Slides for public: contains no confidential information

Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Highly specialised technologies evaluation committee

9 February 2023 (3rd evaluation meeting)

Chair: Peter Jackson

Evidence review group: Kleijnen Systematic Reviews (KSR)

Technical team: Anita Sangha, Mary Hughes, Richard Diaz

Company: Alnylam Pharmaceuticals

NICE

Key abbreviations

CI	Confidence interval	ICER	Incremental cost-effectiveness ratio
CKD	Chronic kidney disease	MA	Marketing authorisation
ECD	Evaluation consultation document	PAS	Patient access scheme
ECM	Evaluation committee meeting	PH1	Primary hyperoxaluria type 1
EQ-5D	European Quality of Life-5 Dimensions	QALY	Quality-adjusted life year
ESKD	End-stage kidney disease	TTO	Time-trade off

Key issue for consideration

Key issues		Impact on ICER
Utility values	**Which utility values should be used in the model for the CKD 4, ESKD and post-transplant health states?** • Company prefer values based on vignette study using EQ-5D valuation • ERG slightly prefer the average EQ-5D utility from the paediatric subgroup in ILLUMINATE-C but also consider the TTO-derived utilities from the vignette study to be plausible	**Large**

Appraisal history

Lumasiran is not recommended, within its marketing authorisation, for treating primary hyperoxaluria type 1 (PH1)

ECM1 - April 2022

- Cost-effectiveness estimates uncertain → additional analyses requested
- ICERs above acceptable range
- Not recommended
- ECD1 released

ECM2 - Oct 2022

- New evidence considered
- Company's key modelling assumption not reflective of clinical practice
- Revised model and additional analyses requested
- Not recommended
- ECD2 released

Today - Feb 2023

- Updated PAS
- Revised model and updated base case assumptions
- Consultation comments

RECAP

Disease background

PH1 is a rare genetic disorder of oxalate metabolism

Causes

- Oxalate is normally filtered by the kidneys and removed in the urine:
  - in PH1, the liver produces excess oxalate which builds up in the kidneys and urinary tract
  - excess oxalate binds with calcium resulting in the formation of oxalate crystals

Symptoms and prognosis

- Chronic deposition of calcium oxalate crystals in the kidneys results in progressive loss of renal function and can cause acute kidney injury
- As renal impairment progresses, oxalate levels in the body rise and oxalate crystals may be deposited across the body (known as systemic oxalosis)
- Symptoms are most severe for people with infantile onset of PH1 with significantly reduced survival compared to those with later onset of disease

Current treatments

Current treatments (referred to as standard care) depend on a person's kidney function

- **Preserved renal function**: supportive measures such as following a low-oxalate diet, increased fluid intake (hyperhydration), crystallisation inhibitor use (such as citrate supplementation), pyridoxine (vitamin B6) supplementation*
- **Advanced stages of renal decline:** dialysis may be initiated to slow the build up of systemic oxalate and/or replace lost renal function
- **ESKD:** a liver-kidney transplant may be needed to eliminate the source of excess oxalate production and restore lost kidney function

*around 5-10% of people with PH1 have the potential to fully respond to pyridoxine, but treatment may still not result in normalisation of oxalate levels

RECAP

Lumasiran (Oxlumo, Alnylam Pharmaceuticals)

Full marketing authorisation (UK)	Lumasiran is indicated for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups
Mechanism of action	Ribonucleic acid interference (RNAi) therapeutic which targets an enzyme (glycolate oxidase) to reduce oxalate production in the liver
Administration	Subcutaneous injection, dosing based on body weight
Price	• The list price is £61,068.98 per 94.5 mg vial (excluding VAT) • The company has a confidential commercial arrangement (simple discount patient access scheme – **updated post ECM2**)

Company's positioning of lumasiran (narrower than MA)

- People with PH1 who have not already had a liver or liver-kidney transplant, in particular:
  - all children with elevated oxalate levels despite standard care
  - in adults, treatment limited to those in later stages of CKD with exceptions for those with progression/severe comorbidities in earlier stage kidney disease
- Treatment administered over a person's lifetime or until liver-kidney transplantation

RECAP

Key clinical evidence

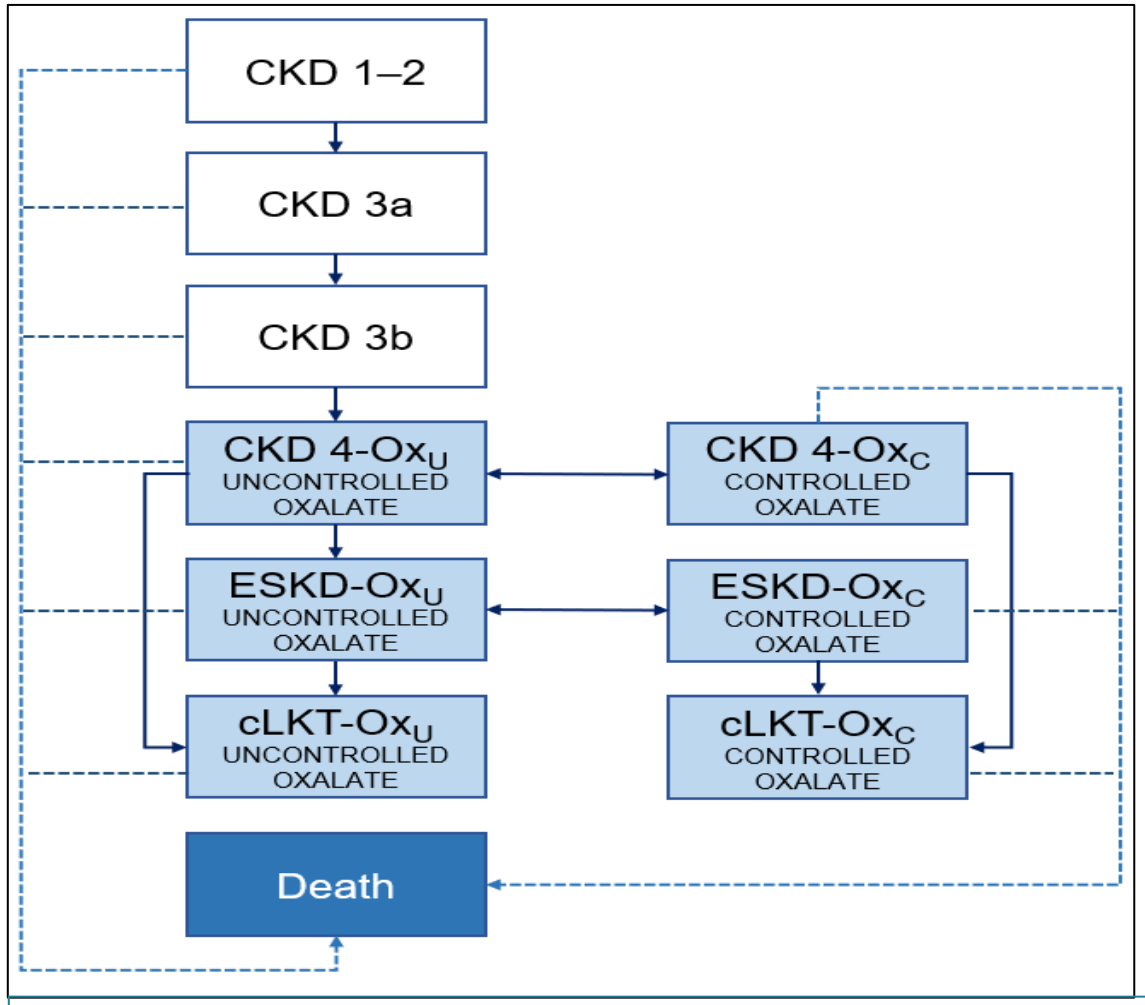
Clinical trial	Description of trial
ILLUMINATE-A (key clinical trial)	• Phase 3, randomised, double blind, placebo-controlled (6-months duration) • People aged ≥6 years with PH1 and relatively preserved renal function (n=39) • **Primary outcome → percentage change in 24-hour urinary oxalate excretion from baseline to month 6 for lumasiran versus placebo:** ○ **effect size: -53.5% (95% CI: -62.3 to -44.8), p value: 1.685×10^{-14}** • Single arm extension period (ongoing until January 2024)
ILLUMINATE-C • **EQ-5D data from this trial used to validate base case assumptions**	• Phase 3, single-arm, open-label (6-months duration) • People with PH1 and advanced renal disease • Extension period (ongoing until July 2025)

ECD2 summary of decision problem and clinical evidence

Committee conclusions remain unchanged following ECM1

Issue	Committee consideration
Population	• Company's positioning of lumasiran is narrower than MA but largely aligns with how clinicians would expect to use lumasiran in clinical practice
Comparator	• Company's approach to exclude isolated liver transplant (included in NICE scope) is reasonable as most people would have a liver-kidney transplant
Clinical evidence (based on 6-month randomised phase of ILLUMINATE-A)	• Lumasiran plus standard care is effective in reducing oxalate levels compared with standard care alone • Treatment with lumasiran is likely to affect health-related quality of life but unclear how large such an effect would be • Limitations in evidence base but appropriate for decision-making given rarity of the condition

Company's Markov model (1)



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

Key: CKD = chronic kidney disease; cLKT = combined/sequential liver-kidney transplant; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; Ox$_C$ = controlled oxalate levels; Ox$_U$ = uncontrolled oxalate levels

RECAP

Company's Markov model (2)

- Model compares lumasiran and standard care in people with PH1
- Cycle length of 6 months over lifetime time horizon
- CKD stages used as health states as loss of kidney function is the main feature of PH1
- 9 health states defined by CKD stage, plasma oxalate levels, and/or transplant status, plus death
- For CKD 4 and ESKD states:
  - people modelled to have controlled oxalate if plasma oxalate ≤ 50 micromol/litre or uncontrolled if above
  - only people in lumasiran cohort can move to states with controlled oxalate levels
  - people may undergo liver-kidney transplant → assumed higher probability of transplant in people with controlled oxalate

Committee considered that the company's model structure reflected the general course of the condition, but assuming higher rates of transplant for people with controlled than with uncontrolled oxalate did not reflect clinical practice

Probability of transplant: company & ERG assumptions at ECM2

Per-cycle probability	Controlled oxalate		Uncontrolled oxalate	
	Company	ERG	Company	ERG
2nd committee meeting Updated base case post ECM1	**0.192 (child), 0.122 (adult)** NHS Blood & Transplant 2021		**0.005** (Metry 2022)	**0.012** (Metry 2022)

Company and ERG applied data from Metry 2022 differently:

- Metry 2022: retrospective cohort study of people with PH1 in the OxalEurope registry who underwent liver or kidney transplantation
  - study did not stratify people according to their oxalate level
- Difference in company and ERG per cycle probabilities using Metry 2022:
  - ERG included both combined and sequential liver-kidney transplants, company included combined only
  - company calculated rate per maximum follow up of study, ERG calculated rate using average age of patients in the registry who had been followed since birth

Dialysis assumptions

Background: how dialysis rates were modelled in CKD 4

- Proportion having high or normal intensity dialysis differed by treatment arm and age
- At 2nd meeting → committee preferred the company's scenario which assumed that 50% of adults and 100% of children in CKD 4 would be on high-intensity dialysis because this aligned better with clinical expert opinion

Dialysis	Proportion in model (company base case in ECM2)
High-intensity dialysis (standard care arm)	
CKD 4 - children	100%
CKD 4 - adults	25%
ESKD	100%
Normal-intensity dialysis (lumasiran arm)	
CKD 4 - children	50%
CKD 4 - adults	0%
ESKD	100%

Utility values (1)

Background (1): Vignette study

- CKD 1-3b health states utility values are from EQ-5D data collected in ILLUMINATE A
- Vignette study used to estimate utilities for CKD 4 and ESKD health states for people with uncontrolled oxalate on high-intensity dialysis and post-transplant health states
- Vignette valuation: company preferred EQ-5D-5L (mapped to 3L); ERG preferred TTO as considered these aligned better with utilities measured in ILLUMINATE-A

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

Utility values (2)

Background (2): ILLUMINATE-C

- 1st meeting → committee requested EQ-5D data from ILLUMINATE-C to derive more accurate utility estimates for the late CKD states
- 2nd meeting → company considered that EQ-5D data from ILLUMINATE-C is not robust because of small sample size of study, but provided EQ-5D scores at initial valuation for a subgroup (mainly children with advanced kidney disease on dialysis – see table)
  - Company: subgroup utilities aligned more closely with the EQ-5D-derived utilities from vignette study
  - ERG scenario analysis applied the average utility from this subgroup to children in CKD 4 and all people in ESKD (with uncontrolled oxalate)
  - Committee request → provide average EQ-5D score across all people in ILLUMINATE-C to validate the utilities derived from the vignette study
  - In the absence of this data, committee preferred to use the EQ-5D utility average from subgroup

Patient (n=[redacted])	Index score
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Average	[redacted]

RECAP

ECD2 summary of modelling assumptions

Committee's considerations	Company's ECD2 response
Probability of transplant • Company's model assumes a higher rate of transplant for people with controlled than with uncontrolled oxalate levels, which does not reflect clinical practice → same rate of transplant should be used in revised model	**Revised model submitted.** **Base case updated in line with committee preference**
Dialysis assumptions • Company's scenario which assumes that 50% of adults and 100% of children in CKD 4 would be on high-intensity dialysis aligns better with clinical expert opinion • Frequency of high-intensity dialysis would be no more than 6 days/week based on clinical expert opinion	**Revised assumptions.** **Base case updated in line with committee preference**
Utility values • Prefer to use the EQ-5D utility average from the paediatric subgroup in ILLUMINATE-C to estimate utilities for the late CKD health states	**New discussion + scenarios.** **No change to base case preference**

ECD2 summary of cost-effectiveness results and other considerations

Issue	Committee's considerations
Cost-effectiveness results	• Committee considered that it had not been presented with a cost-effectiveness estimate which was suitable for decision making
Other considerations	• No evidence to show impact of stopping rule with lumasiran (had been presented by company as scenario analyses) • Lumasiran is not a curative treatment (prevents excess oxalate production, but does not clear existing oxalate burden in the body) → lower discount rate not appropriate • QALY weighting → estimated QALY gains from the model were too uncertain to decide on whether weighting should be applied • No equality issues relevant to the recommendations

Consultation comments

Comments received from:

- Alnylam Pharmaceuticals (company)
- British Association for Paediatric Nephrology
- UK Kidney Association

Summary of comments from the British Association for Paediatric Nephrology

- 4 infants (with infantile oxalosis) under 1 year of age commenced compassionate use lumasiran on a clinically urgent basis in the last 2 years:
  - 2 infants → rapid decline in kidney function was reversed and they remain clinically well without the need for dialysis
  - 2 infants → improvement in urine output and kidney function whilst on dialysis and have avoided urgent liver transplantation or progression to systemic oxalosis
- Families are concerned about the possibility that their child may need to discontinue lumasiran, given the clear improvements in their health and quality of life
- UK paediatric clinicians caring for children with PH1 have expressed concern that this highly effective pivotal therapy may not be available via the NHS

Summary of comments from the UK Kidney Association (1)

Company's model

- Broadly agree with the committee's conclusions regarding proposed improvements to the model used to calculate cost effectiveness
- Areas of difficulty: using cut-off plasma oxalate values as an indication for transplantation and the assumption that CKD stage and health state can be correlated
  - modelling in this way is too rigid and completely omits some very important indications e.g. infantile oxalosis, for which the model is not valid
  - clinical factors guiding treatment decisions include: rate of worsening of renal function (regardless of baseline CKD stage), systemic oxalosis, and age
  - if transplant is needed, delaying it is not usually in the patient's best interest
  - impact of recurrent kidney stone disease (symptoms, interventions, time off work/school, etc) has not been considered but is an important clinical outcome [N.B renal stone event rates are included in the model]

Summary of comments from the UK Kidney Association (2)

Use of lumasiran and impact if not recommended

- Evidence and clinical need for the emergency use of lumasiran in infantile oxalosis and post-renal transplant oxalosis in a previously undiagnosed person:
  - both represent very severe clinical phenotypes and affect <5 per year nationally
- There is a high risk that the UK will become an international outlier if lumasiran is not recommended at all (it is currently available across Europe and the USA)
- There are a number of people currently on extended clinical trials with lumasiran:
  - as trials come to an end, concern from patients (and their families) about how they will continue on treatment that was clinically beneficial to them
  - this creates a potential for clinical harm, which is difficult to defend as the UK is now the only major European country that does not have a recommendation for siRNA medications [such as lumasiran] for PH1

Company's response to ECD2

Company's modelling assumptions:

- Probability of transplant
- Dialysis assumptions
- **Key issue: utility values**

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Probability of transplant

Revised model

Company ECD2 response

- Company has revised model in line with committee preference (by using the same rate of liver-kidney transplant for people with controlled and uncontrolled oxalate)
- Revised model uses ERG's estimated per-cycle probability from ECM2 because it:
  - also includes sequential liver-kidney transplants reported by Metry 2022
  - used the average age of the Metry study cohort who had been in the registry from birth (rather than the maximum follow up from the study)

Per-cycle probabilities	Controlled oxalate		Uncontrolled oxalate	
	Company	ERG	Company	ERG
2nd committee meeting Updated base case post ECM1	**0.192 (child), 0.122 (adult)** NHS Blood & Transplant 2021		**0.005** (Metry 2022)	**0.012** (Metry 2022)
3rd committee meeting Updated base case post ECM2	**0.012** (Metry 2022)		**0.012** (Metry 2022)	

Dialysis assumptions (1)

Revised assumptions

Background - recap

- At 2nd meeting → committee preferred the company's scenario which assumed that 50% of adults and 100% of children in CKD 4 would be on high-intensity dialysis because this aligned better with clinical expert opinion

Company ECD2 response

- Base case revised to align with committee preferred assumption in ECM2
- Dialysis rates in scenario are applied to both treatment arms since the committee expected that half of adults and all children in CKD 4, whether receiving lumasiran or not, would still have dialysis to remove established oxalate deposits from the body (N.B. people receiving lumasiran are assumed to have normal intensity dialysis)
- Frequency of high-intensity dialysis has reduced from 7 days/week to 6 days/week in the model based on clinical expert opinion in ECM2 (>6 days is not manageable)

Dialysis assumptions (2)

Revised assumptions

Dialysis	Proportion in model (company base case in ECM2)	Proportion in model (company revised base case in ECM3)
High-intensity dialysis (standard care arm)		
CKD 4 - children	100%	**100%**
CKD 4 - adults	25%	**50%**
ESKD	100%	100%
Normal-intensity dialysis (lumasiran arm)		
CKD 4 - children	50%	**100%**
CKD 4 - adults	0%	**50%**
ESKD	100%	100%

Key issue: Utility values (1)

Large impact on ICER

New discussion + scenarios

Company ECD2 response (1): Lack of face validity of requested EQ-5D scores from ILLUMINATE-C

- Explored individual EQ-5D index scores from adults in ILLUMINATE-C but considered these to be unsuitable to report for decision making because:
  - patients reported EQ-5D scores that exceeded those reported by people without PH1 in the same CKD stages and also general population norm values (including some patients who reported scores of 1.0, implying perfect health)
  - such high scores lack credibility given that these people have advanced PH1 and most of whom who are having frequent dialysis
  - this may due to the “disability paradox” in which people with chronic and disabling diseases may adapt to their condition and value their health states higher than does the general population
  - disability paradox has affected scores for adults to a greater extent than for children because they have had more time to adapt to and accept their disease

Key issue: Utility values (2)

Large impact on ICER

New discussion + scenarios

Company ECD2 response (2): retained preference for vignette-based utilities over ILLUMINATE-C

- Company present scenario analysis applying the average EQ-5D of [redacted] from the paediatric subgroup in ILLUMINATE-C, but consider the small sample size of the subgroup introduces uncertainty
- While EQ-5D values observed within this subgroup generally did not lack face validity, the degree of impact of the disability paradox on these values is unknown
- However, EQ-5D values observed within this subgroup provide the best utility data against which to validate the vignette utility values for people in CKD 4 and ESKD, rather than using EQ-5D data from people in CKD 1- 3b from ILLUMINATE-A
- Unknown impact of disability paradox in paediatric subgroup together with lack of validity in the adult utilities from ILLUMINATE-C means that it is necessary to use utilities from the vignette study

Key issue: Utility values (3)

Large impact on ICER

New discussion + scenarios

ERG comments (1)

- Accept ‘disability paradox’ as a potential explanation for some high utility values from ILLUMINATE-C
- Agree that there is a mismatch between the population in which the trial utilities were initially compared against vignette study data (CKD 1 to 3b) by the ERG, and the population in which vignette study data were used in the model (CKD 4 and ESKD)

Key issue: Utility values (4)

Large impact on ICER

New discussion + scenarios

Company ECD2 response (3): EQ-5D vs TTO for vignette valuation

- NICE guidance states that EQ-5D is preferred over TTO for vignette valuation
- EQ-5D derived utilities, when compared with TTO-derived utilities, are numerically closer to the utilities elicited directly from the paediatric subgroup in ILLUMINATE-C
- Histograms of scores indicate that validity issues may exist with the TTO-derived scores (unlike for EQ-5D index scores) including:
  - many implausibly high scores (near/above normal values for healthy individuals and in some cases as high as 1.0) and large discontinuity between -1.0 and 0 in the distribution
- Appropriate to retain EQ-5D valuation of the vignettes for utilities in late CKD states

Key issue: Utility values (5)

Large impact on ICER

New discussion + scenarios

ERG comments (2)

- ERG agrees that EQ-5D valuations of vignettes is preferred by NICE guidance (when choosing between EQ-5D and TTO valuations of vignettes)
- In a systemic literature review of utilities for kidney disease health states, the EQ-5D utilities for haemodialysis and peritoneal dialysis were 0.67 and 0.57, respectively
  - for people with CKD + complications, the EQ-5D utilities for acute phase of a stroke and bone fractures were 0.5 and 0.35, respectively
  - these complications are not the same as PH1, but may be reflective of people whose quality of life has decreased due to CKD, dialysis + another health issue
  - these values raise doubts about the validity of EQ-5D utilities from vignette study
- ERG slightly prefer the average EQ-5D utility from the paediatric subgroup in ILLUMINATE-C as it is based on measurement of quality of life among patients
- TTO-derived utilities from the vignette study are also considered plausible by the ERG, and are provided as a scenario analysis

Key issue: Utility values (6)

Large impact on ICER

New discussion + scenarios

Company ECD2 response (4): new scenario for TTO-derived utilities from vignette study

- Company also provided scenario which recalculated average TTO values after excluding individual values from the analysis if they exceeded the values for people without PH1 in CKD 4 or ESKD (considered clinically implausible by the company)
- How utility values for people without PH1 were obtained: model health state utility values for people with PH1 in CKD 4 and ESKD were adjusted to reflect differences in the use of dialysis and absence of systemic oxalosis complications in non-PH1 related CKD 4 and ESKD

	Utility values for people without PH1		Recalculated average TTO values		Original average TTO values	
Health state	Child	Adult	Child	Adult	Child	Adult
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESKD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue: Utility values (7)

Large impact on ICER

New discussion + scenarios

ERG comments (3)

- ERG is not convinced on the company's scenario which excludes TTO scores above the expected utility value for people without PH1 in CKD 4 and ESKD because:
  - there will be variation in utilities in the healthy population, so as long as the high utilities for people with PH1 are not higher than the high utilities for people without PH1, the claim of clinical implausibility cannot be made
  - ERG were unable to reproduce the utilities for people without PH1 in these health states, based on the information provided by company

Which utility values should be used in the model for the CKD 4, ESKD and post-transplant health states?

Cost effectiveness

The company considers that the ICERs are confidential but ICER ranges have been presented for transparency

Cost effectiveness results – company revised base case

Deterministic base case results – includes updated lumasiran PAS (discounted results)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard care	[redacted]	[redacted]			

Probabilistic base case results – includes updated lumasiran PAS (discounted results)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Lumasiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard care	[redacted]	[redacted]			

ICERs with the approved PAS are "around the threshold"

Company deterministic scenario analyses

ICERs include updated lumasiran PAS (discounted results)

No.	Scenario (applied to company base case)	Impact of scenario on ICER	ICER (£/QALY)
1	**Company revised base case**		[redacted]
2	**Utility values: average EQ-5D utility of [redacted] from paediatric subgroup in ILLUMINATE-C** applied to children in CKD 4 and all people in ESKD (with uncontrolled oxalate levels)	**Large**	[redacted]
3	**Utility values: average TTO-derived vignette utilities applied to CKD 4 and ESKD after recalculation** to exclude values above utilities for non-PH1 patients in these CKD stages	**Large**	[redacted]

ICERs for company scenarios with the approved PAS are "above the threshold" but below £350,000 per QALY gained

ERG scenario analysis

ICERs include updated lumasiran PAS (discounted results)

Scenario	Impact of scenario on ICER	ICER (£/QALY)
Company revised base case		[redacted]
ERG scenario: using TTO-derived utilities from the vignette study		
○ deterministic results	**Large**	[redacted]
○ probabilistic results	**Large**	[redacted]

ICERs for ERG scenario with the approved PAS are "above the threshold" but below £500,000 per QALY gained

QALY weighting

- ICER greater than £100,000 per QALY, judgements take account of the **magnitude of benefit** and the additional **QALY weight** that would be needed to support recommendation
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Incremental QALYs gained	Weighting
Less than or equal to 10	1
11 to 29	Between 1 and 3 (equal increments)
Greater or equal to 30	3

Scenario (deterministic results)	Incremental QALYs	
	Undiscounted	Discounted
Company revised base case	[redacted]	[redacted]
Company scenario 1: average EQ-5D utility ([redacted])	[redacted]	[redacted]
Company scenario 2: recalculated average TTO	[redacted]	[redacted]
ERG scenario: TTO utilities from vignette study	[redacted]	[redacted]

Subgroup 1: Infants with infantile onset of PH1

Deterministic ICERs include updated lumasiran PAS (discounted results)

- Provided by ERG at request of NICE. For this subgroup analysis, it is assumed that all patients in the model are infants with severe disease

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
1	**Subgroup 1: results with company's updated base case assumptions**	[redacted]	[redacted]	[redacted]
Company and ERG scenario analyses applied to subgroup				
2	**Average EQ-5D utility of [redacted] from paediatric subgroup in ILLUMINATE-C**	[redacted]	[redacted]	[redacted]
3	**Average TTO-derived vignette utilities after recalculation**	[redacted]	[redacted]	[redacted]
4	**TTO-derived vignette utilities**	[redacted]	[redacted]	[redacted]

- **ICERs for subgroup 1, scenarios 2 and 3 are lower than ICERs for whole population**
- **ICER for scenario 4 is slightly higher than ICER for whole population**

Subgroup 2: Patients of all ages with infantile onset of PH1

Deterministic ICERs include updated lumasiran PAS (discounted results)

- Provided by ERG at request of NICE
- 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 transplant

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
1	**Subgroup 2: results with company's updated base case assumptions**	[redacted]	[redacted]	[redacted]
Company and ERG scenario analyses applied to subgroup				
2	**Average EQ-5D utility of [redacted] from paediatric subgroup in ILLUMINATE-C**	[redacted]	[redacted]	[redacted]
3	**Average TTO-derived vignette utilities after recalculation**	[redacted]	[redacted]	[redacted]
4	**TTO-derived vignette utilities**	[redacted]	[redacted]	[redacted]

ICERs for all scenarios are lower than the ICERs for whole population

QALY weighting: subgroups

- ICER greater than £100,000 per QALY, judgements take account of the **magnitude of benefit** and the additional **QALY weight** that would be needed to support recommendation
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Incremental QALYs gained	Weighting
Less than or equal to 10	1
11 to 29	Between 1 and 3 (equal increments)
Greater or equal to 30	3

Scenario (deterministic results)	QALY weight	
	Infants with infantile onset	All ages with infantile onset
Company revised base case (subgroups)	2.1	3.0
Company scenario 1: average EQ-5D utility ([redacted])	1.8	3.0
Company scenario 2: recalculated average TTO	1.9	3.0
ERG scenario: TTO utilities from vignette study	1.0	2.6

Other considerations

- Equality issues
- Factors affecting the guidance

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Equality issues considered in ECM2 (1)

Stakeholder comments

- PH1 disproportionately affects populations in which consanguineous marriages are common. So, it is more common in people from Middle Eastern, North African, and South Asian family origin
- PH1 disproportionately affects young people, their families and carers
- People who have clinical features of PH1 but are not referred to a specialist centre because of geographical distance or inadequate referral pathways may experience inequalities in care
- People who have been diagnosed with metabolic kidney stone disease may also struggle to access and attend specialist centres because of where they live
- PH1 gene can be found in all people and is not limited to a single ethnic group, so [if recommended] lumasiran should be available to anyone in need of this treatment

Equality issues considered in ECM2 (2)

Committee considerations in ECD2

- Issues related to differences in the prevalence or incidence of a disease and about healthcare implementation cannot be addressed in a highly specialised technology evaluation
- The committee was mindful of its obligations in relation to the Equality Act 2010 and that it can only recommend the use of lumasiran within its marketing authorisation.
- Conclusion → there are no equality issues relevant to the recommendations

Are there any additional equality issues that need to be considered?

Factors affecting the guidance (1)

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' HRQoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and how the guidance might strengthen it • Treatment continuation rules

Factors affecting the guidance (2)

- In forming the guidance, committee will take account of the following factors:

Value for money	Impact beyond direct health benefits
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key issue for consideration

Key issues		Impact on ICER
Utility values	**Which utility values should be used in the model for the CKD 4, ESKD and post-transplant health states?** • Company prefer values based on vignette study using EQ-5D valuation • ERG slightly prefer the average EQ-5D utility from the paediatric subgroup in ILLUMINATE-C but also consider the TTO-derived utilities from the vignette study to be plausible	**Large**