NICE National Institute for Health and Care Excellence

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Lumasiran for treating primary hyperoxaluria type 1 [ID3765]

Lead team presentation

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Company: Alnylam Pharmaceuticals
ECM1: 13 April 2022

Key abbreviations

AGT	Alanine-glyoxylate aminotransferase	ICER	Incremental cost-effectiveness ratio
CI	Confidence interval	LYG	Life years gained
CKD	Chronic kidney disease	MA	Marketing authorisation
cLKT	Combined liver-kidney transplantation	PH	Primary hyperoxaluria
EAMS	Early Access to Medicines Scheme	PH1	Primary hyperoxaluria type 1
ECM	Established clinical management	QALY	Quality-adjusted life year
eGFR	Estimated glomerular filtration rate	RCT	Randomised controlled trial
eMIT	Drugs and pharmaceutical electronic market information tool	SD	Standard deviation
ESKD	End stage kidney disease	SE	Standard error
EQ-5D	European Quality of Life-5 dimensions	SmPC	Summary of product characteristics
HRQoL	Health-related quality of life	TTO	Time trade off

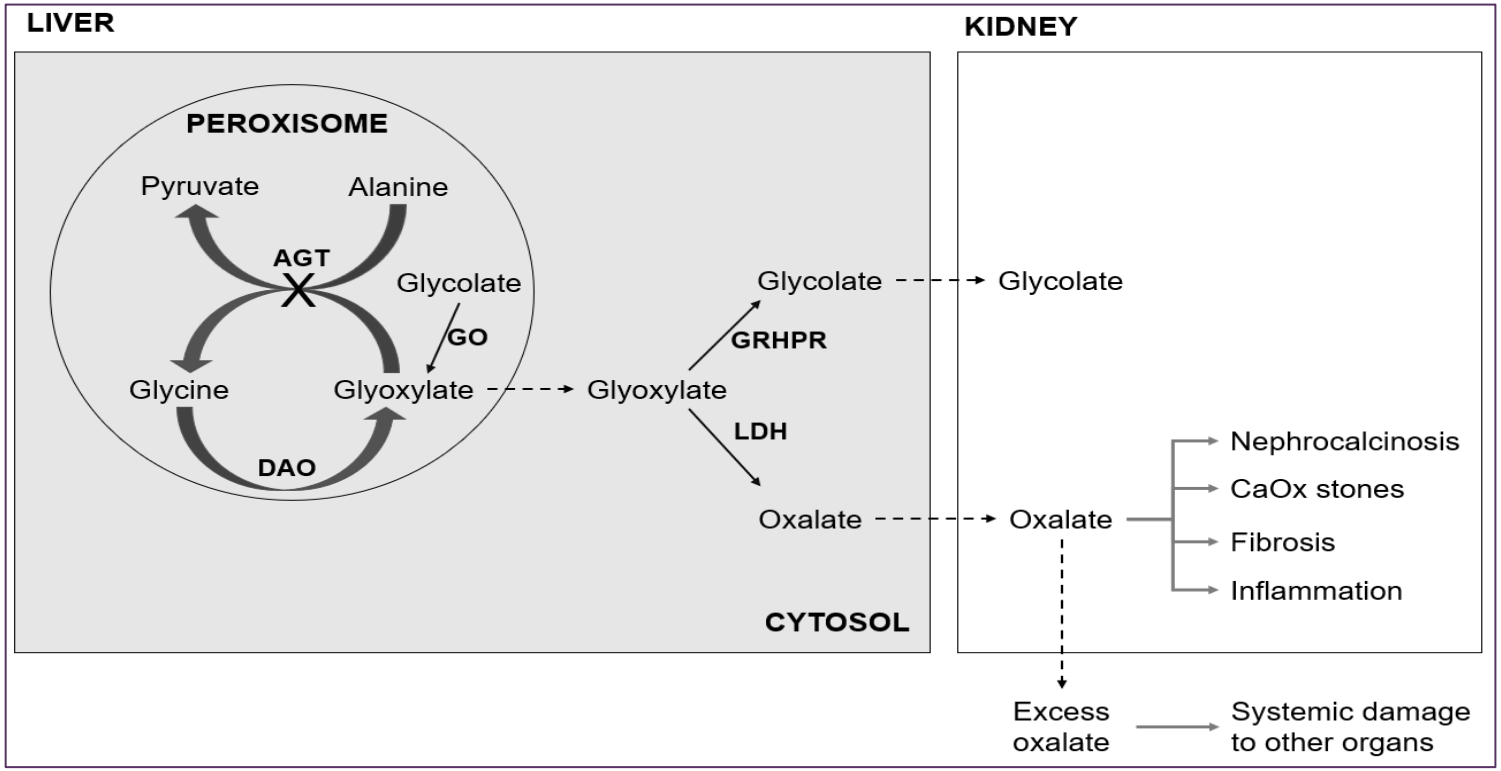
Overview of disease background

- Primary hyperoxaluria (PH) is a group of rare, genetic disorders of oxalate metabolism and includes subtypes 1 (PH1), 2 and 3.
- PH1 is the most common of all subtypes (70-80% of PH cases) and the most severe.
- 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.
- The incidence of PH1 in Europe has been estimated as 1 in 100,000 live births per year.
- Company considers that [redacted] people would be eligible for treatment with lumasiran in year 1 rising to [redacted] people in year 5.
- However, the number of people expected to receive lumasiran is likely to be lower based on company's expected uptake ([redacted] in year 1→ [redacted] uptake, [redacted] in year 5 → [redacted] uptake)

Sources: Company submission, NICE final scope [ID3765]

Pathophysiology of PH1

- PH1 is caused by a mutation of the AGXT gene which causes a deficiency of the liver-specific enzyme, alanine-glyoxylate aminotransferase (AGT).
- AGT catalyses transamination of glyoxylate to glycine.
- The deficiency of AGT leads to the accumulation of glyoxylate substrate and subsequent overproduction of oxalate.
- Oxalate readily binds to calcium, to form toxic calcium oxalate crystals which trigger an inflammatory response.



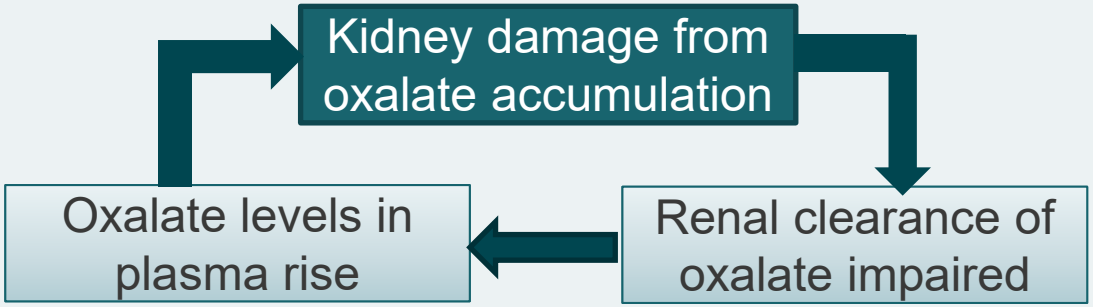
Source: company submission

Diagnosis of PH1

- PH1 is present from birth and clinical manifestations often appear in childhood and continue into adulthood.
- PH1 can remain undiagnosed for several years after the onset of symptoms due to:
    - rarity of disease
    - non-specific symptoms (e.g. renal stones, renal impairment)
- Diagnostic tools include biochemical urine analysis and genetic studies:
    - excess oxalate excretion in the urine can indicate hyperoxaluria
    - subsequent genetic testing can then determine whether hyperoxaluria is associated with an underlying genetic defect (as occurs in PH), and determine which gene is involved (AGXT if PH1).
- Some people are diagnosed following familial screening, which focuses on siblings of already diagnosed patients.
- Pre-natal screening for PH1 is not routinely performed in the UK.

Disease burden (1)

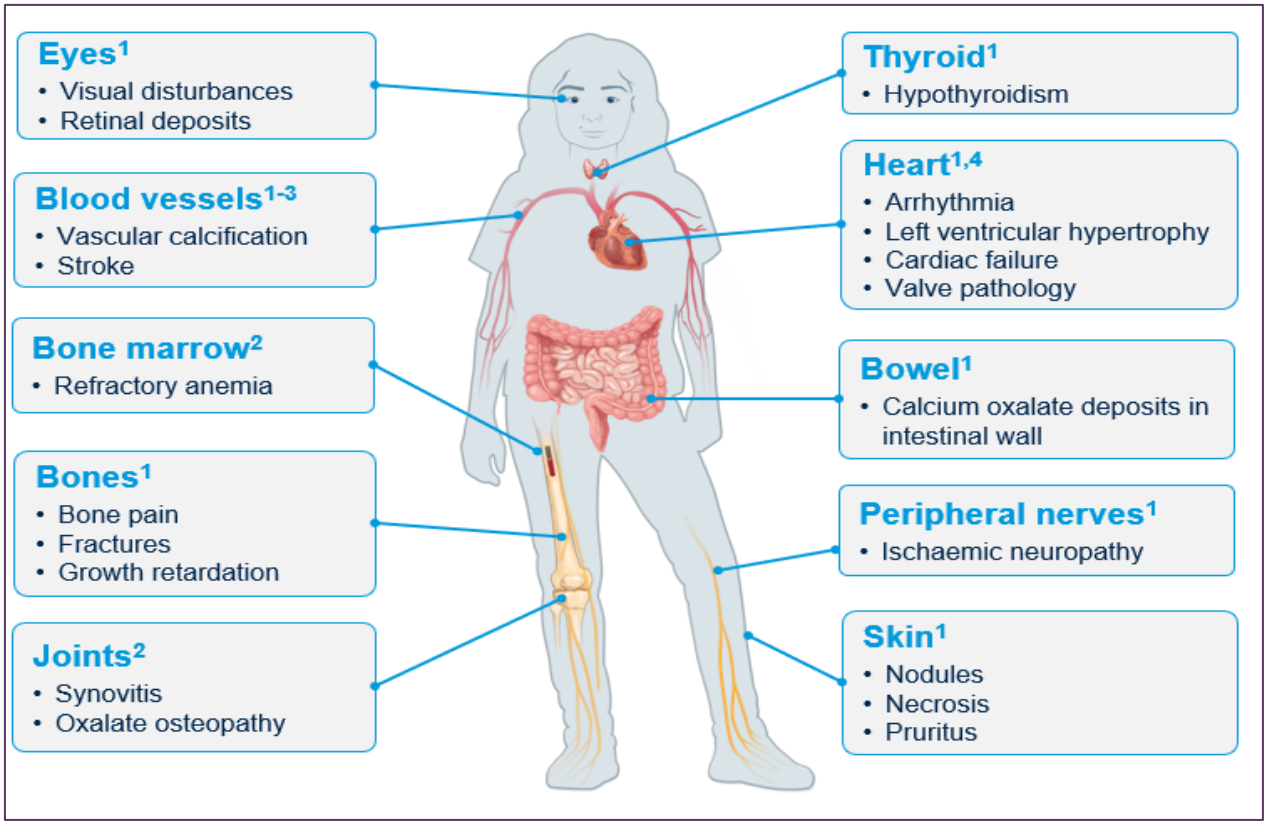
- Severity of symptoms may vary significantly between people with PH1 and disease progression can be rapid and unpredictable.
- Chronic deposition of calcium oxalate crystals in the kidneys results in progressive loss of renal function and can cause acute kidney injury.
- Oxalate may also result in acute kidney injury due to aggregation into stones causing obstruction of urinary outflow.
- Feedback loop results in continued kidney damage:



- Excess oxalate accumulation often causes progression to end stage kidney disease (ESKD) because of loss of renal function.
- Symptoms are most severe for people with infantile onset of PH1, with rapid progression to ESKD and significantly reduced survival compared to those with later onset of disease.

Disease burden (2)

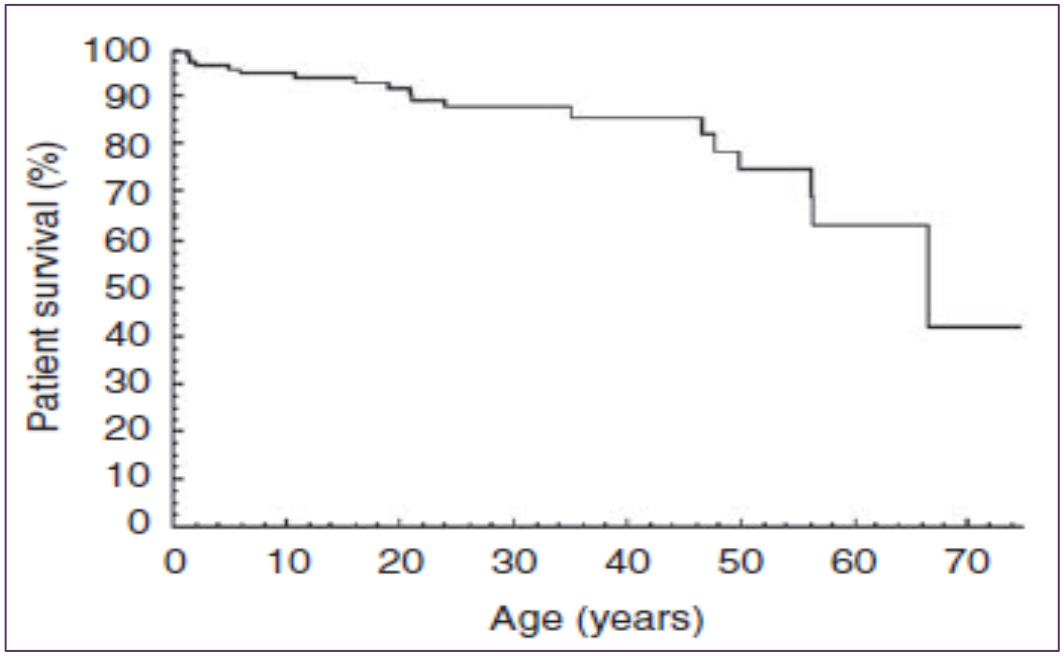
- As renal impairment progresses, oxalate levels in the body rise and oxalate crystals may be deposited across the body (known as systemic oxalosis).
- Systemic oxalosis can cause severe complications such as vision loss, fractures, cardiac insufficiency, skeletal pain, skin ulcers, arrythmias and peripheral neuropathy.
- In children, systemic deposition of oxalate may cause failure to thrive, growth retardation and disability due to bone, joint and eye damage.



Source: company submission

Life expectancy in people with PH1

- Mortality in PH1 is largely due to ESKD, dialysis, transplantation or systemic oxalosis complications.
- No published data on the average life expectancy of people with PH1 in the UK.
- European registry data (OxalEurope) reported cumulative survival rates of 95%, 93%, 85% and 74% at ages 5, 10, 30, and 50 years, respectively, in a cohort of 526 people with PH1.
- A study (Harambat 2010) has also published cumulative overall survival in a cohort of 155 people with PH1 – see figure below. Cumulative survival rates were similar to the OxalEurope Registry findings.



Source: company submission

Lumasiran (Oxlumo, Alnylam Pharmaceuticals)

Marketing authorisation (MA)	Lumasiran is indicated for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups. (Full UK MA received January 2021)
Mechanism of action	Ribonucleic acid interference (RNAi) therapeutic which uses gene silencing to target an enzyme (glycolate oxidase) in the liver which reduces oxalate production.
Administration	Subcutaneous injection, dosing based on body weight: • loading dose → administered monthly for 3 months • maintenance dose → monthly if body weight <10 kg, every 3 months if body weight ≥10 kg.
Price	The list price is £61,068.98 per 94.5 mg vial (excluding VAT) If the technology is approved it will be provided to the NHS with a confidential discount (simple discount patient access scheme).

- Treatment is likely to be administered over a person's lifetime or until combined/sequential liver-kidney transplantation.
- Homecare may be appropriate but will not be required for all patients given the infrequent dosing schedule and periodic monitoring requirements.
- Lumasiran is available to [redacted] people who entered the Early Access to Medicines Scheme (EAMS) before marketing authorisation was obtained. Data collection was not mandated for these people.

Current treatment options (1)

Earlier stages of disease (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 - around 5-10% of people with PH1 retain some level of AGT activity and have the potential to fully respond to pyridoxine, but treatment may still not result in normalisation of oxalate levels.
- Treatment of renal stones may occur at all stages of disease and may include shockwave lithotripsy and percutaneous nephrolithotomy.

Advanced stages of renal decline

- Dialysis may be initiated to slow the build up of systemic oxalate and/or replace lost renal function:
  - people with PH1 require more frequent haemodialysis and peritoneal dialysis sessions (6-7 times/week compared with 3 times/week for conventional dialysis schedules which are usually insufficient for lowering oxalate levels)
  - dialysis schedules in PH1 may not be sufficient to consistently lower oxalate levels.

Current treatment options (2)

End stage kidney disease (ESKD)

- Liver transplantation (with or without kidney transplant) can eliminate PH1 as the source of excess oxalate production is removed.
- Company considers that a combined/sequential liver-kidney transplant is required:
  - transplantation of the liver resolves the overproduction of oxalate in the liver
  - transplantation of the kidney is required to restore lost renal function and eliminate the need for continued dialysis.
- Transplantation is associated with morbidity and mortality, with outcomes often dependant on a person's oxalate levels prior to transplantation.

Company's positioning of technology

- People with PH1 who have not already received a liver or combined liver-kidney transplant:
  - all children with elevated oxalate levels despite established clinical management should be eligible for treatment with lumasiran
  - in adults, lumasiran treatment should be limited to those in later stages of chronic kidney disease with exceptions for those with progression or severe comorbidities in earlier stages of kidney disease
  - currently unknown if lumasiran would be initiated in people with early-stage disease without rapid signs of progression or if treatment will vary by individual characteristics.

⊙ ***Is the company's positioning of lumasiran appropriate?***

NHS England and Improvement perspective

- There are no national NHSE clinical commissioning policies for PH1.
- Currently, the treatment of people with PH1 is provided in adult specialist renal services, adult renal transplant centres and specialist renal services for children.
- 2 adult and 2 paediatric specialist renal centres* are members of the Hyperoxaluria Rare Disease Collaborative Network which are not commissioned services but would provide a structure through which the technology could be distributed if recommended.
- There may be a reduced need for dialysis and organ transplantation if lumasiran is recommended for people with PH1. However, this will not have a significant impact on resource use given the small population size and the high volume of need for both dialysis and organ transplantation for other clinical indications.
- If lumasiran was recommended:
    - this would represent a step-change in the care of people with PH1
    - no additional training of NHS staff would be required.

*Centres include: Birmingham Women's and Children's NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Great Ormond Street Hospital, Royal Free London NHS Foundation Trust

Comments from 2 patient and professional organisations and 1 clinical expert (1)

Burden of disease

- PH1 reduces life expectancy, particularly in early infancy due to systemic oxalosis.
- The physical and psychosocial impact of living with PH1 is significant for patients and carers. Most patients surveyed considered their quality of life to be poor, with their ability to carry out daily activities often impacted.
    - *"The support required for daily living demands an arduous regime, a cycle of medication administration alongside navigating the impact that those medicines have on the patient."*
- There is a lack of understanding of the condition amongst healthcare professionals which results in delayed diagnosis or misdiagnosis and a lack of psychosocial support for patients.
    - A young adult living with PH1 was interviewed - their parents struggled to understand and manage the condition and when they reached adulthood they sought help from a peer support group.

Comments from 2 patient and professional organisations and 1 clinical expert (2)

Current treatment and unmet need

- Patients and carers often find current treatments for PH1 debilitating, anxiety inducing and difficult to adhere to. Treatments often require specialist hospital admissions and regular outpatient follow-up which are associated with significant resource use.
    - Despite these difficulties, most patients and carers surveyed feel that current treatment options enable them to control their symptoms well.
    - Biggest drawbacks of current treatment: ‘demanding’ intake of fluids, continuous medication, increased hospital visits as the disease progresses, reliance on transplants and the risks/challenges/anxiety associated with organ rejection, surgical complications, and further medication.
- Pyridoxine is clinically effective in less than 25% of all people with PH1, depending on genetic mutation. Currently, there are no available treatments for pyridoxine non-responders with progressive disease.

Comments from 2 patient and professional organisations and 1 clinical expert (3)

Current treatment and unmet need

- Allowing the disease to progress untreated often leads to organ damage and the need for transplantation which is expensive, difficult for the patient, and has generally unfavourable long-term outcomes (affects whole body not just the kidneys).
    - 50% of patients surveyed commented that prescription medication is often followed by a kidney/liver transplant as a form of treatment and condition management.
    - Without effective treatment kidney failure occurs in patients at a young age and reduces life expectancy.
    - Even with treatment, school attendance can be challenging due to ill health, giving limited opportunity to be able to eventually gain full time employment.

Metabolic Support UK case study

Parent/carer with 2 children living with PH1 (patients Y and Z)

- **Patient Y:** diagnosed with severe infantile PH1 at 7 months, severe renal failure, currently dialysis dependent and has received a liver transplant, parent/carer describes the patient's bones as 'fragile and wrecked' and experiences oxalate deposits in their eyes.
- **Patient Z (currently aged 10):** diagnosed at the age of 2, less severe PH1, required emergency kidney stone surgery, will require a liver transplant, suffers from multiple stomach aches and recurrent kidney stones.
    - received a ureteroscopy and so high intake of fluids → frequent incontinence: *"there has been a battle at school who don't understand why it is necessary for her to leave the classroom so often for the toilet".*
- Current treatment for Patients Y and Z includes daily potassium citrate and pyridoxine to prevent kidney stones and drinking lots of fluids:
    - Parent/carer described adherence issues with potassium citrate due to taste: *"a vile medicine which you have to drink and it's like pure lemon juice, very difficult to get a child to take it"*
    - Parent/carer wants to avoid dialysis/transplants for Patient Z after experience with transplant for Patient Y which was 'life-altering' and 'hugely disruptive'. Also concerned about immunosuppression and the longevity of a transplant.

Comments from 2 patient and professional organisations and 1 clinical expert (4)

Lumasiran offers benefits to people with PH1

- This technology represents a step-change in the treatment of a life threatening condition, and meets an area of clinical need.
- Lumasiran has the potential to reduce rate of kidney stone formation and slow progression to ESKD, preventing the need for dialysis and future liver/kidney transplants.
- Increased life expectance has been observed from real-world data in infants with infantile oxalosis phenotype treated with lumasiran via the EAMS.
- The treatment will be easy to administer in hospitals or community and is less onerous compared to current treatments. Because lumasiran is administered by injection, this may be difficult for some people, particularly in young children or those with needle phobia.
- Data from the trials show a clinically significant reduction in urinary oxalate excretion in people treated with lumasiran and the trial populations reflect likely future usage in the UK.
- Trial data indicates that injection-related adverse events are mild, but long term safety is yet to be established.

We would like to thank Metabolic Support UK, the UK Kidney Association and the clinical expert for their submissions.

Company decision problem → compared to NICE scope

Population	People with PH1 (who have not already undergone a liver transplant or a combined liver-kidney transplant – re-defined after clarification) **→ narrower than NICE scope as shown by text in brackets**
Intervention	Lumasiran [with established clinical management (ECM) – see below]
Comparators	ECM without lumasiran: - pyridoxine, oxalate-controlled diet, liver transplant with a combined or sequential kidney transplant, haemodialysis, hyperhydration **→ isolated liver transplant not included as the company considers that it is not standard practice and may be associated with poorer outcomes compared to combined/sequential liver-kidney transplantation.** **→ ERG considers that no evidence was provided to support this assumption and impact of exclusion is uncertain.**
Outcomes	Oxalate levels, change in eGFR, need for liver transplant with a kidney transplant, mortality, adverse events of treatment, health-related quality of life **→ need for isolated liver transplant not included** **→ 2 additional outcomes included: renal stone events and systemic oxalosis**

- ***Should isolated liver transplant be included as a relevant comparator?***
- ***Would lumasiran be used in people who continue to have high oxalate levels post-transplantation?***

Summary of clinical evidence

Clinical trial	Description of trial
ILLUMINATE-A	• Phase 3, randomised, double blind, placebo-controlled (6-months duration → **complete**) • Extension period (3-month blinded extension, 51-months open label period with both arms receiving lumasiran → **ongoing until January 2024)**
ILLUMINATE-B	• Phase 3, single-arm, open-label (6-months duration → **complete**) • Extension period (54-months → **ongoing until August 2024**)
ILLUMINATE-C	• Phase 3, single-arm, open-label (6-months duration → **complete**) • Extension period (54-months → **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**

- All participants continued their stable ECM (including hyperhydration, crystallisation inhibitors, pyridoxine) until month 12 for ILLUMINATE-A and month 6 for ILLUMINATE-B.
- Participants were able to continue their stable pyridoxine treatment until at least month 6 in ILLUMINATE-C.
- No indirect comparison analyses were conducted.

Clinical evidence - ILLUMINATE-A

Results for 6-month primary analysis

Population	People aged ≥6 years with PH1 and relatively preserved renal function
Setting	16 study sites in 8 countries: 3 UK sites with [redacted] participants
Intervention	Lumasiran + ECM (n=26)
Comparator	Matched placebo + ECM (n=13)
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}
Key secondary outcomes from baseline to month 6 (unless stated otherwise)	• Absolute change in 24-hour urinary oxalate, percentage and absolute changes in plasma oxalate were all reduced in the lumasiran compared to placebo arm. • eGFR remained relatively stable for both treatment groups and no deaths were recorded. HRQoL→ mean (SD) change in the EQ-5D VAS was [redacted] for the lumasiran arm and [redacted] for the placebo arm. • Rate of renal stone events (per person year) 12 months prior to the trial compared to during the 6-month double-blind period reduced in the lumasiran arm and increased in the placebo arm

ERG comments on comparability of baseline characteristics:

- HRQoL → assuming comparability, the difference is not clinically meaningful.
- Rate of renal stone events → groups were not comparable at baseline.

*Data are expressed as least squares mean. Calculated as the mean change or mean percent change during months 3–6. Corrected for body surface area.

Clinical evidence - ILLUMINATE-B and ILLUMINATE-C

Results for 6-month primary analysis in terms of oxalate levels

	ILLUMINATE-B* (n=18)	ILLUMINATE-C (n=6 cohort A, n=15 cohort B)
Population	Infants and children aged <6 years with PH1 and relatively preserved renal function	People with PH1 and advanced renal disease: ○ Cohort A: people who do not yet require dialysis ○ Cohort B: people who are on dialysis
Setting	9 study sites in 5 countries: 1 UK site with [redacted] participants	15 study sites in 10 countries
Intervention	Lumasiran + ECM	Lumasiran + ECM
Percentage change in plasma oxalate from baseline to month 6	Effect size: -31.7%** (95% CI: -39.5 to -23.9)	• Cohort A effect size: -33.33% (95% CI: -81.82 to 15.16) • Cohort B effect size†: -42.43% (95% CI: -50.71 to -34.15)
Absolute change in plasma oxalate from baseline to month 6 (micromol/litre)	Effect size: -5.2** (95% CI: -6.2 to -4.2)	• Cohort A effect size: -35.28 (95% CI: -56.32 to -14.24) • Cohort B effect size†: -48.33 (95% CI: -55.85 to -40.80)

*Primary outcome of trial was outside of NICE scope (percent change in spot urinary oxalate: creatinine ratio from baseline to month 6). **Data are expressed as least squares mean. † Predialysis plasma oxalate in Cohort B.

Please note this slide has been updated post committee to correct factual inaccuracies.

Clinical evidence – ALN-GO1-001B and ALN-GO1-002

	ALN-GO1-001B (n=20) (Randomised phase, n=3 for each lumasiran cohort and n=1 for placebo for each lumasiran cohort. Open-label phase, n=8)	**ALN-GO1-002 (n=20)** (n=8 cohort 1) (n=7 cohort 2) (n=5 cohort 3)
Population	People aged ≥6 years with PH1 with urinary oxalate ≥0.7 mmol/1.73m^2/day and eGFR >45 mL/min/1.73m^2	People who were previously enrolled in ALN-G01-001B.
Intervention/ comparator	• Lumasiran dosing varied: ○ Cohort 1: 1 mg/kg monthly ○ Cohort 2: 3 mg/kg monthly ○ Cohort 3: 3 mg/kg every 3 months • Placebo	Lumasiran initiated at the same dosing regimen as in ALN-G01-001B.*
Outcome	Percentage change from baseline to day 85: • Urinary and plasma oxalate levels reduced in lumasiran cohorts versus placebo (where data available)	Relative to baseline in ALN-G01-001B: • Urinary and plasma oxalate levels decreased

ERG comments

- In ALN-GO1-001B, only 1 participant was randomly allocated to the placebo group in each of the 3 lumasiran cohorts which would not have reduced selection bias.
- Study was therefore not recognised by the ERG as a 'full RCT'.

*Cohort 1 were subsequently transitioned to Cohort 3 dosing to align with intended phase 3 maintenance dose.

Key issues relating to clinical evidence

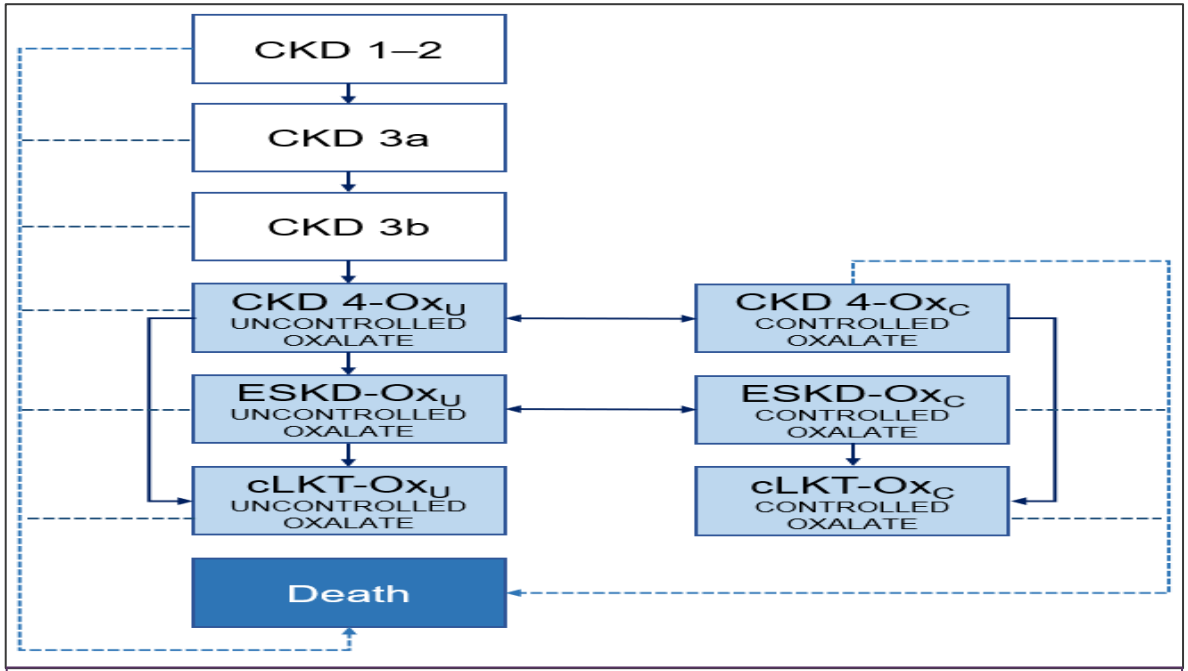
Issue		Impact
1	Low volume of robust clinical effectiveness evidence	
2	Proportion of people with PH1 eligible for lumasiran may be higher than stated	
3	Intermediate outcomes used may not link directly to relevant clinical endpoints	

 **Model driver**

 **Unknown impact**

 **Small impact**

Company's Markov model (1)

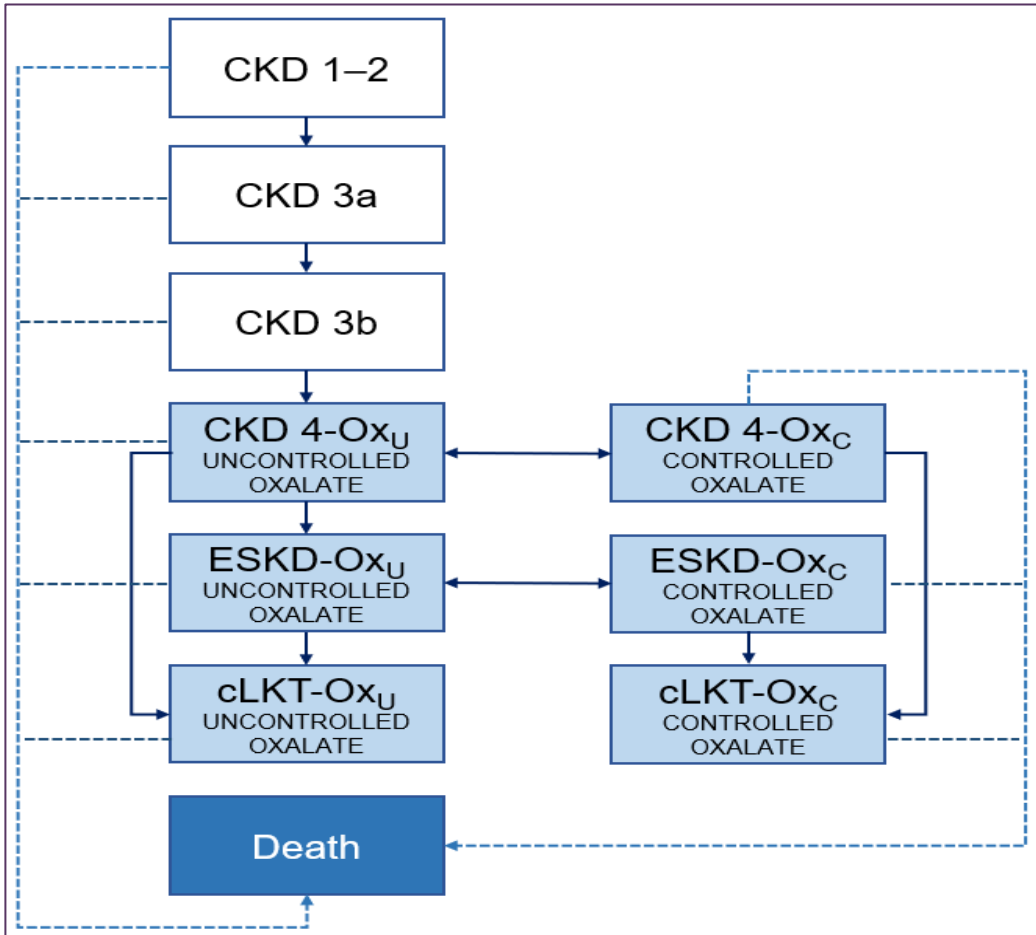


Key: CKD = chronic kidney disease; cLKT=combined/sequential liver-kidney transplantation; ESKD = end stage kidney disease; Ox_C=controlled oxalate levels; Ox_U=uncontrolled oxalate levels

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 ECM in a simulated cohort of people with PH1.
- No disease-specific classification system exists for categorising disease severity in PH1, so company used CKD stages as health states (loss of kidney function main feature of PH1).
- CKD stages are defined by estimated glomerular filtration rate (eGFR) –see table above.
- 9 health states defined by CKD stage, plasma oxalate levels, and/or transplant status, plus death.
- A threshold of 50 micromol/litre plasma oxalate was used to distinguish between controlled versus uncontrolled oxalate levels.
- Cycle length of 6 months over a lifetime time horizon.

Company's Markov model (2)



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

- For the CKD 4 and ESKD health states, transition between the uncontrolled oxalate and controlled oxalate states is permitted.
- People on ECM progressing beyond CKD 3b or entering the model with late-stage disease are assumed to have uncontrolled oxalate levels, only people in the lumasiran cohort can move to the states with controlled oxalate levels.
- People in the CKD 4 controlled oxalate health state are assumed to be stable and do not experience further disease progression.
- People in CKD 4 or ESKD health states may undergo combined/sequential liver–kidney transplantation → those with uncontrolled oxalate are assumed to have poorer outcomes post transplantation than those with controlled oxalate.
- Treatment with lumasiran is continued across all CKD stages (including early stages).

⊙ ***Is a plasma oxalate threshold of* 50 micromol/litre appropriate for determining systemic oxalosis in people with PH1?**

Baseline model cohort characteristics

Characteristic	Model input	Source
Initial age (years)		
Paediatric population	[redacted]	ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C at baseline, children <18 years
Adult population	[redacted]	ILLUMINATE-A and ILLUMINATE-C at baseline, adults ≥18 years
Mean weight (kg)		
Paediatric population	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline, children <18 years
Adult population	[redacted]	ILLUMINATE-A and ILLUMINATE-C at baseline, adults ≥18 years
Percentage of males	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline
Percentage of paediatric patients	[redacted]	Pooled ILLUMINATE-A, and ILLUMINATE-B, and ILLUMINATE-C at baseline

- Same model structure used for paediatric and adult populations but separate starting inputs were used for each population.
- Results of economic analysis are reported as the weighted average of both paediatric and adult populations.

Key issues relating to cost effectiveness

Issue		Impact
4	Modelling of disease progression	
5	Probability of transplantation	
6	Time trade off values vignettes	
7	Dialysis regimes	

Model driver **Unknown impact** **Small impact**

Key issues

Key issue 1: Low volume of robust clinical effectiveness evidence

- Company submission consists of 2 small RCTs, both with a maximum follow-up period of 6-months for the double-blind phase.
- Both RCTs have non-comparative extension phases and 2 additional single-arm studies were identified.

ERG comments

- ERG identified examples where groups were not comparable at baseline which makes conclusions for these outcomes unreliable.
- Some of the outcomes have been analysed in subtly different ways (such as oxalate in terms of absolute and percentage change) which may increase the risk of type I errors.
- Larger RCTs comparing lumasiran with relevant comparators would decrease uncertainty. However, due to the rare nature of the disease, these trials are not available.
- ERG has limited confidence that some of the observed effects in the non-randomised evidence truly reflect the treatment effects of lumasiran.

⊙ ***How robust is the clinical evidence for lumasiran in terms of decision-making?***

Key issue 2: Proportion of people with PH1 eligible for lumasiran may be higher than stated

- It is estimated that there are [redacted] people with PH1 in the UK based on the National Registry of Rare Kidney Diseases (RaDaR) estimates of the overall hyperoxaluria population in the UK and published diagnosis rates.
- Clinical expert opinion assumes that [redacted] of these people (n=[redacted]) have not already undergone transplantation and that there will be approximately [redacted] new people with PH1 eligible for lumasiran each year (ERG could not confirm the above incidence figure).
- Company considers that [redacted] people would be eligible for treatment with lumasiran in year 1.

ERG comments

- Recruitment to RaDaR is voluntary and the number of recruits will likely be a subset of the total number with the disease:
  - the total eligible population for lumasiran may be larger than stated in the company submission.
- However, as the disease is rare, the impact on the current estimation of the budget impact is likely to be small.
- Further data is needed to provide a more accurate estimate of the eligible target population.

⊙ ***Does the committee consider that a higher proportion of people would be eligible for treatment with lumasiran than estimated by the company?***

Key issue 3: Intermediate outcomes used may not link directly to relevant clinical endpoints (1)

- Change in urinary and plasma oxalate levels (measured in trials) are intermediate outcomes.
- Intermediate outcomes were used to predict clinical endpoints (e.g. mortality) and health-related quality of life (HRQoL).
- Company considers that measures of oxalate levels have been shown to predict renal function in people with PH1. Therefore, measures of oxalate production can be used to predict loss of HRQoL and mortality (due to renal disease), in line with the NICE scope.
- Submission from clinical expert states that:
  - urinary oxalate excretion is a widely accepted marker of kidney stone risk and long term kidney failure risk in people with PH1 who are able to pass urine
  - measures of plasma oxalate levels are helpful in people who are anuric (kidneys not producing any urine).

ERG comments

- 6-month follow-up in the RCTs may not be long enough to detect clinical endpoints and trials are likely to be statistically underpowered to detect clinical endpoints.
- Company did not undertake statistical methods for surrogate endpoint evaluation, so any prediction of the treatment effect on the final outcome (e.g. mortality, HRQoL) cannot be evaluated.

Key issue 3: Intermediate outcomes used may not link directly to relevant clinical endpoints (2)

ERG comments continued

- Recent study in people with PH1 who had neither undergone dialysis nor transplantation, suggested that plasma oxalate levels may have limited validity to predict clinical endpoints because of fluctuating values within individuals.*
- ERG remains uncertain about the extent to which urinary or plasma oxalate levels can predict clinical endpoints or HRQoL and note that this is likely to result in uncertainty when attempting to interpret the treatment effect for lumasiran.

⊙ ***Is the use of oxalate levels appropriate to predict renal function, mortality and HRQoL in people with PH1?***

*Hillebrand P, Hoppe B. Plasma oxalate levels in primary hyperoxaluria type I show significant intra-individual variation and do not correlate with kidney function. *Pediatr Nephrol* 2020;35(7):1227-1233.

Key issue 4: Modelling of disease progression

- Plasma oxalate levels are used as a surrogate outcome for kidney function in the model.
- Model assumes that disease progression (in terms of decreasing eGFR) depends on changes in plasma oxalate levels over time.

ERG comments

- Disease progression would also likely occur in people who sustain a steady, but very high, plasma oxalate level over time, so the company's model may underestimate the effect of lumasiran on eGFR (kidney function).
- In response to clarification, company provided an exploratory analyses using an alternative model structure which stratified the risk of progression through CKD stages based on data from the ILLUMINATE studies:
  - CKD 1 to 3b cohort split people into 2 separate strata: 1) people with normal or near normal oxalate levels and 2) people with above normal oxalate levels. The transition probabilities between CKD stages were differentiated for each stratum.
- ERG is uncertain if company's scenario addresses the issue. It considers that clinical expert opinion may be useful to validate the modelled length of time spent in each CKD class for people having ECM starting in CKD stages 1 to 3b.

Impact on ICER – small

- Company's exploratory analyses reduced the ICER.

⊙ ***Is the company's modelling of disease progression appropriate?***

Key issue 5: Probability of transplantation (1)

- **For people in CKD 4 and ESKD health states with controlled oxalate:**

  3-year rates of combined liver-kidney transplantation were estimated based on data from NHS Blood and Transplant 2021 and then transformed into a 6-month cycle probability:

  – company assumed that 100% of people in these health states would be placed on a waiting list and therefore transplantation rate is only dependant on organ availability.

- **For people in CKD 4 and ESKD health states with uncontrolled oxalate:**

  The company estimated liver-kidney transplantation rate based on a French study (Compagnon 2014) and transformed this into a 6-month cycle probability.

ERG comments

- The difference in transplantation probability between patients with controlled and uncontrolled plasma oxalate lacks face validity. Using these probabilities to find out how long people would have to wait for transplant would be on average:
  - 2.5 years for the paediatric cohort and 4 years for the adult cohort with controlled oxalate
  - 83 years for children and adults with uncontrolled oxalate (considered unrealistic)
- Compagnon 2014 reported data from 1979 to 2010. It seems plausible that during this period a shift from predominantly kidney transplantations to combined liver-kidney transplantations has taken place, which may explain the underestimate of the transplantation probability for people with uncontrolled oxalate.

Key issue 5: Probability of transplantation (2)

ERG comments continued

- Instead, the ERG prefers to estimate the probability of transplantation for people with uncontrolled oxalate in CKD 4 and ESKD health states by:
  - assuming that 50% of people having ECM in CKD 4 and ESKD health states would be placed on the transplantation waiting list, compared to 100% in the lumasiran group
  - ERG notes that this choice of percentage is arbitrary but considers it to be more realistic that the currently used estimate
  - scenarios using 25% and 75% of ECM patients entering transplantation waiting list were also explored by the ERG.
- ERG considers that evidence on transplantation rates in UK patients with PH1 (controlled and uncontrolled plasma oxalate) could inform model inputs in line with clinical practice.

Impact on ICER – significant

- Increasing the transplantation probability for people with uncontrolled oxalate levels increases the ICER (50% of eligible ECM population on waiting list - ERG base case)

⊙ ***What is the probability of transplantation in people with uncontrolled oxalate levels who are on a waiting list for a combined liver-kidney transplant?***

Key issue 6: Time trade off values vignettes (1)

- Utility values for people in CKD 1 to CKD 3b health states were obtained from pooled patient-level EQ-5D data collected at [redacted] in the ILLUMINATE-A study.
- Utility values for people in CKD 4 and ESKD health states could not be obtained from the ILLUMINATE-A study and HRQoL data from the ILLUMINATE-C study were not considered appropriate by the company.
- Therefore, the company conducted a health-state vignette study to estimate utilities for CKD 4 and ESKD health states with uncontrolled oxalate on high-intensity dialysis (represents ECM arm of model):
  - General public were interviewed to value the health states and completed the EQ-5D-5L questionnaire for each vignette, ranked the vignette on the visual analogue scale (from 0 to 100), and completed a TTO exercise to arrive at sets of utility values
  - Utility decrements were applied for systemic oxalosis complications that were not captured in the health-state vignettes.
  - Utility values for the post transplantation health states were also obtained from the vignette study with a one-off disutility applied for the burden of transplantation.
  - For the other health states*, the company used the utility decrement of CKD 4/ESKD relative to CKD 1–3b in non-PH1 populations (obtained from the literature) and applied it to the utility values obtained from ILLUMINATE-A to derive base utility values. To these values utility decrements related to systemic oxalosis complications and dialysis were applied.

*Includes CKD 4/ESKD with uncontrolled oxalate and normal intensity dialysis and CKD 4/ESKD with controlled oxalate and normal-/high intensity dialysis.

Key issue 6: Time trade off values vignettes (2)

Company base case uses EQ-5D-5L based valuation of the vignettes (mapped to EQ-5D-3L) to estimate utilities for CKD 4 and ESKD (uncontrolled oxalate and high-intensity dialysis) and post transplantation health states in the model.

ERG comments

- EQ-5D-5L may not be reliable in neurological or ophthalmologic conditions:
  - in the vignette study for paediatric patients, [redacted]
- For CKD 1-3b health states, the ERG considers that:
  - utilities derived from the EQ-5D-5L based valuation of the vignettes lack face validity when compared to utilities measured in the ILLUMINATE-A study
  - utilities derived from TTO valuations of the vignettes align better with the utilities measured in the ILLUMINATE-A study and so are more plausible– see next slide.
- Therefore, the ERG base case used the TTO valuations of the vignettes to estimate utilities for the CKD 4 and ESKD (uncontrolled oxalate and high-intensity dialysis) and post transplantation health states.

Key issue 6: Time trade off values vignettes (3)

EQ-5D-3L baseline utility values for CKD 1 to 3b

	Adults		Children	
	Mean	SE	Mean	SE
ILLUMINATE A [redacted] (company and ERG base case)	[redacted]	[redacted]	[redacted]	[redacted]

Utility data derived from health-state vignettes – mean (SD)

	Adult		Child	
	EQ-5D-5L	TTO	EQ-5D-5L	TTO
CKD 1-2	[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]

Impact on ICER – significant

- Changing the valuation of the vignettes from EQ-5D to TTO increases the ICER (ERG base case)

⊙ ***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 7: Dialysis regimes (1)

- In the model, it is assumed that all people in the ECM arm (both CKD 4 and ESKD) receive high-intensity dialysis (either haemodialysis or combined haemodialysis and peritoneal dialysis) for 7 days per week.
- In the lumasiran arm, no people with CKD 4 receive any type of dialysis and all people with ESKD receive normal-intensity dialysis.
- Company's submission includes estimates of the proportions of people in CKD 4 and ESKD who make use of dialysis regimens based on UK clinical expert opinion:
  - There are currently [redacted] people with PH1 receiving dialysis for 6 days per week.
  - However, experts estimated that haemodialysis for 6 days a week may be considered for [redacted] of people and that peritoneal dialysis (for an expected 7 days per week) may be considered for [redacted] of people in ESKD**, but not in CKD stage 4.**

ERG comments

- The company's assumption that all people in the ECM arm (both CKD 4 and ESKD) receive high-intensity dialysis for 7 days per week is in sharp contrast with the experts' estimates, lacks justification and therefore cannot be considered plausible.
- It is not clear what the inputs for people in the lumasiran arm receiving normal-intensity dialysis are based on.
- A patient record study (chart review) may help to find dialysis schedules to inform the model with inputs that are in line with clinical practice.

Key issue 7: Dialysis regimes (2)

Proportions of people receiving various dialysis regimens in the model

Population	Dialysis	Probability
High-intensity dialysis (ECM arm – CKD 4 and ESKD)		
Paediatric	Haemodialysis, 7 x week	[redacted]
	Haemodialysis, 6 x week plus peritoneal dialysis 7 x week	[redacted]
Adult	Haemodialysis, 7 x week	[redacted]
	Haemodialysis, 6 x week plus peritoneal dialysis 7 x week	[redacted]
Normal-intensity dialysis (lumasiran arm – ESKD)		
Paediatric	Haemodialysis, 3 x week	[redacted]
	Peritoneal dialysis 7 x week	[redacted]
Adult	Haemodialysis, 3 x week	[redacted]
	Peritoneal dialysis 7 x week	[redacted]

Impact on ICER – significant

- ERG scenario analysis changed the percentage of people on ECM receiving dialysis in CKD stage 4 from 100% to [redacted], in line with expert opinion, which increased the ICER.

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

Cost effectiveness results – company base case post clarification

ICERs include lumasiran PAS and eMIT price for pyridoxine

Deterministic ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
ECM	[redacted]	22.01	[redacted]	[redacted]	1.89	[redacted]	[redacted]
Lumasiran	[redacted]	23.89	[redacted]				

Inc = incremental

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
ECM	[redacted]	[redacted]	[redacted]
Lumasiran			

Company consider that the ICERs are confidential but with the approved PAS are in the region of £500,000 per QALY gained.

Cost effectiveness results – ERG base case (1)

ICERs include lumasiran PAS and eMIT price for pyridoxine

Deterministic ICERs

Assumption	ICER (£/QALY)
Company base case after clarification	[redacted]
1. Error correction: ERG corrected the transition probability from uncontrolled oxalate to controlled oxalate CKD 4/ESKD health states to 0.89 rather than [redacted] in the first cycle	[redacted]
2. ERG change 1 – probability of transplantation (key issue 5)	[redacted]
3. ERG change 2 – survival post transplantation: (see next slide)	[redacted]
4. ERG change 3 – TTO values vignettes (key issue 6)	[redacted]
ERG base case (1 to 4 combined)	[redacted]

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
ECM	[redacted]	[redacted]	[redacted]
Lumasiran			

ERG base case ICERs are above £1,000,000 per QALY gained.

Cost effectiveness results – ERG base case (2)

ERG change 2 – survival post transplantation

- Company used data from a study in people with PH1 (Jamieson 2005) to model overall survival following combined/sequential liver–kidney transplantation (cLKT).
- Study estimated survival curves stratified according to a person's pre-operative condition: very good, good, fair and poor. The company assumed that:
  - survival for people in very good/good condition would be reflective of survival for people in the post-cLKT state with controlled oxalate
  - survival for people in fair/poor condition would be reflective of survival for people in the post-cLKT state with uncontrolled oxalate.
- As the survival in the study was based on all participants on ECM, the ERG base case prefers to assume that the overall survival in the study is representative of survival for the ECM group
  - Change in post-transplantation survival for ECM group has a small impact on the ICER.

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 base case (post clarification)	[redacted]	[redacted]
ERG corrected company base case	[redacted]	[redacted]
ERG base case	[redacted]	[redacted]

Other issues for consideration (1)

Comments raised by company, patient/professional organisations and expert

Innovation

- Lumasiran is the first approved treatment specifically for PH1 with clear evidence of efficacy in clinical trials. Treatment is likely to prevent disease progression, reduce the number of kidney stone procedures required and reduce/remove the need for dialysis and transplantation.
- *"Lumasiran represents a paradigm shift in the management of PH1 by offering a pharmacologic option that can normalise or near-normalise oxalate overproduction, the central driver of morbidity in patients with PH1"*
- *"This technology has the potential to be revolutionary. It is one of the few major breakthroughs in the prevention of kidney stones in the last few years."*

Equality

- PH1 disproportionately affects populations in which rates of consanguinity are high, therefore 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 (mostly female).
- People who have clinical features of PH1 but are not referred for assessment to a specialist centre because of geographical distance or inadequate referral pathways may experience inequalities in care.

Other issues for consideration (2)

Carer disutility

- Company applied a caregiver disutility of [redacted] for the CKD 4 and ESKD health states [estimated by multiplying disutility per caregiver ([redacted]) by the average number of caregivers per patient ([redacted])].
- The company assumes that the caregiver tasks in CKD 4 and ESKD health states are equivalent and so the same caregiver disutilities can be applied, however the ERG notes that no literature was provided to support this assumption.
- The company uses the estimated disutility regardless of the intensity of the dialysis being given. Since people on lumasiran will only need normal dialysis and people on ECM will need intensive dialysis, the ERG considers that applying the same disutility to all people in CKD 4 and ESKD states will lead to a conservative estimate of the ICER.

Drug wastage

- Company's model assumes no vial sharing for lumasiran.
- ERG considers that the costs due to drug wastage for lumasiran are high.
- In response to clarification, the company stated that it will not be possible to provide lumasiran in vials of smaller quantities to reduce wastage.
- **SmPC states that lumasiran is provided in a single use vial. The committee can only recommend the use of lumasiran within its marketing authorisation.**

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 the 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

Issue		Impact
1	Low volume of robust clinical effectiveness evidence	
2	Proportion of people with PH1 eligible for lumasiran may be higher than stated	
3	Intermediate outcomes used may not link directly to relevant clinical endpoints	
4	Modelling of disease progression	
5	Probability of transplantation	
6	Time trade off values vignettes	
7	Dialysis regimes	

Model driver Unknown impact Small impact