paediatric and adult patients from CKD3b to CKD4 and from CKD4 to ESKD on a recently published study by Singh et al. (2022), which reported the rate of eGFR decline as a function of CKD stage in patients with PH1 enrolled in the Rare Kidney Stone Consortium (RKSC) registry.[11] In this study it was shown that the rates of eGFR decline increased with higher CKD stage.

As explained in Section 3.6.1, in the revised CEA the company assumed that only those adult patients in CKD1–3a who showed signs of rapid progression (considered similar to CKD3b) would be initiated on lumasiran. Therefore, the rate of eGFR change in adults in CKD1–3a was assumed to be the same as the rate of progression in CKD3b, to model the fast rate of progression that would prompt treatment with lumasiran.

The resulting rates of eGFR decline by CKD stage in the ECM arm of the revised model are shown in Table 5. Note that in the original CS, change in eGFR was not used for the CKD4 group, and all other values were assumed to be -2.83.

Table 6. Per-cycle changes in eGFR in the ECM arm, by health state.

Model health state	Paediatric	Adult
CKD1-2	-2.83*	-7.35‡
CKD3a	-2.83*	-7.35‡
CKD3b	-7.35†	-7.35†
CKD4	-8.30†	-8.30†

CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate

*Calculated as the rate of change in plasma oxalate in ILLUMINATE-A multiplied by the rate of change in eGFR per unit change in plasma oxalate reported by Shah et al. (2020),[19] as in the original model.
†Calculated from the annual change reported by Singh et al. (2022)[11] divided by 2 to obtain change per cycle.
‡For adults in CKD1–3a, only those who are fast progressors are considered eligible for treatment, and therefore the eGFR progression of CKD3b per Singh et al. (2022) [11] is applied to the CKD1–2 and CKD3a health states.

ERG comment:

The result of this new approach proposed by the company is that now the probability to move from CKD4 to ESKD is no longer age dependent (approximately 1% at age 1, 5% at age 65), but a fixed value of 58% across ages. This represents a significant change to the model input, so the ERG explored both approaches to assess their validity. When studying the paper by Harambat et al. (2010),[20] the ERG realized that the curve showing survival free from ESKD is not specific to PH1 patients who are already in the CKD4 stage, but is based on follow-up data from patients in various stages of CKD. With this in mind, it makes sense that the probability of moving the ESKD conditional on being in CKD4 is much higher that the probability of moving to ESKD of the average PH1 patient. Thus, it appears that in the previous model submission an incorrect approach was used, which has now been corrected.

3.6 Subpopulations of PH1 patients treated with lumasiran

3.6.1 Patients initiating lumasiran

At the first Committee meeting, the clinical experts indicated that they would likely treat all paediatric patients with lumasiran, and in the adult population all patients in CKD3b or higher, and only those adults in earlier stages (i.e., CKD1 to 3a) experiencing rapid progression. This change was implemented in the revised CEA by adjusting the distribution of the cohort at model start to assume (arbitrarily) that 50% of all prevalent adult patients in CKD1 to 3a are fast progressors. The resulting health-state distribution (after rescaling the overall distribution to account for exclusion of patients in CKD1-3a who are not fast progressors) for adults at model start following this change is shown in Table 7.

To test the sensitivity of model results to the assumed proportion of adults in CKD1 to 3a who are fast progressors, we also performed a series of scenario analyses in which this parameter was varied: 10%, 25%, 75%, and 100%. The health-state distributions for adults at model start in these scenarios are presented in Table 7.

Table 7. Health-state distribution among adults at model start in scenario analyses with different proportions of fast progressors among prevalent adult patients in CKD1 to 3a.

	Percentage of fast progressors among prevalent adult patients in CKD1–3a				
	10%	**25%**	**50%**	**75%**	**100%**
Proportion (%) of adult cohort in:			**Base case**		
CKD1–2	7	15	26	33	38
CKD3a	2	5	8	10	12
CKD3b	22	19	16	14	12
CKD4	18	16	13	11	10
ESKD	51	45	37	32	28

CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease

3.6.2 Lumasiran continuation rule

During consultation with the clinical experts, both considered it to be a plausible hypothesis that, upon maturity, a patient with paediatric-onset PH1 with mature kidneys could potentially sustain clearance of a higher background rate of oxalate production than they were able to sustain as a child with immature kidneys, and that as a result, even oxalate production rates that were above normal to some extent during maturity might not lead to increased morbidity or mortality in such patients. Thus, the company considered that in the absence of severe renal impairment, it could be appropriate to pause lumasiran treatment at maturity to assess whether a patient with PH1 is able to remain stable without lumasiran intervention, with criteria for re-initiation of treatment with lumasiran in the event that the patient showed signs of progression.

One of the experts referred to burosumab for X-linked hypophosphataemia in children and young people[21] as a treatment with similar continuation rules.

In the absence of any data to inform the proportion of patients that would remain stable following lumasiran treatment interruption, the company did not incorporate a continuation rule in the revised base-case analysis, but instead performed scenario analyses in which lumasiran therapy is discontinued in patients with paediatric-onset PH1 in the lumasiran arm of the model who are in CKD1 to 3b upon onset of adulthood (i.e., at age 18 years). Re-initiation of treatment is modelled by returning different proportions of these discontinued patients to lumasiran therapy over time. The curves for patients remaining off treatment in these scenarios are shown in Figure 1; these curves yield the following proportions of patients resuming treatment within 10 years: 10%, 30%, 50%, 70%, and 90%.

Figure 1. Proportion of patients with paediatric-onset PH1 remaining off lumasiran treatment over time following discontinuation upon adulthood.

KM = Kaplan–Meier

4 Company model results

In this section we present the main findings based on the companies revised model. For the complete set of results we refer to the Company resubmission post-ECD document.[1]

4.1 Base-case analysis

Results of the revised base-case analysis are presented in Table 8. Lumasiran is estimated to yield an additional [redacted] QALYs at an additional cost of £[redacted]. Given the large gain in undiscounted QALYs ([redacted], a weighting factor of 3.0 would apply, implying a willingness-to-pay threshold of £300,000/QALY.

Table 8. Base-case effectiveness and cost results

Technology	LYs	Disc LYs	QALYs	Disc QALYs	Costs (£)	Disc Costs (£)
Lumasiran	56.82	23.74	[redacted]	[redacted]	[redacted]	[redacted]
ECM	48.84	22.38	[redacted]	[redacted]	[redacted]	[redacted]
Difference, lumasiran vs. ECM	**7.99**	**1.36**	[redacted]	[redacted]	[redacted]	[redacted]

ECM = established clinical management; Disc = discounted; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year

Table 9 presents the resulting incremental cost-effectiveness ratios (ICERs) in terms of cost per life-year gained and per QALY gained for lumasiran compared with ECM. The discounted ICER for lumasiran vs ECM was £[redacted]/QALY.

Table 9. Base-case cost-effectiveness results

ICER	Undiscounted		Discounted	
	Cost/LY	**Cost/QALY**	**Cost/LY**	**Cost/QALY**
Lumasiran vs. ECM	[redacted]	[redacted]	[redacted]	[redacted]

ECM = established clinical management; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year

The disaggregated results (not shown) indicate that the majority of QALYs for lumasiran were accrued in CKD1 to 3b (with an approximately [redacted]-fold higher accrual of QALYs in CKD1–2 compared with ECM) and post-cLKT. Patients on ECM lost QALYs mainly in the ESKD health state. Similarly, costs disaggregated by health state showed that costs were primarily accrued in CKD1–2 for lumasiran, but in ESKD for ECM.

Furthermore, when exploring the disaggregated costs by category of cost, it is shown that the majority of costs for lumasiran were attributable to drug acquisition; in contrast, the main cost component for ECM was dialysis. Systemic oxalosis costs were [redacted] higher for ECM than for lumasiran.

4.2 Scenario analyses

As shown in Table 10, most of the variation in incremental cost-effectiveness ratio (ICER) results among the scenario analyses performed for this resubmission was accounted for by differences in incremental costs rather than incremental quality-adjusted life years (QALYs). Due to the relative consistency in QALY gain, the QALY weight of 3.0 was maintained for all of these scenarios. The ICERs varied from £[redacted] to £[redacted].

Table 10. Results of scenario analyses

Scenario	#	Parameter settings	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	QALY weight
Base case	0		[redacted]	[redacted]	[redacted]	[redacted]
ECM cohort on dialysis in CKD4	1	Adults: 50% Paediatric: 100%	[redacted]	[redacted]	[redacted]	[redacted]
	2	Adults: 0% Paediatric: 100%	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of fast-progressors among adults in CKD1–3a	3	10%	[redacted]	[redacted]	[redacted]	[redacted]
	4	25%	[redacted]	[redacted]	[redacted]	[redacted]
	5	75%	[redacted]	[redacted]	[redacted]	[redacted]
	6	100%	[redacted]	[redacted]	[redacted]	[redacted]
Paediatric-onset cohort in CKD1–3b at adulthood onset discontinues lumasiran treatment: proportion restarting treatment at 10 y	7	10%	[redacted]	[redacted]	[redacted]	[redacted]
	8	30%	[redacted]	[redacted]	[redacted]	[redacted]
	9	50%	[redacted]	[redacted]	[redacted]	[redacted]
	10	70%	[redacted]	[redacted]	[redacted]	[redacted]
	11	90%	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup with infantile onset of PH1	12	Infants only	[redacted]	[redacted]	[redacted]	[redacted]
	13	Patients of all ages	[redacted]	[redacted]	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year

The largest change in the ICER compared with the base-case scenario was seen with the scenarios in which patients with paediatric-onset disease who are in CKD1 to 3b at the onset of adulthood discontinue lumasiran treatment. The size of the reduction in the ICER for these patients was highly sensitive to the proportion of these patients requiring resumption of lumasiran therapy in future.

In contrast, the ICER was relatively insensitive to variation in the proportion of adult patients in CKD1 to 3a who were fast progressors and thus eligible for lumasiran treatment, varying by only £[redacted]/QALY when this proportion was changed from 10% to 100%.

4.3 Sensitivity analyses

One-way sensitivity analysis

In the one-way sensitivity analysis (OWSA) performed as described in the CS, the percentage change in results from the base-case analysis following lower and upper variation in the 10 most influential model parameters is shown in Table 11 and Figure 2. The most influential variables in the OWSA were the discount rates on costs and outcomes, and patient adherence to lumasiran therapy.

Table 11. Percentage change in base-case results following lower and upper variation in the 10 most influential model parameters

Parameter	Lower value	Upper value
Discount rate costs	[redacted]	[redacted]
Discount rate outcomes	[redacted]	[redacted]
Lumasiran drug adherence	[redacted]	[redacted]
Distribution CKD at baseline, CKD stage 1-2	[redacted]	[redacted]
Distribution CKD at baseline, ESRD	[redacted]	[redacted]
Constant parameter in general pop utility equation	[redacted]	[redacted]
Initial age (years), paediatric	[redacted]	[redacted]
High-intensity dialysis cost (£), per cycle, Adults	[redacted]	[redacted]
High-intensity dialysis cost (£), per cycle, Paediatric	[redacted]	[redacted]
Absolute change in POx in ILLUMINATE-A, placebo arm, ECM - any cycle	[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; POx = plasma oxalate

Figure 2. Tornado diagram of the change from base-case ICER results following lower and upper variation in the 10 most influential model parameters

CKD = chronic kidney disease; ECM = established 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) performed as described in the CS are summarised in Table 12. Figure 3 and Figure 4 show the individual PSA simulation results and cost-effectiveness acceptability curve, respectively.

Table 12. 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]

CI = confidence interval; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 3. Results of the 1000 simulations in the PSA for the ICER of lumasiran vs. ECM

ECM = established clinical management; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 4. Cost-effectiveness acceptability curve for the PSA

PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; WTP = willingness-to-pay

5 Exploratory and sensitivity analyses undertaken by the ERG

In section 3.1 the ERG comments discussed the alternative probability of transplantation for the ECM group, based on the same study as the company used to derive that transition probability. As a result, the ERG considers the value 0.0123 a more valid estimate than the 0.005 as estimated by the company and included it in the ERG preferred base case.

In section 3.2 the valuation of the CKD and ESRD health states was discussed, and we concluded that, despite the clear uncertainty about which utility valuation method gives the best utility values, the ERG still prefers the TTO valuations. So, these values were included in the ERG preferred base case.

5.1 ERG base case analysis

The results from the ERG deterministic base-case are shown in Table 13. It is clear that the two changes together have a large impact on the ICER. Additionally, the number of undiscounted QALYs gained is now [redacted], leading to a QALY weight of [redacted], which reduces the threshold ICER [redacted] per QALY gained. In Table 14 we can see that changing the valuation of the vignettes from EQ-5D to TTO has the largest impact of the two changes.

Table 13 ERG discounted base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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 14: Isolated impact of the ERGs preferred model assumptions

Preferred assumption	Section in this report	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	QALY weight
Company base-case	4.1	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 1 – Probability of transplantation	3.1.1	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 2 - TTO values vignettes	3.2	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case – both changes combined	-	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year

5.2 ERG probabilistic sensitivity

The ERG also conducted a PSA on their preferred base-case, with results shown in Table 15. The probabilistic ICER, averaged over 1,000 simulations, was [redacted], which is in line with the deterministic ICER shown in Table 13. Figure 5 and Figure 6 show the individual PSA simulation results and cost-effectiveness acceptability curve, respectively. At the threshold ICER of [redacted] per QALY gained, the probability that lumasiran is cost effective compared to ECM was [redacted]%.

Table 15. ERG probabilistic base-case 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]

CI = confidence interval; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year

Figure 5 Probabilistic sensitivity analysis scatterplot ERG base-case

Figure 6 Cost effectiveness acceptability curve ERG base-case

5.2 ERG scenario analysis

In their submission, the company showed the EQ-5D utility values from [redacted] patients in the ILLUMINATE-C study, with an average value of [redacted]. We applied that value to children in CKD4 and ESKD, and adults in ESKD. For adults in CKD4 we retained the EQ-5D utility from the vignette study of [redacted]. Table 16 shows the results for that scenario.

Table 16 Results of ERG scenario analysis

Scenario	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	QALY weight
ERG base-case – TTO values vignettes	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D utility ILLUMINATE-C	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Ínc. = incremental; QALY = quality-adjusted life year

Below we present the scenario analyses done by the company, but now using the ERG base case as a starting point. We can see that the ICERs for scenarios 1-11 range between [redacted].

Table 17 Scenario and subgroup analysis

Scenario	#	Parameter settings	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	QALY weight
Base case	0		[redacted]	[redacted]	[redacted]	[redacted]
ECM cohort on dialysis in CKD4	1	Adults: 50% Paediatric: 100%	[redacted]	[redacted]	[redacted]	[redacted]
	2	Adults: 0% Paediatric: 100%	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of fast-progressors among adults in CKD1–3a	3	10%	[redacted]	[redacted]	[redacted]	[redacted]
	4	25%	[redacted]	[redacted]	[redacted]	[redacted]
	5	75%	[redacted]	[redacted]	[redacted]	[redacted]
	6	100%	[redacted]	[redacted]	[redacted]	[redacted]
Paediatric-onset cohort in CKD1–3b at adulthood onset discontinues lumasiran treatment: proportion restarting treatment at 10 y	7	10%	[redacted]	[redacted]	[redacted]	[redacted]
	8	30%	[redacted]	[redacted]	[redacted]	[redacted]
	9	50%	[redacted]	[redacted]	[redacted]	[redacted]
	10	70%	[redacted]	[redacted]	[redacted]	[redacted]
	11	90%	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup with infantile onset of PH1	12	Infants only	[redacted]	[redacted]	[redacted]	[redacted]
	13	Patients of all ages	[redacted]	[redacted]	[redacted]	[redacted]

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