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Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Highly specialised technologies evaluation committee

12 October 2022 (2nd 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	HRQoL	Health-related quality of life
CKD	Chronic kidney disease	ICER	Incremental cost-effectiveness ratio
cLKT	Combined liver-kidney transplantation	MA	Marketing authorisation
DSU	Decision Support Unit	PAS	Patient access scheme
ECD	Evaluation consultation document	PH	Primary hyperoxaluria
ECM1	Evaluation committee meeting 1	QALY	Quality-adjusted life year
eGFR	Estimated glomerular filtration rate	RCT	Randomised controlled trial
ESKD	End stage kidney disease	RDCN	Rare Disease Collaborative Network
EQ-5D	European Quality of Life-5 dimensions	TTO	Time-trade off

Key issues for consideration

Key issues		Impact on ICER
Transplant probability	Which transplant probability should be used in the model for people with uncontrolled oxalate levels?	
Utility values	Which valuation of the health-state vignettes is more appropriate to derive utilities for the CKD 4, ESKD and post-transplantation health states?	
Dialysis assumptions	Are the company's modelling assumptions on the use of dialysis in CKD 4 and ESKD health states clinically plausible?	

 Model driver

 Small impact

Disease background (1)

Primary hyperoxaluria (PH) is a group of rare, genetic disorders of oxalate metabolism and includes subtypes 1, 2 and 3. PH1 is the most common of all subtypes and the most severe

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
  - the excess oxalate also binds with calcium resulting in the formation of oxalate crystals

Incidence

- Incidence of PH1 in Europe has been estimated as 1 in 100,000 live births per year

Symptoms and prognosis (1)

- 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)
- In children, systemic deposition of oxalate may cause failure to thrive, growth retardation and disability due to bone, joint and eye damage

Sources: Company submission, NICE final scope [ID3765]

Disease background (2)

Symptoms and prognosis (2)

- Severity of symptoms may vary significantly between people with PH1 and disease progression can be rapid and unpredictable
- Symptoms are most severe for people with infantile onset of PH1 with significantly reduced survival compared to those with later onset of disease
- Mortality in PH1 is largely due to end-stage kidney disease (ESKD), dialysis, transplantation or systemic oxalosis complications

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:** liver transplant (with or without kidney transplant) can eliminate PH1 as the source of excess oxalate production is removed

*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

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) in the liver to reduce oxalate production
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 ECM1**)

Company's positioning of technology (narrower than MA)

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

Summary of clinical evidence

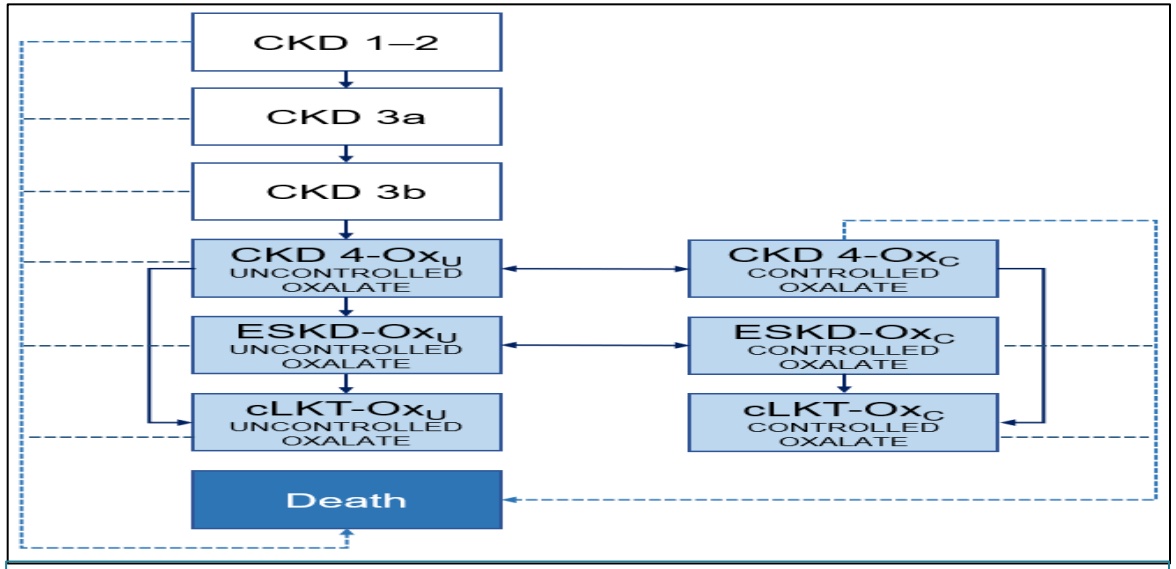
Clinical trial	Description of trial
ILLUMINATE-A (key clinical trial)	• Phase 3, randomised, double blind, placebo-controlled (6-months duration) • People aged ≥6 years with PH1 and relatively preserved renal function (n=39) • **Primary outcome → percentage change in 24-hour urinary oxalate excretion 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-B	• Phase 3, single-arm, open-label (6-months duration) • Children aged <6 years with PH1 and relatively preserved renal function • Extension period (ongoing until August 2024)
ILLUMINATE-C	• Phase 3, single-arm, open-label (6-months duration) • People with PH1 and advanced renal disease • Extension period (ongoing until July 2025)
ALN-GO1-001B	• Phase 1/2, randomised, placebo-controlled, dosing study* → study completed
ALN-GO1-002	• Phase 2, open label extension safety study of people who were previously enrolled in ALN-GO1-001B → ongoing until June 2023

* ERG did not recognise study as a 'full RCT' because only 1 person was randomly allocated to the placebo group in each of the 3 lumasiran dosing cohorts which would not have reduced selection bias

ECD summary of decision problem and clinical evidence

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 – model structure



Key: CKD = chronic kidney disease; cLKT=combined/sequential liver-kidney transplant; ESKD = end stage kidney disease; Ox_C=controlled oxalate levels; Ox_U=uncontrolled oxalate levels

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)

- Company model compares lumasiran and standard care in a simulated cohort of people with PH1
- CKD stages used as health states because loss of kidney function is the main feature of PH1
- CKD stages are defined by a person's estimated glomerular filtration rate (eGFR)
- 9 health states defined by CKD stage, plasma oxalate levels, and/or transplant status, plus death
- Cycle length of 6 months over lifetime time horizon
- Lumasiran is continued across all CKD stages

For CKD 4 and ESKD health states:

- 50 micromol/litre plasma oxalate threshold used to distinguish between controlled/uncontrolled oxalate
  - only people in the lumasiran cohort can move to states with controlled oxalate levels
- People may undergo liver–kidney transplant

Committee considered that the company's model structure reflected the general course of the condition

RECAP

Company's Markov model – key modelling assumptions

Disease progression (standard care arm)

- CKD 1 to 3b → modelled based on the changes in plasma oxalate levels measured in ILLUMINATE-A in combination with relationship between eGFR and plasma oxalate (Shah 2020)
- CKD 4 to ESKD → modelled using ESKD-free survival curves from PH1 population (Harambat 2010)

Probability of transplant

- Differs by whether a person's oxalate levels are controlled or uncontrolled
- Company and ERG had different estimates for people with uncontrolled oxalate

Utility values

- CKD 1 to 3b → based on pooled EQ-5D data from ILLUMINATE A
- CKD 4 and ESKD (for people with uncontrolled oxalate on high-intensity dialysis) and post-transplant health states → derived from vignette study
- Valuation of vignettes: company preferred EQ-5D-5L; ERG preferred time-trade off (TTO)

Dialysis rate and regimen (people with CKD 4 or ESKD)

- % having dialysis and regimen (high or normal intensity) differs by:
  - chronic kidney disease health state (CKD 4 or ESKD)
  - treatment arm

ECD summary of modelling assumptions

Committee's considerations	Company ECD response
Disease progression • Measures of oxalate levels are appropriate in predicting kidney function in people with PH1 • Modelling of disease progression is sufficient for decision-making	New data used to inform disease progression rates after CKD 3b. Base case updated.
Probability of transplant • Probability of transplant for people with uncontrolled oxalate levels in CKD 4 and ESKD (representing standard care) is likely underestimated → prefer to assume that 50% of these people would be placed on transplant waiting list	New evidence. Base case updated.
Utility values • Prefer TTO valuations of the vignettes to estimate utilities for late CKD and post-transplant states rather than company preferred EQ-5D approach	**New discussion + data for validation.** **No change to base case preference**
Dialysis assumptions • Some inconsistences between dialysis assumptions in the model and expert opinion heard in ECM1	New base case assumptions + scenarios
Survival after transplant • Prefer to assume that survival after transplant for people on standard care is based on all patients in the study by Jamieson 2005	Updated to committee preferences in revised base case

ECD summary of cost-effectiveness results and other considerations

Issue	Committee's considerations
Cost-effectiveness results	• Committee's preferred ICERs for lumasiran versus standard care were significantly above £1,000,000/QALY gained (exact ICERs are confidential) • ICERs for all scenarios were above the range that NICE considers to be an acceptable use of NHS resources
Other considerations	• 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 • ICERs higher than £300,000/QALY gained → applying any QALY weighting would not impact decision on whether to recommend lumasiran • No equality issues relevant to the recommendations

ECD preliminary recommendation:

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

Consultation comments

Comments received from:

- Alnylam Pharmaceuticals (new evidence and updated model)
- Metabolic Support UK (including responses from members)
- UK Kidney Association
- 2 clinical experts
- 4 public responses

NICE National Institute for Health and Care Excellence

Key themes from consultation comments (1)

Burden of disease

- People with PH1 experience painful kidney stones from a young age
- Kidney failure develops over time and is associated with systemic oxalosis, intensive dialysis, and often transplantation plus psychological stresses and interruptions in life, school and work
- Systemic oxalosis can be severe, life threatening and affect all parts of the body
- The disease burden is significant for the person with PH1 but also for their family members

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"The ECD…fails to emphasise the severity of the condition and the overall impact on the patient and caregiver quality of life."

***Patient X**: "I was diagnosed with hyperoxaluria in 2016 following several kidney stone events….I distinctly remember the agony that came with every stone… I remember saying to my mother 'I want to die' as the pain was so intolerable"*

Key themes from consultation comments (2)

Current treatment and unmet need

- Current treatment includes drinking copious amounts of water and taking medication such as citric acid or vitamin B6, which standalone are often ineffective in lowering oxalate levels
- There is a high rate of renal failure because people with PH1 need more frequent and longer dialysis sessions but these may not be sufficient to prevent the build up of oxalate in the body
- Lumasiran is the only effective treatment. Only a few people have the vitamin B6 responsive allele - no other way to lower oxalate levels
- The only other treatment option is a liver-kidney transplant which is accompanied by a great deal of risk and a reduction in quality of life for patients

"In recommending that Lumasiran not be used...NICE recommends patients to find the other non-existent drugs necessary to mitigate kidney damage and adverse health effects of the disease."

"My younger brother, who was diagnosed with PH1 at 8 years old....drinks 4 litres of water daily in addition to several medications to efforts to reduce his oxalate levels"

"It is almost impossible to have a life while requiring nearly continuous dialysis while waiting and praying for a transplant."

Key themes from consultation comments (3)

Benefits of lumasiran - case studies

- *"Lumasiran makes it possible for my brother to maintain his quality of life and will delay, and perhaps even prevent altogether, the need for a transplant, a 'treatment' option with a very low success rate..."*
- *"My daughter is currently receiving lumasiran...Her plasma oxalate and urine oxalate levels are now normal and her kidney function and nephrocalcinosis remain stable. My husband who had taken 2 years of work to care for her can return to full time work..."*
- ***Patient X:*** *"This medicine has turned my life around. Not only has it stopped any future stones from forming, it has meant that I can live a normal life and go to school... It has also meant that I no longer require the transplants which would have been wholly detrimental to my quality of life."*
- ***Parents of Patient X:*** *"He has had no further kidney stone events, imaging shows that there is no new build-up of oxalate in his kidneys. Both his blood and urine oxalate levels are close to normal and most importantly he can lead a normal life. His hospital visit frequency is down to once every three months...it has transformed our lives too..."*

Key themes from consultation comments (4)

Cost-effectiveness and preliminary recommendation

- The recommendation should be reconsidered as lumasiran is a lifesaving and life-altering treatment for people with PH1 and their families
- Cost-effectiveness estimates will differ for people who develop renal failure and complications of systemic oxalosis in early childhood compared to those with modest renal decline in adulthood
- The cost of repeated procedures for kidney stone treatment, dialysis and transplantation will exceed the cost of lumasiran
- Cost-effectiveness estimates do not take into account the cost to society when people with PH1 (or their carers) are not able to work due to illness, dialysis or transplantation
- Quality-of-life gain with lumasiran needs to be considered in decision-making

"As a clinician who has seen significant benefit to NHS patients treated with lumasiran…the initial recommendation is disappointing. We hope that a revised submission will represent value to the NHS and allow treatment of severely affected patients such as infants with a severe phenotype of [PH1].."

"It is nothing short of a tragedy to finally have an effective treatment available but yet not be able to use it to help those with PH1"

Key themes from consultation comments (5)

Measures of oxalate levels

Use of plasma vs urinary measures of oxalate in clinical practice

- Evidence for urinary oxalate as a valid surrogate measure [of kidney function], less for plasma oxalate. Work-up for transplantation would not rely on plasma oxalate levels
- Urinary oxalate is a widely accepted marker of the risk of future decline in kidney function and progression (it is not a marker of kidney function at the time of the sample)
- Urinary oxalate levels are used as a marker of prognosis in children who pass urine, plasma oxalate levels are a useful marker of prognosis in children with end stage kidney disease

50 micromol/litre cut-off for uncontrolled oxalate

- Threshold is based on expert opinion as part of PH diagnosis, not for systemic oxalosis diagnosis.
- Data from Ogawa 2006 suggests that non-PH dialysis patients have a plasma oxalate level of 50 micromol/litre and that oxalosis might start >100 micromol/litre
- Plasma oxalate levels vary between laboratories → threshold may not be appropriate
- Disease progression (kidney function decline) will likely happen in people who sustain a steady but high urinary or plasma oxalate level over time

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ERG comments: increasing the plasma oxalate threshold in the model to distinguish between controlled and uncontrolled oxalate levels has little impact on the ICER

Comments on factual accuracy of ECD

ECD	Text in ECD	Clarification from clinical expert
3.8	• Clinical experts explained that lumasiran would be offered to children with evidence of calcium oxalate deposition but whose kidney function had not declined • It would also be offered to all children with normal kidney function if they had high plasma oxalate levels or a family history of the severe infantile phenotype	• Lumasiran would be offered to all infants with evidence of a severe infantile phenotype - not just a family history of infantile phenotype • Children with normal kidney function do not have high plasma oxalate levels - lumasiran would be offered to all children with reduced kidney function
3.12	Committee understood that people with PH1 have their condition managed at 1 of the 4 centres which form the Hyperoxaluria Rare Disease Collaborative Network (RDCN) and that if lumasiran was recommended it would be provided within these centres	Lumasiran is not solely provided at the 4 centres contributing to the RDCN. This network advises and supports clinicians in use of lumasiran in their own centres, closer to patients' homes

Key issues

Company's modelling assumptions:

- Probability of transplant
- Utility values
- Dialysis assumptions

NICE National Institute for Health and Care Excellence

New evidence

Key issue: Probability of transplant in CKD 4 + ESKD (1)

	Controlled oxalate		Uncontrolled oxalate	
Green boxes = committee preference ECM1	Company	ERG	Company	ERG
<u>First committee meeting</u> • Per-cycle transplant probability • Probabilities are applied to CKD 4 and ESKD health states	**0.192 (children), 0.122 (adults)** NHS Blood and Transplant 2021 Assumption → 100% lumasiran on waiting list		**0.007** (Compagnon 2014)	Assumption → 50% standard care on waiting list
<u>Second committee meeting</u> Updated base case after ECD	**No change**		**0.005** (Metry 2022)	**0.012** (Metry 2022)

Background

- Using company probabilities, the ERG estimated it would take 2.5 years (children), 4 years (adults) with controlled oxalate and 83 years for children and adults with uncontrolled oxalate to have transplant (**company response to ECD noted error in ERG estimates, ERG agrees on error**)
- ERG considered that difference in transplantation probability between people with controlled and uncontrolled plasma oxalate lacked face validity
- ERG assumption resulted in higher transplant probability for people with uncontrolled oxalate
- Committee considered that there was uncertainty around the ERG's probability of transplant in people with uncontrolled oxalate but that it aligned more closely with clinical opinion heard in ECM1

New evidence

Key issue: Probability of transplant in CKD 4 + ESKD (2)

Company ECD response

- Updated literature search identified a retrospective cohort study by Metry 2022
- Metry 2022 included people with PH1 in the OxalEurope registry who underwent liver or kidney transplantation across 8 countries in Europe:
  - company consider study to be a more appropriate source for transplant rate than the French study used in submission (Compagnon 2014) because of its larger size and geographic scope
- Company consulted with 2 UK clinical experts who considered that:
  - OxalEurope is one of the best sources of PH1 data available and reflects UK PH1 population
  - company's calculations of liver-kidney transplant rates in the model are logical
- Clinical expert considered that the rate of transplant based on revised probability per cycle for people on standard care (1 liver-kidney transplant every 2-3 years) is reasonable

ERG comments (1)

- ERG agrees that Metry 2022 may be suitable source for estimating probability of transplantation but is unclear why other studies identified in the company's search were not considered further
- Probability of transplant fluctuates with age groups so company's approach of using one overall probability for people with PH1 represents an extreme simplification of clinical reality

New evidence

Key issue: Probability of transplant in CKD 4 + ESKD (3)

ERG comments (2)

- ERG included an additional 37 sequential liver-kidney transplants which were observed in study
- ERG considered it unlikely that all people would be observed for 41 years → [redacted] and included people who had been followed up since birth. ERG estimates higher rate of transplant

	Company	ERG
Population in Metry	993 with PH1	[redacted] with PH1 + follow up since birth
Annual rate of transplants	159 transplants over 41 years follow up = 3.9/year	196 over [redacted] years (average age of Metry cohort who have been in registry from birth)= [redacted]
Estimate of Metry population in CKD 4 or ESKD health states	993 * 0.376 (Singh 2021 [study from which CKD stage distribution was derived for the company submission) = 373	[redacted] * 0.376 = [redacted]
Estimate of annual rate of transplants in CKD 4 or ESKD	3.9/373= 0.01	[redacted]/[redacted]= [redacted]
Estimate of rate per cycle (6 months)	0.005	0.012

New evidence

Key issue: Probability of transplant in CKD 4 + ESKD (4)

Comments from clinical expert (paediatric nephrologist)

- Currently there is around 1 transplant every 2 to 3 years in children with PH1 in the UK
- This rate seems to line up with the company's estimate, considering the size of the UK paediatric PH1 population and how it compares to the size of the OxalEurope cohort
- It is extremely difficult to make any firm conclusions about how transplant rates vary with age as:
  - it depends on a combination of individual patient characteristics
  - it depends on practices at the level of the individual institution and team caring for the patient
  - very few transplants take place overall
- Data from the only UK tertiary referral centre for paediatric combined transplantation shows that liver or liver-kidney transplantation occurred in 14 children over a 32-year period (1990 to 2022)

Which transplant probability should be used in the model for people with uncontrolled oxalate levels?

New evidence

Key issue: Utility values (1)

Background (1)

- Utility values for people in CKD 4 and ESKD health states could not be obtained from ILLUMINATE-A and HRQoL data from ILLUMINATE-C were not considered appropriate by the company
- Company did a vignette study to estimate utilities for the CKD 4 and ESKD health states for people with uncontrolled oxalate on high-intensity dialysis and post-transplant health states in the model
- For the remaining CKD and ESKD health states, the company used data from the ILLUMINATE-A study and the literature to estimate utility values
- Company base case used the EQ-5D-5L based valuations of the vignettes (mapped to EQ-5D-3L)
- ERG considered that utilities derived from the EQ-5D-based valuation of the vignettes for the CKD 1 to 3b health states lacked face validity compared with those measured in ILLUMINATE-A
    - committee agreed with ERG's preference for TTO valuations of the vignettes

	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]				
CKD 3b	[redacted]	[redacted]				
CKD 4	[redacted]	[redacted]		[redacted]	[redacted]	
ESKD	[redacted]	[redacted]		[redacted]	[redacted]	
Post-cLKT	[redacted]	[redacted]		[redacted]	[redacted]	

New evidence

Key issue: Utility values (2)

Background (2)

- Committee suggested company to provide EQ-5D data from ILLUMINATE-C and to conduct an analysis to derive more accurate utility estimates for the late CKD and post-transplant health states

Company ECD response (1)

- There is a lack of robust EQ-5D data from ILLUMINATE-C for each subgroup included in the model and so it is not feasible to derive utilities for the advanced-disease health states from this study
- EQ-5D scores at initial valuation for a subgroup from ILLUMINATE-C (mainly children on dialysis - see below) show closer agreement with the utilities derived by EQ-5D rather than TTO valuation

Patient (n=[redacted])	Index score	Vignettes - child	
		EQ-5D-5L	TTO
		[redacted] (CKD 4) [redacted] (ESKD)	[redacted] (CKD 4) [redacted] (ESKD)
Average	[redacted]		

New evidence

Key issue: Utility values (3)

Company ECD response (2)

- NICE DSU guidance states that EQ-5D is preferred over TTO for vignette valuation
- This preference is reflected in the updated NICE methods and process manual (2022)
- EQ-5D method is better suited to capturing complexity and specific impacts of PH1 health states

ERG comments

- ERG agrees that using the EQ-5D valuations of the vignettes is the preferred choice based on current NICE methods guidance
- It may be acceptable to deviate from this because utilities measured in ILLUMINATE-A are more aligned with the TTO-derived utilities than the EQ-5D-derived utilities from the vignette study
- Average of the utilities from the [redacted] patients in ILLUMINATE-C sits between the EQ-5D-derived utilities and the TTO-derived utilities providing little support for one option over the other
- ERG preference is to retain the TTO values which significantly increases the ICER
- ERG scenario analysis using the average utility observed from ILLUMINATE-C significantly reduces the ICER

Which valuation of the health-state vignettes is more appropriate to derive utilities for the CKD 4, ESKD and post-transplantation health states?

Key issue: Dialysis assumptions (1)

Background: how dialysis rates are modelled

- In standard care arm (CKD 4 and ESKD) all people have high-intensity dialysis for 7 days per week
- In lumasiran arm, no people with CKD 4 have dialysis & all people with ESKD have normal-intensity dialysis
- ERG considered there to be a disconnect between the dialysis schedules suggested by the company's clinical experts and the schedules used in the model
- Clinical experts in ECM1 suggested that:
  - although ideal dialysis regimen for people with uncontrolled oxalate is high intensity haemodialysis 7 times a week NHS capacity/practicalities for patients/families means the frequency of dialysis is reduced to around 3-4 times/week with a maximum of 6 days/week
  - dialysis would be considered for children and adults with CKD 4 to prevent disease progression ahead of transplant, but that it is more frequently used in ESKD
- Committee: people having lumasiran with ESKD would still have dialysis but less intensive dialysis
- Committee: suggested for the company to provide scenario analyses which varied the intensity of dialysis schedules to identify inputs that were more clinically plausible:
  - for people having standard care in CKD 4
  - for people having lumasiran in ESKD

Key issue: Dialysis assumptions (2)

Company ECD response

- Company has updated dialysis assumptions in its base case analysis and performed scenarios exploring alternative proportions of adults with CKD 4 on standard care having dialysis

Dialysis	Proportion in model (company original base case)	Proportion in model (company revised base case)	Scenario analysis 1	Scenario analysis 2
High-intensity dialysis (standard care arm)				
CKD 4 - children	100%	100%	100%	100%
CKD 4 - adults	100%	**25%**	**50%**	**0%**
ESKD	100%	100%		
Normal-intensity dialysis (lumasiran arm)				
CKD 4 - children	0%	**50%**	50%	50%
CKD 4 - adults	0%	0%	0%	0%
ESKD	100%	100%		

Key issue: Dialysis assumptions (3)

Comments from clinical expert (paediatric nephrologist)

- Company's revised assumptions for children appear to be appropriate
- For children with PH1 producing very high levels of oxalate (as would be the case for all those without effective treatment) it would be critical for them to have high-intensity dialysis to slow systemic oxalate accumulation as much as possible, starting at CKD 4
- For children who are receiving lumasiran, and particularly where lumasiran is started very soon after diagnosis, there will be less need for dialysis to remove oxalate from systemic deposition
  - there may be cases where children do need dialysis such as to remove oxalate from deposits that were built up before lumasiran was started and where a diagnosis was delayed
  - it is unclear what proportion of peoplw would fall into this category of needing dialysis in CKD 4 while on lumasiran, but 50% seems to be a reasonable assumption

Are the company's modelling assumptions on the use of dialysis in CKD stage 4 and ESKD health states clinically plausible?

Other issues

Company's modelling assumptions:

- Survival after transplant
- Rate of disease progression
- Subpopulations treated with lumasiran
- Lumasiran continuation rule

Other issues: company's modelling assumptions (1)

Small impact on ICER

Company's ECD response: survival after transplant

- Company used data from a study (Jamieson 2005) in people with PH1 having standard care to model overall survival after a liver–kidney transplant
- The study estimated survival curves based on a person's pre-operative condition (very good, good, fair and poor). Company assumed that:
  - survival for people in very good and good condition would be reflective of survival for people with controlled oxalate levels
  - survival for people in fair and poor condition would be reflective of survival for people with uncontrolled oxalate levels
- As survival in the study was based on all people having standard care, the ERG and committee preferred to assume that overall survival in Jamieson 2005 is representative of survival for all people in the standard care group
- **Company base case updated to align with committee's preference on survival after transplant**

New evidence

Other issues: company's modelling assumptions (2)

Large impact on ICER

Company's ECD response: rate of disease progression (standard care arm)

- The original model based the transition probability for CKD 4 → ESKD on the ESKD-free survival curves reported by Harambat 2010 in the absence of a placebo arm in lumasiran studies
- Company's revised base case uses transitions from CKD 3b → CKD 4 and from CKD 4 → ESKD using a new study by Singh 2022 which reported the rate of eGFR decline as a function of CKD stage in people with PH1
- ERG considers that:
  - ESKD-free survival curve in Harambat 2010 is not specific to people with PH1 who are already in CKD 4, but is based on follow-up data from people in various stages of CKD
  - it makes sense that the probability of moving to ESKD (for people in CKD 4) is much higher that the probability of moving to ESKD for the average person with PH1
  - an incorrect approach was used in the previous model which has now been corrected

Other issues: company's modelling assumptions (3)

New assumption and scenarios

Small impact on ICER

Company's ECD response: subpopulations treated with lumasiran

- Clinical expert opinion in ECM1 highlighted that lumasiran would be initiated in all adults in CKD 3b or higher and only in those adults with earlier stages (CKD 1 to 3a) experiencing rapid progression
- Company has adjusted the health state distribution of the cohort at model start to assume that 50% of all prevalent adult in CKD 1 to 3a are fast progressors
- Company provided scenario analyses which varied the proportion of adults in CKD 1 to 3a who are fast progressors (10%, 25%, 75% and 100%)

New scenarios

Other issues: company's modelling assumptions (4)

Large impact on ICER

Company's ECD response: lumasiran continuation rule (1)

- Company considers that upon maturity, a person with paediatric-onset PH1 with mature kidneys could potentially sustain clearance of a higher background rate of oxalate production than they were able to sustain as a child with immature kidneys, and so:
  - oxalate production rates that were above normal during maturity might not lead to increased morbidity or mortality in such people
  - in the absence of severe renal impairment, it could be appropriate to pause lumasiran treatment at maturity with criteria for re-initiation of treatment if there are signs of progression
- Company has not included a continuation rule in its base case because there is no data available to inform the proportion of people that would remain stable after lumasiran treatment interruption
- Company scenario analyses:
  - lumasiran is discontinued in people with paediatric onset PH1 who are in CKD 1-3b upon onset of adulthood
  - re-initiation of treatment is modelled by returning different proportions of these discontinued patients to lumasiran over time within 10 years (10%, 30% 50%, 70%, 90%)

New scenarios

Other issues: company's modelling assumptions (5)

Large impact on ICER

Lumasiran continuation rule (2) - comments from clinical expert (paediatric nephrologist)

- Stopping treatment could be clinically appropriate in this scenario, if the person has reached maturity with stabilised, acceptable renal function
- The decision would very much need to be made on a person-by-person basis
- It might well be a consideration in a young person who is pyridoxine responsive and has shown stability of renal function over the last 3 years, and for young women who have stable renal function and who wish to conceive
- It would be inappropriate to follow this approach for people with infantile-onset disease who reach maturity, because their infantile-onset disease is a sign that they have a fundamentally aggressive disease course that could resume when their treatment is stopped
- If lumasiran treatment is commenced early in children with infantile PH1 at the time of reasonable renal function then it is likely that this level of renal function will be preserved and may sustain them through adolescence

Cost effectiveness

NICE National Institute for Health and Care Excellence

Summary of company and ERG preferred assumptions

Assumption	Company revised base case	ERG revised base case
Probability of transplant for people with uncontrolled oxalate	0.005 (Metry 2022)*	0.012 (Metry 2022)*
Utility values for late CKD and post-transplant states	EQ-5D valuation of vignettes	**TTO valuation of vignettes**
Survival after transplant from Jamieson 2005	**Representative of survival for all people on standard care***	**Representative of survival for all people on standard care**

Assumptions in green boxes = committee preferred assumptions from ECM1
*These assumptions have been updated post ECM1

Additional committee considerations in ECD:

- Scenario analyses which varied the intensity of dialysis schedules in the model would help to identify inputs that were more clinically plausible
- These inputs would form part of its preferred assumptions and it would have liked to have seen separate analyses for the total population, for patients of all ages with infantile onset of PH1 and for infants with infantile onset of PH1 (subgroups included in the company's submission)

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]	-	-	-

Company consider that the ICERs are confidential but with the approved PAS are below £300,000 per QALY gained.

- Total QALYs were negative for people on standard care (change from ECM1 results)
- Most QALYs for lumasiran arm were accrued in CKD stage 1 to 3b and after a liver-kidney transplant
- People on standard care lost QALYs mainly in the ESKD uncontrolled oxalate health state
- Costs were primarily accrued in CKD stage 1 to 2 for lumasiran arm, but in ESKD for standard care arm
- Costs were mostly attributable to drug acquisition for lumasiran arm and dialysis for standard care arm

Company deterministic scenario analyses

ICERs include updated lumasiran PAS (discounted results)

No.	Scenario (applied to company base case)		ICER (£/QALY)
1	Company revised base case		[redacted]
2	Dialysis rates: standard care cohort on dialysis in CKD 4 (has minimal effect on ICER)	Adults 50%, paediatric: 100%	[redacted]
		Adults 0%, paediatric: 100%	[redacted]
3	Subpopulations treated with lumasiran: proportion of fast-progressors among adults in CKD 1 to 3a (lower proportion → lower ICER)	10%	[redacted]
		25%	[redacted]
		75%	[redacted]
		100%	[redacted]
4	Lumasiran continuation rule: paediatric-onset cohort in CKD 1 to 3b at adulthood onset discontinues lumasiran treatment; proportion restarting treatment at 10 years (lower proportion restarting →lower ICER)	10%	[redacted]
		30%	[redacted]
		50%	[redacted]
		70%	[redacted]
		90%	[redacted]

Subgroups

Deterministic ICERs include updated lumasiran PAS (discounted results)

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company revised base case	[redacted]	[redacted]	[redacted]
Subgroup 1: Infants with infantile onset of PH1	[redacted]	[redacted]	Dominant
Subgroup 2: Patients of all ages with infantile onset of PH1	[redacted]	[redacted]	[redacted]

Comments from clinical expert (paediatric nephrologist)

- All people in subgroups 1 and 2 fall into the single group with infantile onset PH1
- There is no necessity to distinguish between the subgroups as their clinical course is similar
- The unmet need is similarly high in both subgroups
- At any point in life whether in infancy or later, people whose first signs of disease appeared when they were infants have a much poorer prognosis, with a significantly higher mortality and faster progression to ESKD

Cost effectiveness results – ERG updated 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]	-	-	-

Company consider that the ICERs are confidential but with the approved PAS are above £300,000 per QALY gained.

ERG deterministic key scenarios

ICERs include updated lumasiran PAS (discounted results)

Scenario	ICER (£/QALY)
Company revised base case	[redacted]
ERG change 1 – probability of transplantation	[redacted]
ERG change 2 – utility values (TTO values vignettes)	[redacted]
Updated ERG base case (1 and 2 combined)	[redacted]
Scenario 1: ERG base case with EQ-5D utility average from ILLUMINATE-C	[redacted]
Subgroup 1: Infants with infantile onset of PH1	Dominant
Subgroup 2: Patients of all ages with infantile onset of PH1	[redacted]

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	Incremental QALYs	
	Undiscounted	Discounted
Company revised base case	[redacted]	[redacted]
ERG updated base case	[redacted]	[redacted]

Other considerations

- Equality issues
- Factors affecting the guidance

Equality issues considered in ECM1

Background

- 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

Committee considerations in ECD

- 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
- Conclusion → there are no equality issues relevant to the recommendations

Consultation comments

- 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 medication

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

Factors affecting the guidance

- 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
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 issues for consideration

Key issues		Impact on ICER
Transplant probability	Which transplant probability should be used in the model for people with uncontrolled oxalate levels?	
Utility values	Which valuation of the health-state vignettes is more appropriate to derive utilities for the CKD 4, ESKD and post-transplantation health states?	
Dialysis assumptions	Are the company's modelling assumptions on the use of dialysis in CKD 4 and ESKD health states clinically plausible?	

 Model driver

 Small impact