NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Documents (ECDs)**

2. **Company comments on the Evaluation Consultation Document (ECD2) including updated PAS from** Alnylam

3. **Consultee and commentator comments on the Evaluation Consultation Document (ECD2)** from:
   a. British Association of Paediatric Nephrology
   b. UK Kidney Association

There were no comments on the second Evaluation Consultation Document (ECD2) received through the NICE website

4. **Evidence Review Group critique of company response to the ECD2**

5. **Evidence Review Group subgroup analyses**

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 Technology Evaluation

Lumasiran for treating primary hyperoxaluria type 1

Response to consultee, commentator and public comments on the second Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Alnylam Pharmaceuticals	**Introduction** Alnylam wishes to thank the HST Evaluation Committee and the Evidence Review Group (ERG) for their thorough review of our company resubmission (dated 30 September 2022) for lumasiran for treating primary hyperoxaluria type 1 (PH1). We are gratified that the draft second Evaluation Consultation Document (ECD2) conveys the Committee's agreement with several important aspects of our resubmission, as reflected in the following conclusions:[1] • The company's positioning of lumasiran is aligned with how clinicians would expect to use lumasiran in clinical practice (Section 3.8). • The evidence base was appropriate for decision making given the rarity of the condition (Section 3.12). • The model structure reflected the general course of the condition (Section 3.17). • The company's modelling of disease progression was sufficient for decision making (Section 3.20). • Applying measures of plasma oxalate levels is appropriate and relevant in predicting kidney function in people with PH1 (Section 3.18). • The company's approach to exclude isolated liver transplant as a part of standard care was reasonable (Section 3.6). However, in the ECD2 the Committee did not recommend lumasiran on the following grounds:[1] The economic model assumes that the probability of having a transplant is higher if a person's plasma oxalate levels are controlled than if they are uncontrolled. Clinical opinion suggests that this does not reflect clinical practice. Therefore, the cost-effectiveness estimates from the model are not appropriate for decision-making. So, lumasiran is not recommended for use. The Committee "concluded that it would have preferred for the company to have provided … a revised model which includes the same rate of liver–kidney transplant for people with controlled and uncontrolled oxalate levels."[1] Accordingly, we have incorporated this assumption in our revised cost-effectiveness analysis (CEA) accompanying this second resubmission (Excel file *ID3765 Lumasiran PH1 CKD1-5 CEM UK_v17.0.xlsm*), along with several other preferred assumptions of the ERG and Committee.	Comments noted. The committee considered the consultation response, revised commercial offer and new evidence from the company. Please see responses to individual issues below.

Consultee	Comment	Response
	In this second resubmission document we describe only the revised methods and results arising from the changes we have implemented following the second Committee meeting. Please refer to our original Company Submission (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 first Committee meeting are described in our previous responses to ERG questions. Revisions to address the first Evaluation Consultation Document (ECD)[2] are described in our first resubmission. We addressed the following three main topics in the current revision of the CEA: • **Transplant probability:** based on discussions in the second Committee meeting and the ECD2 (Sections 3.21–3.22), the same liver–kidney transplant (LKT) rate is now modelled for patients with controlled oxalate levels as for patients with uncontrolled oxalate levels. This revision has been implemented by applying the ERG's proposed per-cycle transplant rate for patients with uncontrolled oxalate levels of 0.0123 based on historical transplant rates to patients in the model with controlled and uncontrolled oxalate levels. This change corresponds exactly to the Committee's request in ECD2 Section 3.33. • **Dialysis rates:** based on discussions in the second Committee meeting and the ECD2 (Sections 3.27–3.28), the frequency of high-intensity dialysis has been reduced from 7 days per week to 6 days per week. Furthermore, for patients in chronic kidney disease (CKD) stage 4, the revised CEA assumes that 50% of adults and 100% of children are on dialysis in both the ECM and lumasiran arms, which the Committee concluded aligns better with clinical expert opinion (ECD2 Section 3.28). This change also corresponds exactly to the Committee's request for the updated model (ECD2 Section 3.33). • **Health-state utilities:** ECD2 Section 3.25 states, "The committee considered that it would like the company to provide the average EQ-5D score across all people included in ILLUMINATE-C to validate the utilities derived from the vignette study. In the absence of this data, the committee concluded that it preferred to use the EQ-5D utility average from the paediatric subgroup in ILLUMINATE-C for which data were previously provided to estimate utilities for the late CKD health states (as per the ERG's scenario analysis)."[1] As explained in detail in Section **Error! Reference source not found.**, Alnylam has concluded that the EQ-5D scores for adults in ILLUMINATE-C are unreliable and would not support decision-making for several important reasons. Briefly, this conclusion takes into consideration testimony from clinicians and patients on the severity of PH1 and the resulting profound impairment of health-related quality of life (HRQoL), particularly in these late stages of disease. The conclusion is also informed by the expectation that patients with PH1 in CKD4 or ESKD should have lower utilities than those reported by patients without PH1 in the same CKD stages, since the former face not only the burden of kidney disease but also the other complications of PH1. Considering these aspects of advanced PH1, we assess the EQ-5D scores from adults in ILLUMINATE-C to be unreliable—and thus unsuitable for inclusion in an average EQ-5D score for modelling purposes—because a substantial proportion of these patients reported scores not only higher than those reported in the literature for non-PH1 patients with CKD4 or ESKD, but also higher than age-matched general population norms, even including some perfect scores of 1.0. We have, therefore, performed a scenario analysis in which we have updated the model using the committee's alternative preferred assumption, using the average utility of [redacted] as calculated by the ERG from the paediatric EQ-5D data previously provided to define the utilities in the uncontrolled-oxalate CKD4 and ESKD health states for the paediatric cohort and the uncontrolled-oxalate ESKD health-state for the adult cohort.[3] This scenario analysis is fully discussed in Section 0. In addition, considering the HRQoL-related	

Consultee	Comment	Response
	aspects noted above, we have reanalysed the time-trade-off (TTO) values from the vignette study, and found similar face validity issues related to reporting of utilities higher than those associated with CKD4 or ESKD without PH1, exceeding general population norms, and even indicating perfect health. Accordingly, we have provided an additional scenario analysis in which we use recalculated health state utilities based on the TTO data from the vignette study, using a plausible set of values constrained not to exceed those for non-PH1 patients with CKD4 or ESKD. Full details of this scenario analysis are presented in Section 0. Alnylam's revised base case continues to incorporate EQ-5D values from the vignette study, and our rationale for retaining this approach as most appropriate for decision-making is explained in Section **Error! Reference source not found.**. An additional change compared with the first resubmission is that we no longer present analyses with a stopping/continuation rule for lumasiran since the Committee concluded that it could not take these analyses into account in its decision making, because there was no evidence to inform estimation of the clinical impact of a stopping rule with lumasiran treatment (ECD2 Section 3.30). Similarly, differential discounting is no longer considered since the Committee concluded that the application of a lower discount rate was not appropriate (ECD2 Section 3.31). We believe that this resubmission with our 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.	
Alnylam Pharmaceuticals	**Transplant probability** In Section 3.33 of the ECD2, the Committee states "that an updated model which included a single probability of liver–kidney transplant for people with controlled and uncontrolled oxalate would be more in keeping with NHS clinical practice."[1] We have implemented this request exactly in the revised CEA base case and all scenario analyses for patients with controlled and uncontrolled oxalate in CKD4 or end-stage kidney disease (ESKD). As in our previous resubmission, the transplant probability is derived from the retrospective cohort study by Metry et al. (2022) of patients with PH1 in the OxalEurope registry who underwent liver or kidney transplantation.[4] However, the revised analysis incorporates the ERG's estimated per-cycle probability of 0.0123, which was informed not only by the data reported by Metry et al. but also by unpublished details about the OxalEurope registry that the ERG elicited in personal communications with clinical experts.[3] The different per-cycle transplant probability compared with our previous calculation of 0.005 is accounted for by the following differences in assumptions:[3] • Our previous calculation considered only the 159 combined liver–kidney transplants (cLKTs) reported between 1978 and 2019, but the ERG also included 37 sequential LKTs reported by Metry et al.[4] • We used in the denominator of our calculation all 993 patients with PH1 in the registry, whereas the ERG included only those patients with follow-up since birth (n=[redacted]). • Our calculation assumed a follow-up period corresponding to the full 41 years covered by the registry, while the ERG considered instead the average age of the [redacted] patients in the registry followed since birth, [redacted] years. We acknowledge that the approach used by the ERG regarding these three points is appropriate for estimating the probability of transplantation in the model, and thus have implemented this approach in the base-case and scenario analyses in the revised CEA.	Comments noted. The committee concluded that the company's updated model was reflective of transplant rates in clinical practice for people with PH1 and was appropriate for decision making. Please see sections 3.21 to 3.22 of the FED.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>Alnylam Pharmaceuticals</td><td>
Dialysis rates in CKD4

In our previous model's base case, dialysis rates differed by treatment arm and patient age category, as shown in Error! Reference source not found.. However, the Committee concluded that our scenario that assumed that 50% of adults and 100% of children in CKD4 would be on dialysis irrespective of treatment arm aligned better with clinical expert opinion, compared with our base-case assumptions (ECD2 Section 3.28), and stated that the updated model should include this preferred assumption (ECD2 Section 3.33).[1] Accordingly, we have incorporated this assumption in the revised CEA base case and both scenario analyses, applying the same dialysis rates in both treatment arms since the Committee expected that half of adult patients and all paediatric patients in CKD4, whether receiving lumasiran or not, would still have dialysis to remove established oxalate deposits from the body (Error! Reference source not found.).

Table 1. Dialysis rates in CKD4 in the previous company CEA and the revised CEA
<table>
<tr><th></th><th colspan="2">Base case</th><th colspan="2">Scenario analysis 1*</th><th colspan="2">Scenario analysis 2*</th></tr>
<tr><th>Age</th><th>Lumasiran</th><th>ECM</th><th>Lumasiran</th><th>ECM</th><th>Lumasiran</th><th>ECM</th></tr>
<tr><td>Previous CEA</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Adults</td><td>0%</td><td>25%</td><td>0%</td><td>50%</td><td>0%</td><td>0%</td></tr>
<tr><td>Paediatric</td><td>50%</td><td>100%</td><td>50%</td><td>100%</td><td>50%</td><td>100%</td></tr>
<tr><td>Revised CEA</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Adults</td><td>50%</td><td>50%</td><td colspan="4"></td></tr>
<tr><td>Paediatric</td><td>100%</td><td>100%</td><td colspan="4"></td></tr>
</table>
CKD = chronic kidney disease; ECM = established clinical management
*No scenario analyses varying dialysis rates are performed for the revised CEA because the Committee specified the preferred rates in the revised base-case analysis in alignment with clinical expert opinion.

In addition, the frequency of high-intensity dialysis has been revised from 7 days per week in our previous model to 6 days per week, because in the second Committee meeting the clinical experts explained that a frequency exceeding 6 days per week is not manageable in NHS clinical practice due to the limited capacity of haemodialysis units and the disruption that intensive dialysis causes to family life (ECD2 Sections 3.27 and 3.28).[1]
</td><td>Comments noted. The committee was satisfied that the company's updated modelling assumptions reflected the expected use of dialysis in people with PH1 on standard care or lumasiran. Please see sections 3.27 to 3.29 of the FED.</td></tr>
<tr><td>Alnylam Pharmaceuticals</td><td>
Health-state utilities

<u>Lack of face validity of EQ-5D measures from adult patients in ILLUMINATE-C</u>

Section 3.25 of the ECD states that the Committee "considered that it would like the company to provide the average EQ-5D score across all people included in ILLUMINATE-C to validate the utilities derived from the vignette study."[1] Careful review of the individual EQ-5D index scores for patients in ILLUMINATE-C confirms that these scores are unreliable, with a substantial number of clinically implausible scores that lack any face validity, which are thus entirely unsuitable to report for decision-making purposes (i.e., in the context of an HST appraisal).

Specifically, among adult patients in ILLUMINATE-C, all of whom had advanced disease in CKD4 or ESKD,[5] a considerable proportion reported EQ-5D scores that exceed not only those reported by patients without PH1 in the same CKD stages (see Section 0 below for expected cut-off values) but also the healthy population norm values, even including some patients who reported scores of 1.0, signifying perfect health. Such high scores completely lack credibility, considering that these are all patients with advanced PH1, most of whom are receiving frequent dialysis,[5]
</td><td>Comments noted. The committee considered the company's response and new scenario analyses. It recognised that there was uncertainty in using the EQ-5D utility average from the subgroup of children from ILLUMINATE-C but considered that this was the best source of utility data to estimate utilities for people with PH1 and advanced kidney disease. This was because the utility values were measured directly from children (or their caregivers) in the trial. It concluded that the EQ-5D utility</td></tr>
</table>

Consultee	Comment	Response
	which both the clinical and patient experts have clearly identified as placing a heavy burden on health-related quality of life (HRQoL), as documented in both the ECD and the ECD2.[1,2] The implausibly high EQ-5D values observed in a substantial proportion of adult patients in ILLUMINATE-C, which obviously do not accurately reflect the heavy burden of advanced PH1 on patients, may be due to the "disability paradox", an effect in which patients with chronic and disabling diseases may adapt to their condition and value their health states higher than does the general population.[6] The disability paradox has been demonstrated for patients with such diverse conditions as haemophilia,[7] Duchenne muscular dystrophy,[8] and stroke.[9] We speculate that the reason the disability paradox appears to have affected scores for adults to a greater extent than for paediatric patients is that the adult patients have been living with PH1 for much longer, and thus have had considerably more time to adapt to and accept their disease. The disability paradox may be less apparently impacting scores from paediatric patients in ILLUMINATE-C. In a review of cost-effectiveness analyses for rare diseases, Postma et al. (2022) note that the disability paradox leads to an underestimation of the disease burden.[10] These authors point out that an economic analysis based on patient-derived utilities affected by this paradox would under-value the effectiveness of treatment relative to the general public's preference. This is especially relevant in the context of the present HST appraisal, given that the NHS is a publicly funded healthcare system, so utility valuations should be reasonable in the perspective of society at large. Notably, the current NICE methods guide specifies that the utility of HRQoL changes should be based on public preferences.[11] Thus, within-trial assessments that assign similar utilities to advanced PH1 health states as to healthy individuals, in a manner that may reflect the unique perspective of adults with PH1 through the lens of the disability paradox, rather than the perspective of the general population, should be regarded with scepticism for modelling and decision-making purposes. The above considerations argue against introduction of the EQ-5D scores for adults in ILLUMINATE-C into the current appraisal process and support our use of EQ-5D utilities from the vignette study in the revised base case. <u>Preference for vignette-based utilities over utilities elicited from the ILLUMINATE-C population</u> While we present a scenario analysis applying the average EQ-5D utility of [redacted] from a paediatric subgroup in ILLUMINATE-C to the uncontrolled-oxalate CKD4 and ESKD health states for paediatric patients and uncontrolled-oxalate ESKD health-state for adult patients, as proposed by the Committee in the absence of presenting the average EQ-5D score of across all patients (ECD2 Section 3.25), we contend that use of EQ-5D utilities from the vignette study is the most appropriate. The small sample size of the paediatric subgroup used for this average (n=8) introduces uncertainty over the extent to which the mean utility value observed in this subgroup reflects the true health state utility in the underlying population from which the subgroup is taken. Furthermore, while the EQ-5D values observed within this subgroup generally did not lack face validity, with none approaching values associated with perfect health, the degree of impact of the disability paradox on these values is unknown. This complicates the use of ILLUMINATE-C data as a direct source of utility data for the CEA. Indeed, this limitation, together with the evident lack of validity in the adult utilities gathered within ILLUMINATE-C, underscores the necessity of using utilities from the vignette study to inform the CEA. We do believe, however, that EQ-5D values observed within this paediatric subgroup provide the best available basis for validating vignette study values in CKD4 and ESKD in the CEA. <u>EQ-5D vs. TTO for vignette valuation</u>	average from the subgroup in ILLUMINATE-C should be used to estimate utilities for the late CKD health states. Please see sections 3.23 to 3.26 of the FED.

Consultee	Comment	Response
	Given the limitations of the EQ-5D data collected directly from ILLUMINATE-C, as described above, we believe that the vignette study is the most appropriate source of utility values for patients in CKD4 and ESKD in the CEA. In our first resubmission, our base case included EQ-5D-derived utilities from the vignette study, in view of the following considerations: • A brief review of the relevant Decision Support Unit (DSU) and NICE methods guidance on the valuation of vignettes confirmed that NICE prefers EQ-5D valuations over TTO valuations,[11-13] as was acknowledged by the ERG in their critique of our resubmission.[3] • The EQ-5D-derived utilities, when compared with TTO-derived utilities, are numerically closer to the utilities elicited directly from a subgroup of paediatric patients in ILLUMINATE-C; these values provide the most robust, directly applicable source of utility data against which to validate vignette study utility values for patients in CKD4 and ESKD. o Previously, the ERG used ILLUMINATE-A trial data to validate results for CKD stages 1-3b from the vignette study conducted to estimate health state utilities in PH1. Based on this validation approach, the ERG preferred that TTO-based values be used over EQ-5D-based values from the vignette study to inform utility values in patients in CKD4 and ESKD in the CEA. Given the mismatch between the population in which the ERG validated trial data against vignette study data (CKD1–3b) and the population in which vignette study data were used in the model (CKD4–ESKD), we contend it is more appropriate to use utilities elicited directly from paediatric patients in ILLUMINATE-C (which exclusively enrolled patients in more advanced stages of PH1) for validation as noted above. In addition, we have conducted further efforts to assess the internal validity of the vignette scores for CKD4 and ESKD. In particular, as shown in Figure 1, the histograms of scores estimated via the two different methods indicate that validity issues may exist with the TTO-derived scores, which follow distributions characterised by the following anomalies: • Many implausibly high scores, considering the expected major HRQoL impairment in advanced PH1; these include scores approaching or in excess of normal values for healthy individuals, and in some cases scores as high as 1.0, representing perfect health • A large discontinuity in the distribution, wherein extreme negative values (at/near -1.0 on the horizontal axis) were elicited from some respondents, followed by a large interval thereafter with no density in the distribution until the value of 0 was reached on the horizontal axis; this feature suggests a virtual floor of 0 (i.e., only positive utilities) for most respondents, despite the potential to assign TTO values as low as -1.0 In contrast, the histograms for EQ-5D index scores appear more typical, with fewer extreme values at either end of the distributions and no large discontinuities or other anomalies suggestive of possible validity concerns. **Figure 1. Comparison of TTO-derived vs. EQ-5D-derived utility scores from the vignette study in CKD4 and ESKD** Valuation method Subgroup TTO EQ-5D **Adult**	

Consultee	Comment	Response
	CKD4 [redacted]	
	ESKD [redacted]	
	Paediatric	
	CKD4 [redacted]	
	ESKD [redacted]	

CKD = chronic kidney disease; ESKD = end-stage kidney disease; TTO = time-trade-off

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

As we noted in our first resubmission, while it is not possible to ascertain precisely the reasons for the differences in mean health state 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-

Consultee	Comment	Response
	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. Further to these observations which we previously raised regarding the difference in mean health state utility values yielded by the two methods, we note that the observation of a large discontinuity between -1.0 and 0 in the distribution of TTO exercise responses is consistent with prior accounts of issues with the use of the TTO method to value health states. Al Sayah et al. (2016) reported on the observation of values clustered at 0 with few negative values, particularly over the interval from -0.5 to 0, in past TTO studies.[15] The authors attributed this finding to confusion in participants' understanding of the TTO task, particularly as it relates to valuation of more severe health states, and noted how this confusion can impact the validity of TTO-derived utilities for such states. Similar limitations of the TTO method were highlighted by NICE in the appraisal of atidarsagene autotemcel for treating metachromatic leukodystrophy (HST18). The lead team presentation for the first Committee meeting in HST18 notes that TTO methods may be conceptually difficult to understand.[16] The presentation also reports that the TTO exercise in the vignette study performed for that appraisal resulted in clustering of TTO values around 0 and around best and worst possible ratings (-1 and 1) across health states.[16] Notably, these issues do not apply to the EQ-5D-derived vignette values for PH1 in the current submission (Figure 1). <u>Summary of utilities in CKD4 and ESKD in the revised base-case and scenario analyses</u> Taking all of the above points into account, 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 base case. Nevertheless, to address the preferences expressed by the Committee and ERG, we are also providing two new scenario analyses, as follows: 1. Average EQ-5D utility of [redacted] from the paediatric subgroup in ILLUMINATE-C is applied to paediatric patients with uncontrolled oxalate in CKD4 and ESKD and adults with uncontrolled oxalate in ESKD. 2. TTO values from the vignette study are applied to patients in CKD4 and ESKD, with average scores recalculated after exclusion of clinically implausible values For the second of these scenario analyses, individual TTO scores in CKD4 and ESKD were excluded from averaging if they exceeded the values for patients without PH1 in CKD4 or ESKD shown in Table 2, which were obtained by taking model health state utilities for patients with PH1 in CKD4 and ESKD and adjusting these utilities as applicable to reflect differences in the use of dialysis and the absence of systemic oxalosis complications in non-PH1-related CKD4 and ESKD; the references and details of how health state utilities are calculated in the model and adjusted for the presence or absence of different dialysis modalities and systemic oxalosis complications were described in Section 10.1.9 of the CS. Our rationale for these thresholds is that we considered it to be clinically implausible that a patient with advanced PH1 would have better HRQoL than a patient without PH1 in the same CKD stage, given the additional burden of the elevated oxalate levels in PH1. For CKD4, the cut-off represented the estimated utility of a patient with controlled oxalate levels, not on dialysis (as would be the case for a patient in CKD4 without PH1), while for ESKD, the cut-off	

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>represented the estimated utility of a patient with controlled oxalate levels, on normal-intensity dialysis (as would be the case for a patient with non-PH1-related ESKD).

Table 2. Utility cut-offs used for recalculating average TTO values for Scenario Analysis #2 in the revised model
<table><tr><th>Health state</th><th>Paediatric</th><th>Adult</th></tr><tr><td>CKD4</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>ESKD</td><td>[redacted]</td><td>[redacted]</td></tr></table>CKD = chronic kidney disease; ESKD = end-stage kidney disease; TTO = time-trade-off

After exclusion of scores exceeding the threshold values in Table 2, the recalculated average TTO utilities for this scenario analysis were as shown in Table 3.

Table 3. Recalculated average TTO values for Scenario Analysis #2 in the revised model
<table><tr><th>Health state</th><th>Paediatric</th><th>Adult</th></tr><tr><td>CKD4</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>ESKD</td><td>[redacted]</td><td>[redacted]</td></tr></table>CKD = chronic kidney disease; ESKD = end-stage kidney disease; TTO = time-trade-off</td><td></td></tr>
<tr><td>Alnylam Pharmaceuticals</td><td>The company presented updated cost effectiveness estimates. These have not been reported here because they were marked as confidential and were subsequently superseded by estimates including a new patient access scheme.

Conclusions

In this second resubmission, Alnylam has undertaken to incorporate the modelling preferences expressed by the Committee and ERG to the fullest extent we considered could be supported by the available evidence. Changes to assumptions about transplant rate and dialysis rate have been made exactly in accordance with the Committee's preferences expressed in the ECD2. Although we retained our previous approach to utilities for patients in CKD4 and ESKD in our base case for the important reasons explained in Section Error! Reference source not found., our Scenario #1 implements the Committee's requested method, while our Scenario #2 replicates the ERG's preferred use of vignette TTO valuation (modified by exclusion of clinically implausible values from the calculation of average utilities).

The revisions to our base-case CEA would have resulted in [redacted] in the ICER compared with the results of the company base-case model accompanying our first resubmission; however, the present results incorporate the [redacted] PAS discount that Alnylam has proposed to the NHS, and consequently the base-case ICER is [redacted] in the revised CEA compared with the first resubmission: £[redacted]/QALY vs. £[redacted]/QALY, respectively. The ICER should also be</td><td>Comments noted. The committee was satisfied that the cost-effectiveness estimates from the model were appropriate for decision making following the company's model revisions in response to the second consultation. It considered that its preferred utility estimate for people with PH1 and advanced kidney disease was highly uncertain, and that this made the cost-effectiveness results from the model uncertain. Because of this, it decided to apply a QALY weighting of 2.0. The committee considered that its preferred ICERs were likely to be within the range NICE normally considers an effective use of NHS resources for a highly specialised technology, given the applied QALY weighting. So, it recommended lumasiran</td></tr>
</table>

Consultee	Comment	Response
	considered in the context that we have retained a number of conservative assumptions from the original model, as described in the CS, 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 Due to the large QALY gain in the revised CEA base case and both scenario analyses, the maximum QALY weighting of 3.0 would apply. We hope that the revisions we have made to the CEA will allow the Committee to conclude that the cost-effectiveness estimates from the model are appropriate for decision-making. **References** 1. National Institute for Health and Care Excellence. Evaluation consultation document 2: Lumasiran for treating primary hyperoxaluria type 1. November 2022. 2. National Institute for Health and Care Excellence. Evaluation consultation document: Lumasiran for treating primary hyperoxaluria type 1. April 2022. 3. O'Meara S, Al M, Wetzelaer P, et al. Lumasiran for treating primary hyperoxaluria type 1 [ID3765]. ADDENDUM: Critique of the company's response to ECD including updated PAS price for lumasiran. Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University; 4 October 2022. 4. Metry EL, Garrelfs SF, Peters-Sengers H, et al. Long-term transplantation outcomes in patients with primary hyperoxaluria type 1 included in the European Hyperoxaluria Consortium (OxalEurope) Registry. *Kidney Int Rep.* 2022;7(2):210-220. 5. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. *Am J Kidney Dis.* 2022:In press. 6. Albrecht GL, Devlieger PJ. The disability paradox: high quality of life against all odds. *Soc Sci Med.* 1999;48(8):977-988. 7. O'Hara J, Martin AP, Nugent D, et al. Evidence of a disability paradox in patient-reported outcomes in haemophilia. *Haemophilia.* 2021;27(2):245-252. 8. Pangalila RF, van den Bos GA, Bartels B, et al. Quality of life of adult men with Duchenne muscular dystrophy in the Netherlands: implications for care. *J Rehabil Med.* 2015;47(2):161-166. 9. Mavaddat N, Sadler E, Lim L, et al. What underlies the difference between self-reported health and disability after stroke? A qualitative study in the UK. *BMC Neurol.* 2021;21(1):315. 10. Postma MJ, Noone D, Rozenbaum MH, et al. Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose? *Orphanet J Rare Dis.* 2022;17(1):157. 11. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. Process and methods [PMG36]. 31 January 2022; https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. Accessed 20 December 2022.	as an option for treating PH1. Please see sections 1.1, 3.35 and 3.39 of the FED.

Consultee	Comment	Response
	12. National Institute for Health and Care Excellence. CHTE methods review: health-related quality of life. Task and finish group report. July 2020; https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/nice-guidance/chte-methods-consultation/Health-related-quality-of-life-task-and-finish-group-report.docx. Accessed 20 December 2022. 13. Rowen D, Brazier J, Wong R, Wailoo A. Measuring and valuing health-related quality of life when sufficient EQ-5D data is not available. Report by the Decision Support Unit. 31 July 2020; https://www.sheffield.ac.uk/nice-dsu/methods-development/measuring-health-related-quality-life. Accessed 20 December 2022. 14. Spencer A, Tomeny E, Mujica-Mota RE, et al. Do time trade-off values fully capture attitudes that are relevant to health-related choices? *Eur J Health Econ.* 2019;20(4):559-568. 15. Al Sayah F, Mladenovic A, Gaebel K, et al. How dead is dead? Qualitative findings from participants of combined traditional and lead-time time trade-off valuations. *Qual Life Res.* 2016;25(1):35-43. 16. National Institute for Health and Care Excellence. ID1666 OTL 200 for metachromatic leukodystrophy: Lead team presentation, 1st HST committee meeting. 15 April 2021; https://www.nice.org.uk/guidance/hst18/documents/1. Accessed 20 December 2022.	
British Association for Paediatric Nephrology	On behalf of the British Association for Paediatric Nephrology, we wish to submit a further clinical perspective on the impact of Lumasiran treatment for young children with Primary Hyperoxaluria type 1. We would be grateful if the committee could consider this additional clinical information which may not be reflected in the health economic model. Four infants under 1 year of age commenced compassionate use Lumasiran treatment on a clinically urgent basis in the last 2 years in UK. All had a life-threatening rapidly progressive infantile oxalosis phenotype. Before the availability of specific treatment, such children would rapidly progress to kidney failure and would start dialysis. Unfortunately, dialysis is very poor with regards to oxalate clearance and without urine output, these children will deposit oxalate everywhere in their body with potentially severe consequences (including bone marrow failure and cardiac failure). This oxalate deposition would progress until the children received a liver and kidney transplant and the kidney transplant would often be endangered by the massive oxalate excretion post-transplant. For 2 of these infants in whom kidney function was deteriorating to the point of requiring dialysis, after commencement of Lumasiran, their rapid decline in kidney function was reversed and they remain clinically well without the need for dialysis. Two further infants commenced treatment at a later stage whilst in established kidney failure requiring dialysis. Both have experienced improvement in urine output and kidney function whilst on dialysis and have avoided urgent liver transplantation or progression to systemic oxalosis with high associated mortality. In the regional multi professional children's kidney stone service, we have noticed an apparent substantial reduction in urological procedures for kidney stones in children with primary hyperoxaluria type 1, which will ultimately help preserve kidney function in this group. Several families of children with primary hyperoxaluria treated with Lumasiran have expressed concern about the possibility that children may need to discontinue treatment, given the clear improvements in their health and quality of life. UK paediatric clinicians caring for children with primary hyperoxaluria have expressed concern that this highly effective pivotal therapy may not be available via the NHS.	Comments noted. The committee considered the views of stakeholders in its decision making. It recognised that people with PH1 and their clinicians would welcome lumasiran as a treatment option for PH1. The committee considered that its preferred ICERs were likely to be within the range NICE normally considers an effective use of NHS resources for a highly specialised technology. So, it recommended lumasiran as an option for treating PH1. Please see sections 1.1, 3.5, 3.35 and 3.39 of the FED.

Consultee	Comment	Response
	As national body of clinicians caring for children with primary hyperoxaluria type 1, we would be grateful if the committee could take these perspectives into consideration alongside the health economic model.	
UK Kidney Association	We broadly agree with the conclusions of the committee regarding proposed improvements to the model used to calculate cost effectiveness. The main areas of difficulty were: using cut-off plasma oxalate values as an indication for transplantation, and the assumption that CKD stage and health state can be correlated. We feel that modelling in this way is too rigid, does not account for the reality of decision making in patients with rare diseases, and completely omits some very important indications e.g. infantile oxalosis, for which the model is not valid. The main clinical factors guiding treatment decisions are: rate of worsening of renal function (regardless of baseline CKD stage), evidence of systemic oxalosis, and age of patient. If transplantation is needed, delaying it is usually not in the patient's best interest. We hope that these factors can be considered in any future model. In addition to use of CKD stages as health states (3.14 in the ECD), we suggest also adding the impact of recurrent kidney stone disease (symptoms, interventions, time off work/school, etc) especially in adult patients. This has not been considered at all in the economic case, yet is an important clinical outcome (and is also specified in the ILLUMINATE trials).	Comments noted. The committee was satisfied that the model structure reflected the general course of PH1. It noted that the company had revised its model in response to consultation by using the same probability of transplant for people with controlled and uncontrolled oxalate levels. The committee concluded that the company's updated model was reflective of transplant rates in clinical practice for people with PH1 and was appropriate for decision making. Please see sections 3.14 to 3.17 and 3.21 to 3.22 of the FED.
UK Kidney Association	We do not understand why it is necessary to postulate a discontinuation rule for paediatric lumasiran-treated patients at age 18. There is no evidence for this and it is not justified clinically. For example, we would not consider stopping pyridoxine (disease modifying drug) therapy in those patients who have responded simply because they have reached adulthood. Instead, national systems that we have proposed via the NHS Rare Disease Collaborative Network for hyperoxaluria, in conjunction with data collection via the National Registry for Rare Kidney Diseases, would be a more effective way to monitor and consider discontinuation of therapy, according to recorded clinical outcomes and the latest published data.	Comments noted. The committee concluded that because there was no evidence to show the impact of a stopping rule with lumasiran it could not take such scenarios into account in its decision making. Please see section 3.31 of the FED.
UK Kidney Association	The European guidelines (Groothoff et al, 2022, Nature Reviews Nephrology, in press) endorsed by European Society of Paediatric Nephrology (ESPN) and the European Renal Association (ERA) recommend treatment with siRNA drugs in pyridoxine-unresponsive patients with primary hyperoxaluria type 1 and any clinical phenotype of progression (such as urine oxalate excretion >1.5x upper limit of normal, any progressive chronic kidney disease or active stone disease). This is a very broad definition, and would require refining via our national clinical networks mentioned above. On the other hand, we feel that there is overwhelming evidence and obvious clinical need for emergency use of lumasiran in patients with development of oxalosis, such as infantile oxalosis and post-renal transplant oxalosis in a previously undiagnosed patient. Both represent very severe clinical phenotypes and are very low in numbers e.g. <5 per year nationally, and as such we suggest that these emergency indications are approved separately outside the economic modelling. This has been done for other conditions e.g. tolvaptan for the polycystic kidney disease indication versus its SIADH indication. Lumasiran is currently available for clinical use throughout Europe and the USA. There is therefore a very high risk that the UK will become an international outlier if lumasiran is not recommended at all. This would be a very bad outcome not just for patients (some of whom may consider moving to a country with access to siRNA drug therapy) but also for UK clinical research. In the UK we have world-class clinical systems for research (e.g. National Registry of Rare Kidney Diseases) and clinical oversight (NHS Rare Disease Collaborative Network following similar protocols to those pioneered by other high-cost drugs, e.g. National Renal Complement Therapeutics Centre). These systems have	Comments noted. The committee considered the views of stakeholders in its decision making. It recognised that there is a significant unmet need for effective and safe treatments for people with PH1. It also recognised that people with PH1 and their clinicians would welcome lumasiran as a treatment option for PH1. The committee considered that its preferred ICERs were likely to be within the range NICE normally considers an effective use of NHS resources for a highly specialised technology. So, it recommended lumasiran as an option for treating PH1. Please see sections 1.1, 3.4 to 3.5, 3.35 and 3.39 of the FED.

Consultee	Comment	Response
	proven clinical and cost effectiveness with many other high-cost drugs. They have demonstrated the benefits to the health economy when clinicians and patients work together to make sensible clinical treatment decisions and the ability to monitor and learn at national level e.g. generation of treatment discontinuation rules or dose/frequency reduction. We therefore feel that even a partial recommendation would allow us to continue development of these protocols for the use of lumasiran. There are a number of patients currently on extended clinical trials with siRNA drugs such as lumasiran. They were selected for enrolment not just because they met the inclusion criteria, but in many cases because there was no other treatment available to prevent worsening kidney function or stone disease. As these trials come to an end, we are seeing increasing concern from patients and their families regarding how they will continue on medications that were found to be clinically very beneficial in their particular case. This creates a potential for clinical harm, which is difficult to defend particularly as the UK is now the only major European country that does not have a recommendation for siRNA medications for primary hyperoxaluria type 1 patients.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies (HST)

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Company resubmission post-ECD2

December 2022

File name	Version	Contains confidential information	Date
ID3765 Alnylam Lumasiran HST Resubmission post-ECD2	**2.0**	**Yes**	**25 January 2023**

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1 Introduction

Alnylam wishes to thank the HST Evaluation Committee and the Evidence Review Group (ERG) for their thorough review of our company resubmission (dated 30 September 2022) for lumasiran for treating primary hyperoxaluria type 1 (PH1). We are gratified that the draft second Evaluation Consultation Document (ECD2) conveys the Committee's agreement with several important aspects of our resubmission, as reflected in the following conclusions:[1]

- The company's positioning of lumasiran is aligned with how clinicians would expect to use lumasiran in clinical practice (Section 3.8).
- The evidence base was appropriate for decision making given the rarity of the condition (Section 3.12).
- The model structure reflected the general course of the condition (Section 3.17).
- The company's modelling of disease progression was sufficient for decision making (Section 3.20).
- Applying measures of plasma oxalate levels is appropriate and relevant in predicting kidney function in people with PH1 (Section 3.18).
- The company's approach to exclude isolated liver transplant as a part of standard care was reasonable (Section 3.6).

However, in the ECD2 the Committee did not recommend lumasiran on the following grounds:[1]

> The economic model assumes that the probability of having a transplant is higher if a person's plasma oxalate levels are controlled than if they are uncontrolled. Clinical opinion suggests that this does not reflect clinical practice. Therefore, the cost-effectiveness estimates from the model are not appropriate for decision-making. So, lumasiran is not recommended for use.

The Committee "concluded that it would have preferred for the company to have provided … a revised model which includes the same rate of liver–kidney transplant for people with controlled and uncontrolled oxalate levels."[1] Accordingly, we have incorporated this assumption in our revised cost-effectiveness analysis (CEA) accompanying this second resubmission (Excel file *ID3765 Lumasiran PH1 CKD1-5 CEM UK_v17.0.xlsm*), along with several other preferred assumptions of the ERG and Committee.

In this second resubmission document we describe only the revised methods and results arising from the changes we have implemented following the second Committee meeting. Please refer to our original Company Submission (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 first Committee meeting are described in our previous responses to ERG questions. Revisions to address the first Evaluation Consultation Document (ECD)[2] are described in our first resubmission.

We addressed the following three main topics in the current revision of the CEA:

- **Transplant probability:** based on discussions in the second Committee meeting and the ECD2 (Sections 3.21–3.22), the same liver–kidney transplant (LKT) rate is now modelled for patients with controlled oxalate levels as for patients with uncontrolled oxalate levels. This revision has been implemented by applying the ERG's proposed per-cycle transplant rate for patients with uncontrolled oxalate levels of 0.0123 based on historical transplant rates to patients in the model with controlled and uncontrolled oxalate levels. This change corresponds exactly to the Committee's request in ECD2 Section 3.33.
- **Dialysis rates:** based on discussions in the second Committee meeting and the ECD2 (Sections 3.27–3.28), the frequency of high-intensity dialysis has been reduced from 7 days per week to 6 days per week. Furthermore, for patients in chronic kidney disease (CKD) stage 4, the revised CEA assumes that 50% of adults and 100% of children are on dialysis in both the ECM and lumasiran arms, which the Committee concluded aligns better with clinical expert opinion (ECD2 Section 3.28). This change also corresponds exactly to the Committee's request for the updated model (ECD2 Section 3.33).
- **Health-state utilities:** ECD2 Section 3.25 states, "The committee considered that it would like the company to provide the average EQ-5D score across all people included in ILLUMINATE-C to validate the utilities derived from the vignette study. In the absence of this data, the committee concluded that it preferred to use the EQ-5D utility average from the paediatric subgroup in ILLUMINATE-C for which data were previously provided to estimate utilities for the late CKD health states (as per the ERG's scenario analysis)."[1] As explained in detail in Section 2.3 below, Alnylam has concluded that the EQ-5D scores for adults in ILLUMINATE-C are unreliable and would not support decision-making for several important reasons. Briefly, this conclusion takes into consideration testimony from clinicians and patients on the severity of PH1 and the resulting profound impairment of health-related quality of life (HRQoL), particularly in these late stages of disease. The conclusion is also informed by the expectation that patients with PH1 in CKD4 or ESKD should have lower utilities than those reported by patients without PH1 in the same CKD stages, since the former face not only the burden of kidney disease but also the other complications of PH1. Considering these aspects of advanced PH1, we assess the EQ-5D scores from adults in ILLUMINATE-C to be unreliable—and thus unsuitable for inclusion in an average EQ-5D score for modelling purposes—because a substantial proportion of these patients reported scores not only higher than those reported in the literature for non-PH1 patients with CKD4 or ESKD, but also higher than age-matched general population norms, even including some perfect scores of 1.0. We have, therefore, performed a scenario analysis in which we have updated the model using the committee's alternative preferred assumption, using the average utility of [redacted] as calculated by the ERG from the paediatric EQ-5D data previously provided to define the utilities in the uncontrolled-oxalate CKD4 and ESKD health states for the paediatric cohort and the uncontrolled-oxalate ESKD health-state for the adult cohort.[3] This scenario analysis is fully discussed in Section 2.3.5. In addition, considering the HRQoL-related aspects noted above, we have reanalysed the time-trade-off (TTO) values from the vignette study, and found similar face validity issues related to reporting of utilities higher than those

associated with CKD4 or ESKD without PH1, exceeding general population norms, and even indicating perfect health. Accordingly, we have provided an additional scenario analysis in which we use recalculated health state utilities based on the TTO data from the vignette study, using a plausible set of values constrained not to exceed those for non-PH1 patients with CKD4 or ESKD. Full details of this scenario analysis are presented in Section 2.3.5. Alnylam's revised base case continues to incorporate EQ-5D values from the vignette study, and our rationale for retaining this approach as most appropriate for decision-making is explained in Section 2.3.

An additional change compared with the first resubmission is that we no longer present analyses with a stopping/continuation rule for lumasiran since the Committee concluded that it could not take these analyses into account in its decision making, because there was no evidence to inform estimation of the clinical impact of a stopping rule with lumasiran treatment (ECD2 Section 3.30). Similarly, differential discounting is no longer considered since the Committee concluded that the application of a lower discount rate was not appropriate (ECD2 Section 3.31).

We believe that this resubmission with our 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

In Section 3.33 of the ECD2, the Committee states "that an updated model which included a single probability of liver–kidney transplant for people with controlled and uncontrolled oxalate would be more in keeping with NHS clinical practice."[1] We have implemented this request exactly in the revised CEA base case and all scenario analyses for patients with controlled and uncontrolled oxalate in CKD4 or end-stage kidney disease (ESKD).

As in our previous resubmission, the transplant probability is derived from the retrospective cohort study by Metry et al. (2022) of patients with PH1 in the OxalEurope registry who underwent liver or kidney transplantation.[4] However, the revised analysis incorporates the ERG's estimated per-cycle probability of 0.0123, which was informed not only by the data reported by Metry et al. but also by unpublished details about the OxalEurope registry that the ERG elicited in personal communications with clinical experts.[3] The different per-cycle transplant probability compared with our previous calculation of 0.005 is accounted for by the following differences in assumptions:[3]

- Our previous calculation considered only the 159 combined liver–kidney transplants (cLKTs) reported between 1978 and 2019, but the ERG also included 37 sequential LKTs reported by Metry et al.[4]
- We used in the denominator of our calculation all 993 patients with PH1 in the registry, whereas the ERG included only those patients with follow-up since birth (n=[redacted]).

- Our calculation assumed a follow-up period corresponding to the full 41 years covered by the registry, while the ERG considered instead the average age of the [redacted] patients in the registry followed since birth, [redacted] years.

We acknowledge that the approach used by the ERG regarding these three points is appropriate for estimating the probability of transplantation in the model, and thus have implemented this approach in the base-case and scenario analyses in the revised CEA.

2.2 Dialysis rates in CKD4

In our previous model's base case, dialysis rates differed by treatment arm and patient age category, as shown in Table 1. However, the Committee concluded that our scenario that assumed that 50% of adults and 100% of children in CKD4 would be on dialysis irrespective of treatment arm aligned better with clinical expert opinion, compared with our base-case assumptions (ECD2 Section 3.28), and stated that the updated model should include this preferred assumption (ECD2 Section 3.33).[1] Accordingly, we have incorporated this assumption in the revised CEA base case and both scenario analyses, applying the same dialysis rates in both treatment arms since the Committee expected that half of adult patients and all paediatric patients in CKD4, whether receiving lumasiran or not, would still have dialysis to remove established oxalate deposits from the body (Table 1).

Table 1. Dialysis rates in CKD4 in the previous company CEA and the revised CEA

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

CKD = chronic kidney disease; ECM = established clinical management
*No scenario analyses varying dialysis rates are performed for the revised CEA because the Committee specified the preferred rates in the revised base-case analysis in alignment with clinical expert opinion.

In addition, the frequency of high-intensity dialysis has been revised from 7 days per week in our previous model to 6 days per week, because in the second Committee meeting the clinical experts explained that a frequency exceeding 6 days per week is not manageable in NHS clinical practice due to the limited capacity of haemodialysis units and the disruption that intensive dialysis causes to family life (ECD2 Sections 3.27 and 3.28).[1]

2.3 Health-state utilities

2.3.1 Lack of face validity of EQ-5D measures from adult patients in ILLUMINATE-C

Section 3.25 of the ECD states that the Committee "considered that it would like the company to provide the average EQ-5D score across all people included in ILLUMINATE-C to validate the utilities derived from

the vignette study."[1] Careful review of the individual EQ-5D index scores for patients in ILLUMINATE-C confirms that these scores are unreliable, with a substantial number of clinically implausible scores that lack any face validity, which are thus entirely unsuitable to report for decision-making purposes (i.e., in the context of an HST appraisal).

Specifically, among adult patients in ILLUMINATE-C, all of whom had advanced disease in CKD4 or ESKD,[5] a considerable proportion reported EQ-5D scores that exceed not only those reported by patients without PH1 in the same CKD stages (see Section 2.3.5 below for expected cut-off values) but also the healthy population norm values, even including some patients who reported scores of 1.0, signifying perfect health. Such high scores completely lack credibility, considering that these are all patients with advanced PH1, most of whom are receiving frequent dialysis,[5] which both the clinical and patient experts have clearly identified as placing a heavy burden on health-related quality of life (HRQoL), as documented in both the ECD and the ECD2.[1,2]

The implausibly high EQ-5D values observed in a substantial proportion of adult patients in ILLUMINATE-C, which obviously do not accurately reflect the heavy burden of advanced PH1 on patients, may be due to the "disability paradox", an effect in which patients with chronic and disabling diseases may adapt to their condition and value their health states higher than does the general population.[6] The disability paradox has been demonstrated for patients with such diverse conditions as haemophilia,[7] Duchenne muscular dystrophy,[8] and stroke.[9]

We speculate that the reason the disability paradox appears to have affected scores for adults to a greater extent than for paediatric patients is that the adult patients have been living with PH1 for much longer, and thus have had considerably more time to adapt to and accept their disease. The disability paradox may be less apparently impacting scores from paediatric patients in ILLUMINATE-C.

In a review of cost-effectiveness analyses for rare diseases, Postma et al. (2022) note that the disability paradox leads to an underestimation of the disease burden.[10] These authors point out that an economic analysis based on patient-derived utilities affected by this paradox would under-value the effectiveness of treatment relative to the general public's preference. This is especially relevant in the context of the present HST appraisal, given that the NHS is a publicly funded healthcare system, so utility valuations should be reasonable in the perspective of society at large. Notably, the current NICE methods guide specifies that the utility of HRQoL changes should be based on public preferences.[11] Thus, within-trial assessments that assign similar utilities to advanced PH1 health states as to healthy individuals, in a manner that may reflect the unique perspective of adults with PH1 through the lens of the disability paradox, rather than the perspective of the general population, should be regarded with scepticism for modelling and decision-making purposes.

The above considerations argue against introduction of the EQ-5D scores for adults in ILLUMINATE-C into the current appraisal process and support our use of EQ-5D utilities from the vignette study in the revised base case.

2.3.2 Preference for vignette-based utilities over utilities elicited from the ILLUMINATE-C population

While we present a scenario analysis applying the average EQ-5D utility of [redacted] from a paediatric subgroup in ILLUMINATE-C to the uncontrolled-oxalate CKD4 and ESKD health states for paediatric patients and uncontrolled-oxalate ESKD health-state for adult patients, as proposed by the Committee in the absence of presenting the average EQ-5D score of across all patients (ECD2 Section 3.25), we contend that use of EQ-5D utilities from the vignette study is the most appropriate.

The small sample size of the paediatric subgroup used for this average (n=8) introduces uncertainty over the extent to which the mean utility value observed in this subgroup reflects the true health state utility in the underlying population from which the subgroup is taken. Furthermore, while the EQ-5D values observed within this subgroup generally did not lack face validity, with none approaching values associated with perfect health, the degree of impact of the disability paradox on these values is unknown. This complicates the use of ILLUMINATE-C data as a direct source of utility data for the CEA. Indeed, this limitation, together with the evident lack of validity in the adult utilities gathered within ILLUMINATE-C, underscores the necessity of using utilities from the vignette study to inform the CEA. We do believe, however, that EQ-5D values observed within this paediatric subgroup provide the best available basis for validating vignette study values in CKD4 and ESKD in the CEA.

2.3.3 EQ-5D vs. TTO for vignette valuation

Given the limitations of the EQ-5D data collected directly from ILLUMINATE-C, as described above, we believe that the vignette study is the most appropriate source of utility values for patients in CKD4 and ESKD in the CEA. In our first resubmission, our base case included EQ-5D-derived utilities from the vignette study, in view of the following considerations:

- A brief review of the relevant Decision Support Unit (DSU) and NICE methods guidance on the valuation of vignettes confirmed that NICE prefers EQ-5D valuations over TTO valuations,[11-13] as was acknowledged by the ERG in their critique of our resubmission.[3]
- The EQ-5D-derived utilities, when compared with TTO-derived utilities, are numerically closer to the utilities elicited directly from a subgroup of paediatric patients in ILLUMINATE-C; these values provide the most robust, directly applicable source of utility data against which to validate vignette study utility values for patients in CKD4 and ESKD.
    - Previously, the ERG used ILLUMINATE-A trial data to validate results for CKD stages 1-3b from the vignette study conducted to estimate health state utilities in PH1. Based on this validation approach, the ERG preferred that TTO-based values be used over EQ-5D-based values from the vignette study to inform utility values in patients in CKD4 and ESKD in the CEA. Given the mismatch between the population in which the ERG validated trial data against vignette study data (CKD1–3b) and the population in which vignette study data were used in the model (CKD4–ESKD), we contend it is more

appropriate to use utilities elicited directly from paediatric patients in ILLUMINATE-C (which exclusively enrolled patients in more advanced stages of PH1) for validation as noted above.

In addition, we have conducted further efforts to assess the internal validity of the vignette scores for CKD4 and ESKD. In particular, as shown in Figure 1, the histograms of scores estimated via the two different methods indicate that validity issues may exist with the TTO-derived scores, which follow distributions characterised by the following anomalies:

- Many implausibly high scores, considering the expected major HRQoL impairment in advanced PH1; these include scores approaching or in excess of normal values for healthy individuals, and in some cases scores as high as 1.0, representing perfect health
- A large discontinuity in the distribution, wherein extreme negative values (at/near -1.0 on the horizontal axis) were elicited from some respondents, followed by a large interval thereafter with no density in the distribution until the value of 0 was reached on the horizontal axis; this feature suggests a virtual floor of 0 (i.e., only positive utilities) for most respondents, despite the potential to assign TTO values as low as -1.0

In contrast, the histograms for EQ-5D index scores appear more typical, with fewer extreme values at either end of the distributions and no large discontinuities or other anomalies suggestive of possible validity concerns.

Figure 1. Comparison of TTO-derived vs. EQ-5D-derived utility scores from the vignette study in CKD4 and ESKD

Subgroup	Valuation method	
	TTO	EQ-5D
Adult		
CKD4	[redacted]	[redacted]
ESKD	[redacted]	[redacted]

Subgroup	Valuation method	
	TTO	EQ-5D
Paediatric		
CKD4	[redacted]	[redacted]
ESKD	[redacted]	[redacted]

CKD = chronic kidney disease; ESKD = end-stage kidney disease; TTO = time-trade-off

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

As we noted in our first resubmission, while it is not possible to ascertain precisely the reasons for the differences in mean health state 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.

Further to these observations which we previously raised regarding the difference in mean health state utility values yielded by the two methods, we note that the observation of a large discontinuity between -1.0 and 0 in the distribution of TTO exercise responses is consistent with prior accounts of issues with the use of the TTO method to value health states. Al Sayah et al. (2016) reported on the observation of values clustered at 0 with few negative values, particularly over the interval from -0.5 to 0, in past TTO studies.[15] The authors attributed this finding to confusion in participants' understanding of the TTO task, particularly as it relates to valuation of more severe health states, and noted how this confusion can impact the validity of TTO-derived utilities for such states.

Similar limitations of the TTO method were highlighted by NICE in the appraisal of atidarsagene autotemcel for treating metachromatic leukodystrophy (HST18). The lead team presentation for the first Committee meeting in HST18 notes that TTO methods may be conceptually difficult to understand.[16] The presentation also reports that the TTO exercise in the vignette study performed for that appraisal resulted in clustering of TTO values around 0 and around best and worst possible ratings (-1 and 1) across health states.[16] Notably, these issues do not apply to the EQ-5D-derived vignette values for PH1 in the current submission (Figure 1).

2.3.5 Summary of utilities in CKD4 and ESKD in the revised base-case and scenario analyses

Taking all of the above points into account, 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 base case. Nevertheless, to address the preferences expressed by the Committee and ERG, we are also providing two new scenario analyses, as follows:

1. Average EQ-5D utility of [redacted] from the paediatric subgroup in ILLUMINATE-C is applied to paediatric patients with uncontrolled oxalate in CKD4 and ESKD and adults with uncontrolled oxalate in ESKD.
2. TTO values from the vignette study are applied to patients in CKD4 and ESKD, with average scores recalculated after exclusion of clinically implausible values

For the second of these scenario analyses, individual TTO scores in CKD4 and ESKD were excluded from averaging if they exceeded the values for patients without PH1 in CKD4 or ESKD shown in Table 2, which were obtained by taking model health state utilities for patients with PH1 in CKD4 and ESKD and adjusting these utilities as applicable to reflect differences in the use of dialysis and the absence of systemic oxalosis complications in non-PH1-related CKD4 and ESKD; the references and details of how health state utilities are calculated in the model and adjusted for the presence or absence of different dialysis modalities and systemic oxalosis complications were described in Section 10.1.9 of the CS. Our rationale for these thresholds is that we considered it to be clinically implausible that a patient with advanced PH1 would have better HRQoL than a patient without PH1 in the same CKD stage, given the additional burden of the elevated oxalate levels in PH1. For CKD4, the cut-off represented the estimated utility of a patient with controlled oxalate levels, not on dialysis (as would be the case for a patient in CKD4 without PH1), while for ESKD, the cut-off represented the estimated utility of a patient with controlled oxalate levels, on normal-intensity dialysis (as would be the case for a patient with non-PH1-related ESKD).

Table 2. Utility cut-offs used for recalculating average TTO values for Scenario Analysis #2 in the revised model

Health state	Paediatric	Adult
CKD4	[redacted]	[redacted]
ESKD	[redacted]	[redacted]

CKD = chronic kidney disease; ESKD = end-stage kidney disease; TTO = time-trade-off

After exclusion of scores exceeding the threshold values in Table 2, the recalculated average TTO utilities for this scenario analysis were as shown in Table 3.

Table 3. Recalculated average TTO values for Scenario Analysis #2 in the revised model

Health state	Paediatric	Adult
CKD4	[redacted]	[redacted]
ESKD	[redacted]	[redacted]

CKD = chronic kidney disease; ESKD = end-stage kidney disease; TTO = time-trade-off

2.4 Summary of revisions

Changes in the revised CEA compared with the model submitted alongside our first resubmission 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 4. 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 4. Base-case effectiveness and cost results

Technology	LYs	Disc LYs	QALYs	Disc QALYs	Costs (£)	Disc Costs (£)
Lumasiran	58.75	24.27	[redacted]	[redacted]	[redacted]	[redacted]
ECM	48.59	21.98	[redacted]	[redacted]	[redacted]	[redacted]
Difference, lumasiran vs. ECM	10.15	2.30	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 5 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 5. Base-case cost-effectiveness results

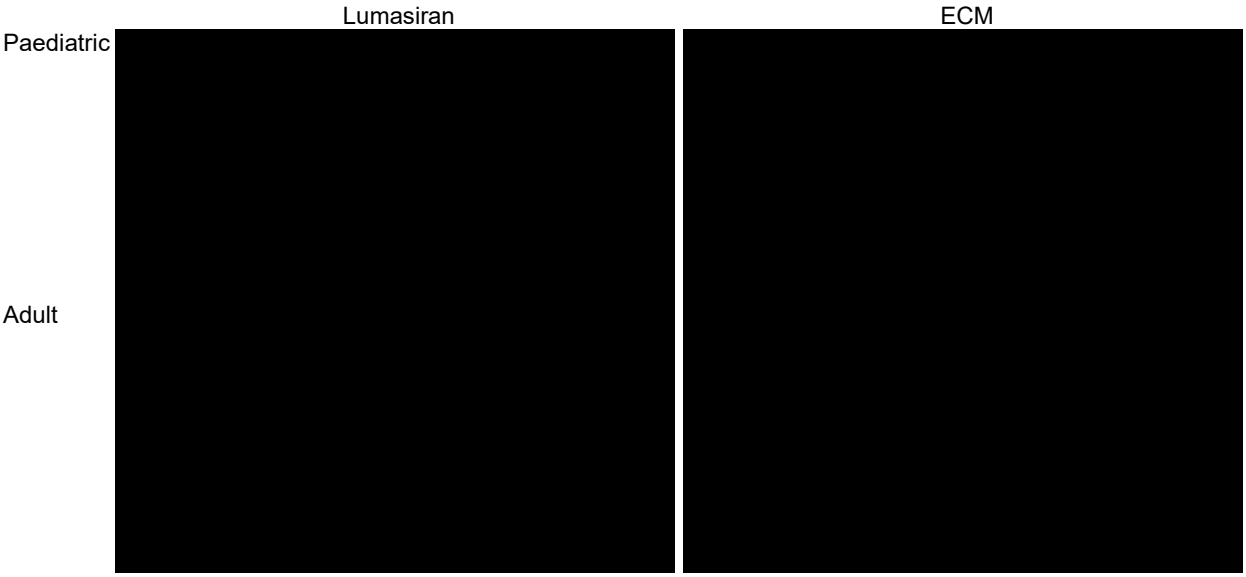
	Undiscounted		Discounted	
ICER	Cost/LY	Cost/QALY	Cost/LY	Cost/QALY
Lumasiran vs. ECM	[redacted]	[redacted]	[redacted]	[redacted]

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 with controlled oxalate levels 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, with many transitioning to cLKT with uncontrolled oxalate levels.

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 6. The majority of QALYs for lumasiran were accrued in CKD1–3b (with an almost [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 6. 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]					
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
Note: the difference in QALYs between lumasiran and ECM may not precisely match incremental costs due to rounding. The values in this table are rounded to two decimal places.

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 7. 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 7. 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
Note: the difference in costs between lumasiran and ECM may not precisely match incremental costs due to rounding. The values in this table are rounded to the nearest integer.

Disaggregated costs by health state

Costs disaggregated by health state are presented in Table 8. Costs were primarily accrued in CKD1–2 for lumasiran, but in ESKD for ECM.

Table 8. 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
Note: the difference in costs between lumasiran and ECM may not precisely match incremental costs due to rounding. The values in this table are rounded to the nearest integer.

3.2 Scenario analyses

As shown in Table 9 and as expected given that the two scenario analyses varied only utilities, all of the variation in ICER results among the three analyses performed for this resubmission was accounted for by

differences in incremental QALYs. Nevertheless, the QALY weight of 3.0 was maintained for all of these scenarios. Compared with the ICER in the base-case analysis, using EQ-5D-derived vignette utility values in CKD4 and ESKD, the ICERs were [redacted] and [redacted] higher for the scenario using the average utility value calculated by the ERG for a subgroup of paediatric patients in ILLUMINATE-C and the scenario using recalculated TTO-derived vignette utility values, respectively.

Table 9. Results of scenario analyses

Scenario	#	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	QALY weight
Base case	0	[redacted]	[redacted]	[redacted]	3.0
Average EQ-5D utility of [redacted] for paediatric patient subgroup in ILLUMINATE-C applied to children in CKD4-OXu and ESKD-OXu, and adults in ESKD-OXu	1	[redacted]	[redacted]	[redacted]	3.0
Mean TTO-derived vignette utilities applied to CKD4 and ESKD after recalculation to exclude individual values above utilities for non-PH1 patients in these CKD stages	2	[redacted]	[redacted]	[redacted]	3.0

CKD = chronic kidney disease; ESKD = end-stage kidney disease; ICER = incremental cost-effectiveness ratio; OXu = uncontrolled oxalate; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life-year; TTO = time-trade-off

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 10 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 10. 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]
Constant parameter in general population utility equation	[redacted]	[redacted]
Initial age (years), paediatric	[redacted]	[redacted]
Cycle probability of LKT in adult cohort, ESKD-OXu	[redacted]	[redacted]
Absolute change in POx in ILLUMINATE-A, placebo arm, ECM - any cycle	[redacted]	[redacted]
Absolute change in eGFR per 1 unit increase in POx, CKD1–3b	[redacted]	[redacted]
High-intensity dialysis cost, per cycle, paediatric	[redacted]	[redacted]
High-intensity dialysis add-on to ECM in ESKD	[redacted]	[redacted]

CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; LKT = liver–kidney transplant; OXu = uncontrolled oxalate; POx = plasma oxalate
Note: results shown are percent change in ICER when each parameter is set to its lower and upper bounds.

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; OXu = uncontrolled oxalate; 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 11. Figure 4 and Figure 5 show the individual PSA simulation results and cost-effectiveness acceptability curve, respectively.

Table 11. 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
Note: differences between lumasiran and ECM in this table may not precisely match incremental values due to rounding.

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

In this second resubmission, Alnylam has undertaken to incorporate the modelling preferences expressed by the Committee and ERG to the fullest extent we considered could be supported by the available evidence. Changes to assumptions about transplant rate and dialysis rate have been made exactly in

accordance with the Committee's preferences expressed in the ECD2. Although we retained our previous approach to utilities for patients in CKD4 and ESKD in our base case for the important reasons explained in Section 2.3, our Scenario #1 implements the Committee's requested method, while our Scenario #2 replicates the ERG's preferred use of vignette TTO valuation (modified by exclusion of clinically implausible values from the calculation of average utilities).

The revisions to our base-case CEA would have resulted in [redacted] in the ICER compared with the results of the company base-case model accompanying our first resubmission; however, the present results incorporate the [redacted] PAS discount that Alnylam has proposed to the NHS, and consequently the base-case ICER is [redacted] in the revised CEA compared with the first resubmission: £[redacted]/QALY vs. £[redacted]/QALY, respectively. The ICER should also be considered in the context that we have retained a number of conservative assumptions from the original model, as described in the CS, 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

Due to the large QALY gain in the revised CEA base case and both scenario analyses, the maximum QALY weighting of 3.0 would apply.

We hope that the revisions we have made to the CEA will allow the Committee to conclude that the cost-effectiveness estimates from the model are appropriate for decision-making.

5 References

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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_v16.0”.

Model aspect	Description of changes
Transplant rate in controlled- and uncontrolled-POx health states	• “Clinical” sheet: the cycle probability of transplant was set to 0.0123 per ERG calculation from data reported by Metry et al. (2022). The same probability of 0.0123 was applied for OXc and OXu health states in rows 90–100. • “Clinical data” sheet: the calculations of transplant rates in OXc and OXu health states per the CS were removed since they are not used.
Proportion on dialysis in CKD4	• “Clinical” sheet: 100% of paediatric cohort and 50% of adult cohort was assigned dialysis in both the ECM arm (rows 169–170) and the lumasiran arm (175–176).
Estimation of utility values in CK4 and ESKD health-states	• “QoL data” sheet range Z32–AG37: added the updated vignette TTO values estimated applying cut-offs to exclude clinically implausible values. These are used to run Scenario Analysis #2. • “QoL data” sheet range AH32–AO37: added the average EQ-5D score estimated by ERG based on ILLUMINATE-C paediatric subgroup data submitted by the company. These are used to run Scenario Analysis #1. • “QoL data” sheet range B36–I37: adjusted the CHOOSE function to select the updated TTO utilities or the ILLUMINATE-C average utility to run the respective scenario. • “LookUps sheet” sheet: cells M30 and M31, added the additional two options to run Scenario Analysis #1 or #2

CKD = chronic kidney disease; CS = company submission; ECM: established clinical management; ESKD = end-stage kidney disease; OXc = controlled oxalate; OXu = uncontrolled oxalate; QoL: quality of life; TTO = time-trade-off

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	On behalf of the British Association for Paediatric Nephrology, we wish to submit a further clinical perspective on the impact of Lumasiran treatment for young children with Primary Hyperoxaluria type 1. We would be grateful if the committee could consider this additional clinical information which may not be reflected in the health economic model.
2	Four infants under 1 year of age commenced compassionate use Lumasiran treatment on a clinically urgent basis in the last 2 years in UK. All had a life-threatening rapidly progressive infantile oxalosis phenotype. Before the availability of specific treatment, such children would rapidly progress to kidney failure and would start dialysis. Unfortunately, dialysis is very poor with regards to oxalate clearance and without urine output, these children will deposit oxalate everywhere in their body with potentially severe consequences (including bone marrow failure and cardiac failure). This oxalate deposition would progress until the children received a liver and kidney transplant and the kidney transplant would often be endangered by the massive oxalate excretion post-transplant. For 2 of these infants in whom kidney function was deteriorating to the point of requiring dialysis, after commencement of Lumasiran, their rapid decline in kidney function was reversed and they remain clinically well without the need for dialysis. Two further infants commenced treatment at a later stage whilst in established kidney failure requiring dialysis. Both have experienced improvement in urine output and kidney function whilst on dialysis and have avoided urgent liver transplantation or progression to systemic oxalosis with high associated mortality.
3	In the regional multi professional children's kidney stone service, we have noticed an apparent substantial reduction in urological procedures for kidney stones in children with primary hyperoxaluria type 1, which will ultimately help preserve kidney function in this group.
4	Several families of children with primary hyperoxaluria treated with Lumasiran have expressed concern about the possibility that children may need to discontinue treatment, given the clear improvements in their health and quality of life.
5	UK paediatric clinicians caring for children with primary hyperoxaluria have expressed concern that this highly effective pivotal therapy may not be available via the NHS.
6	As national body of clinicians caring for children with primary hyperoxaluria type 1, we would be grateful if the committee could take these perspectives into consideration alongside the health economic model.

Insert extra rows as needed

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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 (formerly known as the Renal Association)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We broadly agree with the conclusions of the committee regarding proposed improvements to the model used to calculate cost effectiveness. The main areas of difficulty were: using cut-off plasma oxalate values as an indication for transplantation, and the assumption that CKD stage and health state can be correlated. We feel that modelling in this way is too rigid, does not account for the reality of decision making in patients with rare diseases, and completely omits some very important indications e.g. infantile oxalosis, for which the model is not valid. The main clinical factors guiding treatment decisions are: rate of worsening of renal function (regardless of baseline CKD stage), evidence of systemic oxalosis, and age of patient. If transplantation is needed, delaying it is usually not in the patient's best interest. We hope that these factors can be considered in any future model.
2	In addition to use of CKD stages as health states (3.14 in the ECD), we suggest also adding the impact of recurrent kidney stone disease (symptoms, interventions, time off work/school, etc) especially in adult patients. This has not been considered at all in the economic case, yet is an important clinical outcome (and is also specified in the ILLUMINATE trials).
3	We do not understand why it is necessary to postulate a discontinuation rule for paediatric lumasiran-treated patients at age 18. There is no evidence for this and it is not justified clinically. For example, we would not consider stopping pyridoxine (disease modifying drug) therapy in those patients who have responded simply because they have reached adulthood. Instead, national systems that we have proposed via the NHS Rare Disease Collaborative Network for hyperoxaluria, in conjunction with data collection via the National Registry for Rare Kidney Diseases, would be a more effective way to monitor and consider discontinuation of therapy, according to recorded clinical outcomes and the latest published data.
4	The European guidelines (Groothoff et al, 2022, Nature Reviews Nephrology, in press) endorsed by European Society of Paediatric Nephrology (ESPN) and the European Renal Association (ERA) recommend treatment with siRNA drugs in pyridoxine-unresponsive patients with primary hyperoxaluria type 1 and any clinical phenotype of progression (such as urine oxalate excretion >1.5x upper limit of normal, any progressive chronic kidney disease or active stone disease). This is a very broad definition, and would require refining via our national clinical networks mentioned above. On the other hand, we feel that there is overwhelming evidence and obvious clinical need for emergency use of lumasiran in patients with development of oxalosis, such as infantile oxalosis and post-renal transplant oxalosis in a previously undiagnosed patient. Both represent very severe clinical phenotypes and are very low in numbers e.g. <5 per year nationally, and as such we suggest that these emergency indications are approved separately outside the

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	economic modelling. This has been done for other conditions e.g. tolvaptan for the polycystic kidney disease indication versus its SIADH indication.
5	Lumasiran is currently available for clinical use throughout Europe and the USA. There is therefore a very high risk that the UK will become an international outlier if lumasiran is not recommended at all. This would be a very bad outcome not just for patients (some of whom may consider moving to a country with access to siRNA drug therapy) but also for UK clinical research. In the UK we have world-class clinical systems for research (e.g. National Registry of Rare Kidney Diseases) and clinical oversight (NHS Rare Disease Collaborative Network following similar protocols to those pioneered by other high-cost drugs, e.g. National Renal Complement Therapeutics Centre). These systems have proven clinical and cost effectiveness with many other high-cost drugs. They have demonstrated the benefits to the health economy when clinicians and patients work together to make sensible clinical treatment decisions and the ability to monitor and learn at national level e.g. generation of treatment discontinuation rules or dose/frequency reduction. We therefore feel that even a partial recommendation would allow us to continue development of these protocols for the use of lumasiran.
6	There are a number of patients currently on extended clinical trials with siRNA drugs such as lumasiran. They were selected for enrolment not just because they met the inclusion criteria, but in many cases because there was no other treatment available to prevent worsening kidney function or stone disease. As these trials come to an end, we are seeing increasing concern from patients and their families regarding how they will continue on medications that were found to be clinically very beneficial in their particular case. This creates a potential for clinical harm, which is difficult to defend particularly as the UK is now the only major European country that does not have a recommendation for siRNA medications for primary hyperoxaluria type 1 patients.

Insert extra rows as needed

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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 ECD2

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

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1 Introduction

The company's response and resubmission post-ECD2 focuses on a revised cost-effectiveness analysis (CEA). The revisions involve changes in relation to: estimation of transplant probability; dialysis rates in CKD4; dialysis frequencies; and the health-state utility measurement. In addition, it includes a new PAS price for lumasiran.

The revised CEA has been critiqued by the Evidence Review Group (ERG), whose summaries and comments are provided in this addendum.

2 Revised cost-effectiveness model

In their resubmission post-ECD2, the company addressed the following topics:

1. **Transplant probability:** Following the request of the committee in section 3.33 of ECD2, the company has now used a single probability for the probability of a liver-kidney transplant for patients with controlled and uncontrolled oxalate. A value of 0.0123 was used, which was derived by the ERG in their response to the company comments after ECD1[1] from the retrospective cohort study by Metry et al. (2022)[2] of patients with PH1 in the OxalEurope registry who underwent liver or kidney transplantation.
2. **Dialysis rates:** As requested by the committee in section 3.33 of ECD2 (as it aligns better with clinical expert opinion), the company has set the dialysis rates for patients in CKD stage 4 to the same value for the lumasiran and the ECM group. It is now assumed that 50% of adults and 100% of paediatric patients receive dialysis.
3. **Dialysis frequency:** Based on clinical expert opinion, as heard in ECD2, the company has now revised the frequency of high-intensity dialysis from 7 days per week to 6 days per week.
4. **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).

As the first 3 changes made by the company are based on explicit requests from the committee, they do not require any further discussion by the ERG. For the last issue, about the health state utilities, a short summary of the company's response in their resubmission post-ECD2 is presented, followed by ERG comments, if relevant.

2.1 New Patient Access Scheme

The company proposed a new patient access scheme (PAS) to the NHS, changing the price per vial from [redacted] to [redacted]. All results presented in section 3 and 4 of this addendum are based on this new PAS.

2.2 Health state utilities

2.2.1 EQ-5D measures from patients in ILLUMINATE-C

The committee requested in ECD2, section 3.25, the average EQ-5D score across all people included in ILLUMINATE-C to validate the utilities derived from the vignette study. In their response to ECD2 the company presents justification for not providing this average EQ-5D score. Upon review of the individual EQ-5D utilities, the company observed, *especially among adult patients*, that many utilities exceeded not only those reported by patients without PH1 in the same CKD stages, but also the healthy population norm values.

The company suggests that the so-called disability paradox explains this, the notion that patients with long-lasting disabilities report good or excellent QoL while observers characterize the patients' daily struggles much less favourably. The company considers this issue as support for their use of EQ-5D utilities from the vignette study, rather than utilities based on the EQ-5D directly filled-in by patients.

In addition, the company explains that the average EQ-5D utility of a subgroup of paediatric patients should also not be preferred over the EQ-5D utilities from the vignette study, as it involves a very small sample of only [redacted] patients. In addition, the disability paradox may also play some role in this patient group, though this is less clear as none of the utilities approached 1 (perfect health).

Thus, the company applies the average EQ-5D utility of [redacted] from a paediatric subgroup in ILLUMINATE-C to the uncontrolled-oxalate CKD4 and ESKD health states for paediatric patients and uncontrolled-oxalate ESKD health-state for adult patients in a scenario analysis only.

2.2.2 EQ-5D vs TTO valuation of vignettes

In their response to ECD1, the company argued in favour of the EQ-5D valuation of the vignettes, as this is the preferred approach according to the DSU and NICE methods guidance. The ERG acknowledged this in their critique of the company's response, but also expressed concern about 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 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, the ERG expressed a preference for the TTO values despite the DSU and NICE methods guidance.

In their response to ECD2, the company argues that there is a mismatch between the population in which the ERG validated trial data against vignette study data (CKD1–3b) and the population in which vignette study data were used in the model (CKD4–ESKD), and that thus, the utilities from paediatric patients in ILLUMINATE-C should be used for validation. The average utility of these children (CKD4 and ESKD) is [redacted], whilst the EQ-5D values from the vignette study are [redacted] and [redacted], for CKD4 and ESKD respectively, and the TTO values are [redacted] and [redacted], respectively. This means that the average observed utility sits at one third of the distance between the EQ-5D and TTO value, and the company regards this as a validation of the EQ-5D utility from the vignette study.

To shed further light on the comparison of the EQ-5D and TTO utilities from the vignette study, the company compared histograms of the individual utilities, both for CKD4 and ESKD, and both for adult and paediatric patients. These histograms can be found in the company's response to ECD2, figure 1.

The TTO histograms show, across the stages and age-groups, that a few respondents (UK general public) would arrive at a utility around -1, indicating that they would clearly prefer death. The utilities of the other respondents cover the whole range from 0 to 1.

The EQ-5D histograms show a different distribution, with the range of values starting around -0.6/-0.5 and ending around 0.5/0.6, depending on the stage and the age-group. In addition, the distribution of the EQ-5D values roughly resembles a normal distribution (with the exception of the graph for adults in CKD4, which appears more bi-modal), whilst the distribution of the TTO values is much flatter, reminding more of a uniform distribution.

Based on these characteristics of the histogram, the company concludes that unlike the EQ-5D values, the TTO values raise validity concerns.

The company set out to suggest contributing factors for the differences between the EQ-5D and TTO utility values from the vignette study, which included the following:

- Some participants may have been unwilling to trade off years of life,[3] 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.

2.2.3 Utilities used in revised base case and scenario analyses

Based on the various arguments made by the company, they continue to prefer the EQ-5D utilities based on vignettes for the CKD4 and ESKD health states. In addition, two scenario analyses are explored:

1. Average EQ-5D utility of [redacted] from the paediatric subgroup in ILLUMINATE-C is applied to paediatric patients with uncontrolled oxalate in CKD4 and ESKD and adults with uncontrolled oxalate in ESKD.
2. TTO values from the vignette study are applied to patients in CKD4 and ESKD, with average scores recalculated after exclusion of clinically implausible values (see Table 1).

For the second scenario, the company excluded individual TTO values from the analysis if they exceeded the values for patients without PH1 in CKD4 ([redacted] and [redacted] for paediatric and adult patients, respectively) or ESKD ([redacted] and [redacted] for paediatric and adult patients, respectively), which were obtained by taking model health state utilities for patients with PH1 in CKD4 and ESKD and adjusting these utilities as applicable to reflect differences in the use of dialysis and the absence of systemic oxalosis complications in non-PH1-related CKD4 and ESKD (see Section 10.1.9 of the CS for details of how health state utilities are calculated in the model). The company made these adjustments as they consider it to be clinically implausible that a patient with advanced PH1 would have better HRQoL than a patient without PH1 in the same CKD stage, given the additional burden of the elevated oxalate levels in PH1. For CKD4, the cut-off represented the estimated utility of a patient with controlled oxalate levels, not on dialysis (as would be the case for a patient in CKD4 without PH1), while for ESKD, the cut-off represented the estimated utility of a patient with controlled oxalate levels, on normal-intensity dialysis (as would be the case for a patient with non-PH1-related ESKD).

Table 1 Recalculated average TTO values for Scenario Analysis #2 in the revised model

	Adult		Child	
	Revised TTO	**TTO**	**Revised TTO**	**TTO**
CKS 4	[redacted]	[redacted]	[redacted]	[redacted]
ESKD	[redacted]	[redacted]	[redacted]	[redacted]

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 ERG also accepts the 'disability paradox' as a potential explanation for some high utility values observed amongst patients from the ILLUMINATE C.

Furthermore, the earlier reasoning of the ERG to prefer the TTO valuations of vignettes because 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 is not fully satisfactory, as there is indeed a mismatch between the population in which the trial utilities were compared against vignette study data (CKD1–3b) and the population in which vignette study data were used in the model (CKD4–ESKD).

In addition, the ERG recognizes that the TTO procedure, where time needs to be traded for improved health is a more complex task than filling out the EQ-5D questionnaire based on the description in a vignette. What is interesting in this context is that the UK tariff for the EQ-5D is itself also based on a TTO procedure.

In a systematic literature review of utilities for kidney disease health states,[4] the EQ-5D based utilities for haemodialysis and peritoneal dialysis were 0.67 and 0.57, respectively. When looking specifically at patients with chronic kidney disease with complications, the utilities for the acute phase of a stroke and bone fractures were associated with utilities of 0.5 and 0.35, respectively. Of course a stroke or a bone fracture are not the same as PH1, but they might be considered reflective of patients whose QoL is not only decreased due to chronic kidney disease and dialysis, but also by another health issue. As such, these reported values raise some new doubts for the ERG about the validity of the EQ-5D utilities from the vignette study.

Based on the above, the ERG is now less sure about the preference for the TTO utilities. At the same time, the negative utilities for CKD4 and ESKD in the paediatric population are considered very low, and the ERG wonders if the suggested preference for death is indeed present in the *average* paediatric PH1 patients in CKD4 and ESKD. In light of all considerations, the ERG is inclined to slightly prefer the average EQ-5D utility of [redacted] from the paediatric subgroup in ILLUMINATE-C as it is based on measurement of QoL among patients. However, the ERG will again explore the impact of using the TTO-based utilities as an scenario so that results are available for all options for the CKD4 and ESKD utilities.

Regarding scenario analysis 2, in which the company excluded all TTO scores above the expected utility value for patients without PH1 in CKD4 and ESKD, the ERG is not convinced of the value of this scenario. In essence the company excludes individual responses that were considered clinically implausible as they are above the average of a healthier population. However, in that healthier population there is of course also variation in the utility value of individuals, so as long as the high utilities for PH1 patients are not higher than the high utilities for non-PH1 patients, the claim of clinical implausibility cannot be made.

Additionally, the ERG was unable to reproduce the values for patients without PH1 in CKD4 ([redacted] and [redacted] for paediatric and adult patients, respectively) and ESKD ([redacted] and [redacted] for paediatric and adult patients, respectively), so more explicit guidance from the company is needed in order to verify these values.

3 Company model results

In this section we present the main findings based on the company's revised model. For the complete set of results we refer to the Company resubmission post-ECD2 document.[5]

3.1 Base-case analysis

Results of the revised base-case analysis are presented in Table 2. 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 2. Base-case effectiveness and cost results

Technology	LYs	Disc LYs	QALYs	Disc QALYs	Costs (£)	Disc Costs (£)
Lumasiran	58.75	24.27	[redacted]	[redacted]	[redacted]	[redacted]
ECM	48.59	21.98	[redacted]	[redacted]	[redacted]	[redacted]
Difference, lumasiran vs. ECM	**10.15**	**2.30**	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 3 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 3. 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.

3.2 Scenario analyses

As shown in Table 4, the impact of the two alternative sets of values for utilities in CKD4 and ESKD is relatively limited, with the ICERs varying from £[redacted] to £[redacted]. The QALY weight of 3.0 was maintained for both scenarios.

Table 4. Results of scenario analyses

Scenario	#	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	QALY weight
Base case after ECD2	0	[redacted]	[redacted]	[redacted]	3.0
Average EQ-5D utility of [redacted] for paediatric patient subgroup in ILLUMINATE-C applied to children in CKD4-OXu and ESKD-OXu, and adults in ESKD-OXu	1	[redacted]	[redacted]	[redacted]	3.0
Mean TTO-derived vignette utilities applied to CKD4 and ESKD after recalculation to exclude individual values above utilities for non-PH1 patients in these CKD stages	2	[redacted]	[redacted]	[redacted]	3.0

CKD = chronic kidney disease; ESKD = end-stage kidney disease; ICER = incremental cost-effectiveness ratio; OXu = uncontrolled oxalate; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life-year; TTO = time-trade-off

Compared with the ICER in the base-case analysis, using EQ-5D-derived vignette utility values in CKD4 and ESKD, the ICERs were [redacted] and [redacted] higher for the scenario using the average utility value calculated by the ERG for a subgroup of paediatric patients in ILLUMINATE-C and the scenario using recalculated TTO-derived vignette utility values, respectively.

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 5 and Figure 1. The most influential variables in the OWSA were the discount rates on costs and outcomes, and patient adherence to lumasiran therapy.

Table 5. 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]
Constant parameter in general population utility equation	[redacted]	[redacted]
Initial age (years), paediatric	[redacted]	[redacted]
Cycle probability of LKT in adult cohort, ESKD-OXu	[redacted]	[redacted]
Absolute change in POx in ILLUMINATE-A, placebo arm, ECM - any cycle	[redacted]	[redacted]
Absolute change in eGFR per 1 unit increase in POx, CKD1–3b	[redacted]	[redacted]
High-intensity dialysis cost, per cycle, paediatric	[redacted]	[redacted]
High-intensity dialysis add-on to ECM in ESKD	[redacted]	[redacted]

LKT = liver–kidney transplant; OXc = controlled oxalate; OXu = uncontrolled oxalate; CKD = chronic kidney disease; ECM = established clinical management; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; POx = plasma oxalate

Figure 1. 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; OXc = controlled oxalate; OXu = uncontrolled oxalate; 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 6. Figure 2 and Figure 3 show the individual PSA simulation results and cost-effectiveness acceptability curve, respectively. Based on a threshold ICER of £300,000 (the QALY weight is 3.0), the probability that lumasiran is cost effective compared to ECM is [redacted]

Table 6. Probabilistic sensitivity analysis results

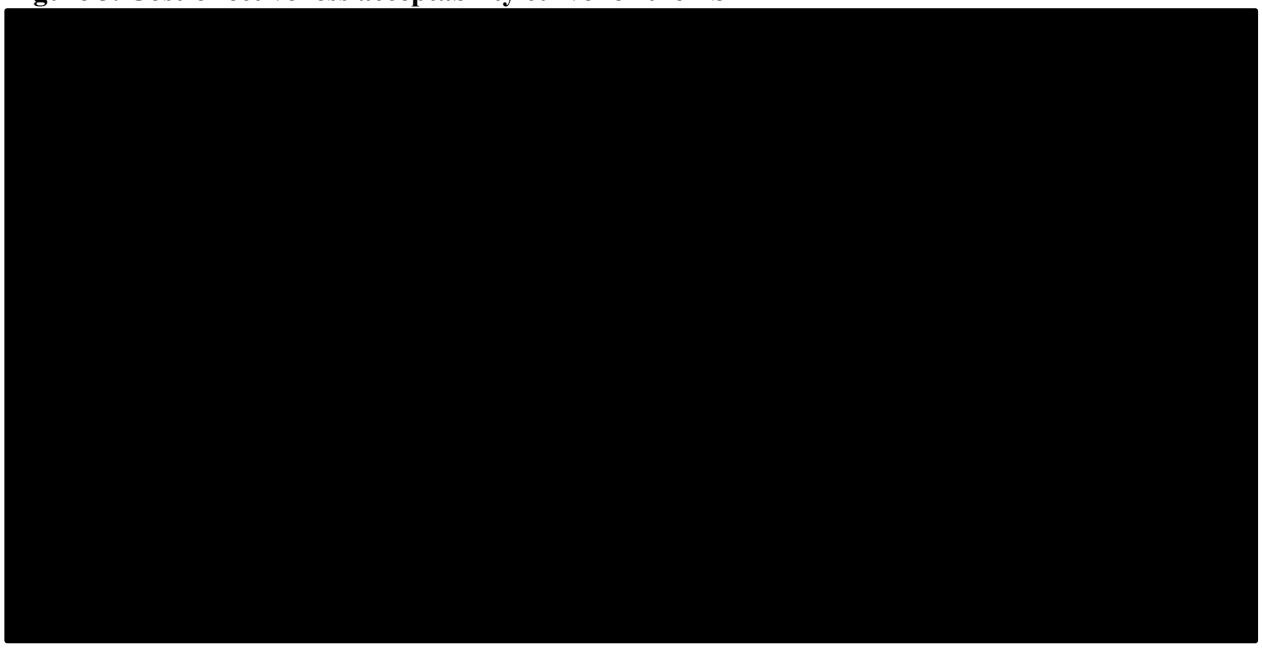
	Costs (£)			QALY			ICER
	Lumasiran	ECM	Incremental	Lumasiran	ECM	Incremental	(£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[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 2. 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 3. Cost-effectiveness acceptability curve for the PSA



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

4 Additional sensitivity analysis undertaken by the ERG

In section 2 the valuation of the CKD and ESRD health states was discussed, and it was concluded that in light of all the uncertainties about which utility valuation method gives the most reliable utility values, the ERG has a small preference for using the observed utilities from ILLUMINATE C, but the TTO valuations are also considered plausible by the ERG. As the company explored the ERG preferred option already in their scenario 1, and the company and the ERG are now aligned on all other assumptions, in this section we will only report on the alternative of using the TTO-based utilities from the vignette study.

The results from this scenario are shown in Table 7. It is clear that using the TTO values has a large impact on the ICER. Additionally, the number of undiscounted QALYs gained is now 23.0, leading to a QALY weight of 2.3, which reduces the threshold ICER to £230,000 per QALY gained.

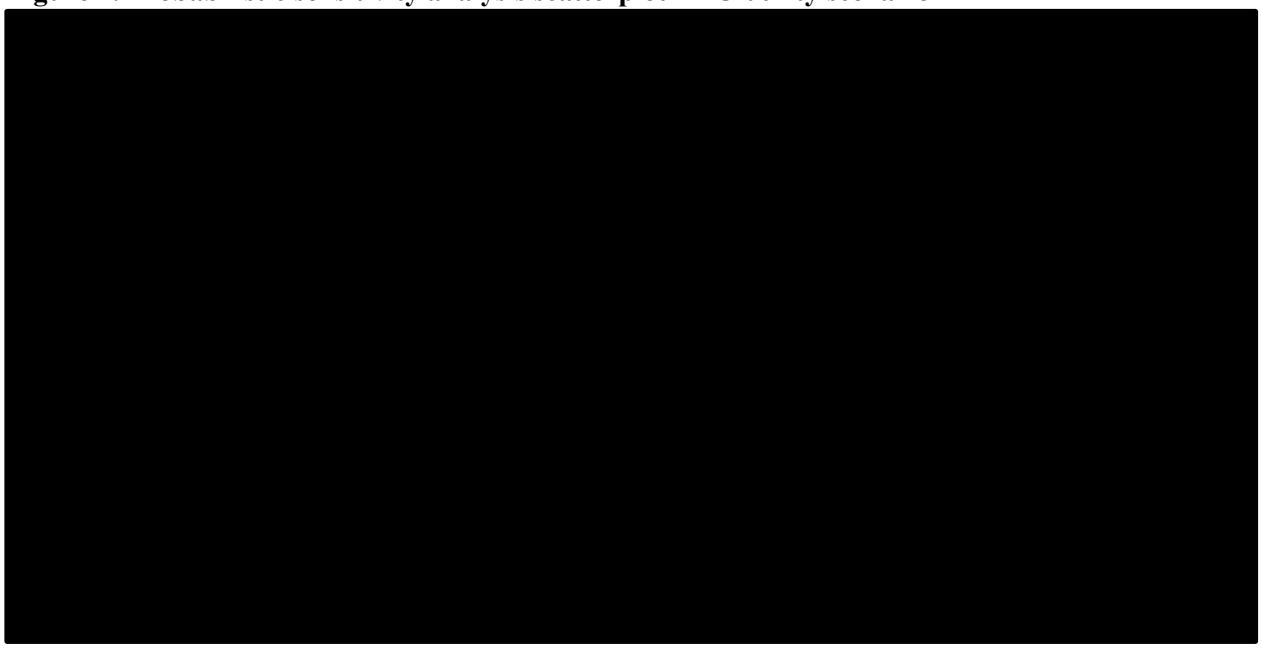
Table 7. Scenario analysis TTO-based utilities

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 v17.0 of the company 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

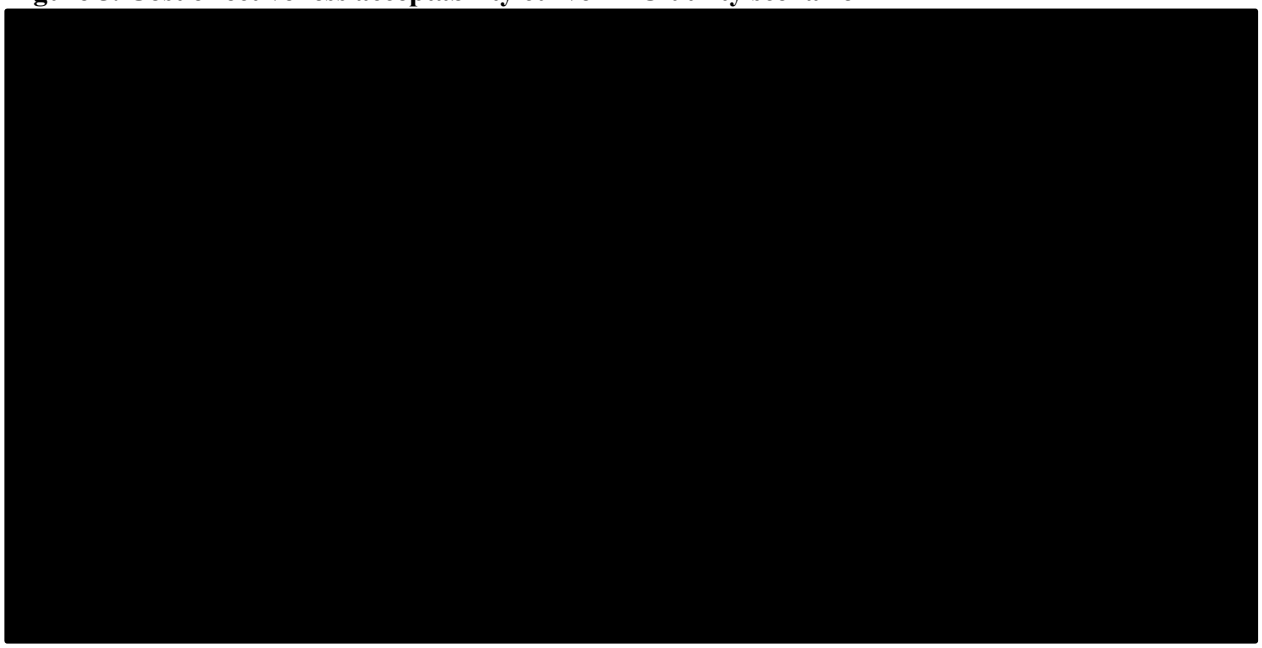
The ERG also conducted a PSA for this scenario showing a probabilistic ICER, averaged over 1,000 simulations, of [redacted], which is in line with the deterministic ICER of the scenario. Figure 4 and Figure 5 show the individual PSA simulation results and cost-effectiveness acceptability curve, respectively. At the threshold ICER of £230,000 per QALY gained, the probability that lumasiran is cost effective compared to ECM was [redacted]%.

Figure 4. Probabilistic sensitivity analysis scatterplot TTO utility scenario



CE = cost effectiveness; TTO = time trade-off; QALY = quality-adjusted life-year

Figure 5. Cost effectiveness acceptability curve TTO utility scenario



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

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Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Subgroup analyses as requested during from the PMB on 1 February 2023

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During the PMB of 1 February a request was made for the subgroup analyses based on patient population, using the revised company model. Below is, for each of the 2 subgroups, first a short description of the population included and then the results comprising of the company base case, their two scenarios, and an ERG scenario for health state utility values.

1. Patients of all ages with infantile onset of PH1

For this subgroup analysis it is assumed that all patients in the model are paediatric patients since these patients are unlikely to reach adulthood without a transplantation. Values for the initial age and average weight of this subgroup are the same as those used for the paediatric population in the base-case analysis and was derived from ILLUMINATE data. The distribution of patients per CKD health state at baseline was also assumed to be the same as in the base-case analysis.

Table 1 Revised company discounted base-case results, patients of all ages with infantile onset of PH1

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	[redacted]	[redacted]				
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on revised CS 25 January 2023

CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; LYG = life-years gained; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life year

Table 2. Scenario analyses on health state utility values, patients of all ages with infantile onset of PH1

Scenario	#	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	QALY weight
Base case after ECD2	0	[redacted]	[redacted]	[redacted]	3.0
Average EQ-5D utility of [redacted] from 8 ILLUMINATE-C patients	1	[redacted]	[redacted]	[redacted]	3.0
Mean TTO-derived vignette utilities after recalculation	2	[redacted]	[redacted]	[redacted]	3.0
TTO-derived vignette utilities	ERG	[redacted]	[redacted]	[redacted]	2.6

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TTO = time-trade-off

2. Infants with infantile onset of PH1

For this subgroup analysis it is assumed that all patients in the model are infants with severe disease. The age at baseline for these patients was defined as the midpoint of the definition used for infant age, thus 0.5 years. The value for the average weight of this subgroup is the same as the one used for the paediatric population in the base-case analysis and was derived from ILLUMINATE data, since infants are expected to become children within one cycle in the model. The distribution of patients per CKD health state at baseline was assumed to be 10% for CKD 4 and 90% for ESKD. These estimates were based on UK clinical expert opinion. Additionally, a hazard ratio (HR) of 6.0 for progression to ESKD was applied to infants with infantile onset of PH1 compared to patients with non-infantile onset. This HR was based on Harambat 2010.[1]

Table 3 Revised company discounted base-case results, infants with infantile onset of PH1

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
ECM	[redacted]	[redacted]	[redacted]				
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on revised CS 25 January 2023

CS = company submission; ECM = established clinical management; ICER = incremental cost effectiveness ratio; LYG = life-years gained; PH1 = primary hyperoxaluria type 1; QALY = quality-adjusted life year

Table 4 Scenario analyses on health state utility values, patients of all ages with infantile onset of PH1

Scenario	#	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	QALY weight
Base case after ECD2	0	[redacted]	[redacted]	[redacted]	2.1
Average EQ-5D utility of [redacted] from 8 ILLUMINATE-C patients	1	[redacted]	[redacted]	[redacted]	1.8
Mean TTO-derived vignette utilities after recalculation	2	[redacted]	[redacted]	[redacted]	1.9
TTO-derived vignette utilities	ERG	[redacted]	[redacted]	[redacted]	1.0

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TTO = time-trade-off

[1] Harambat J, Fargue S, Acquaviva C, Gagnadoux MF, Janssen F, Liutkus A, et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. *Kidney Int* 2010;77(5):443-9.