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HEALTH TECHNOLOGY BRIEFING
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Lumasiran for primary hyperoxaluria type I

NIHRIO ID	17212	**NICE ID**	10027
Developer/Company	Alnylam Pharmaceuticals Inc.	**UKPS ID**	651681

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Lumasiran is in clinical development for the treatment of primary hyperoxaluria type I (PH1). PH1 is a very rare disease caused by certain genetic mutations, in which excess oxalate production results in the deposition of oxalate crystals in the kidneys and urinary tract. This leads to stone formation and kidney failure with significant morbidity and mortality. Treatment options for PH1 include vitamin B6 which is known to reduce the body's production of oxalate, dietary recommendations to prevent kidney stones and combined liver-kidney transplantation before or after development of end-stage kidney failure.

Lumasiran, which is administered as a subcutaneous injection, is designed to reduce the levels of an enzyme called glycolate oxidase produced by the liver. Oxalate production is therefore inhibited. By reducing oxalate production, lumasiran has the potential to prevent the actual disease process that develops in PH1. If licensed, lumasiran may provide the first pharmacological treatment option for patients with PH1 who do not have any approved treatment.

PROPOSED INDICATION

Primary hyperoxaluria type I (PH1) in children and adults.[1]

TECHNOLOGY

DESCRIPTION

Lumasiran (ALN-GO1) is an investigational RNA interference (RNAi) therapeutic agent which utilises the natural cellular process of gene silencing to target glycolate oxidase (GO).[2] Suppression of GO activity should inhibit oxalate production while causing an accumulation of glycolate, which is soluble and thus readily excreted in the urine.[3] By reducing hepatic levels of the GO enzyme, and depleting the substrate necessary for oxalate production, lumasiran has the potential to potentially prevent the pathology that develops in PH1.[4,5]

Lumasiran is in clinical development for the treatment of PH1. In the phase III clinical trial (ILLUMINATE-A; NCT03681184), patients receive multiple doses (3mg/kg once monthly for three consecutive months, then once every three months thereafter)[a] of lumasiran by subcutaneous injection.

INNOVATION AND/OR ADVANTAGES

Currently, no approved therapeutics exist for the treatment of PH1. Whilst vitamin B6 works for a subset of patients, the only effective treatment is a combined liver-kidney transplant which is associated with significant morbidity and mortality. Therefore, there is a significant unmet need for an efficacious and robust treatment to stop liver oxalate production and prevent disease progression without the need for liver transplant in patients with PH1.[3]

Lumasiran utilizes Alnylam's Enhanced Stabilization Chemistry (ESC) - GalNAc conjugate technology, which enables subcutaneous dosing with increased potency and durability.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lumasiran does not currently have a Marketing Authorisation in the EU/UK for any indication.

Lumasiran has the following regulatory designations/awards:[6,7]

- an orphan designation in the EU awarded in 2016 for primary hyperoxaluria
- a PRIME scheme eligibility was granted by the EMA in 2018 for PH1

PATIENT GROUP

DISEASE BACKGROUND

Primary hyperoxaluria (PH) is an ultra-orphan disease caused by genetic mutations, which results in the build-up of overproduction and accumulation of oxalate in the body. This results in the deposition of calcium oxalate crystals in the kidneys and urinary tract,[8] resulting in urolithiasis, nephrocalcinosis, and ultimately kidney failure.[9] As a result of systemic oxalosis, multi-organ damage occurs which affects bones, eyes, skin and the heart.[8]

[a] Information provided by Alnylam Pharmaceuticals

There are three main types of PH that are inherited in an autosomal recessive pattern: PH1, PH2 and PH3. PH1 is caused by a deficiency of the liver specific, peroxisomal enzyme alanine/glyoxylate aminotransferase (AGT),[9] and is the most severe primary hyperoxaluria[10] and accounts for approximately 80% of cases.[11] Approximately 50% of patients will have kidney failure by age 15 years, and about 80% will have end-stage renal disease by age 30 years.[8]

Symptoms associated with PH1 normally occur in childhood, with nearly half of cases presenting before 4 years of age.[12]

CLINICAL NEED AND BURDEN OF DISEASE

PH1 has an estimated prevalence of 1 to 3 cases per 1 million population and an incidence rate of approximately 120,000 live births per year in Europe.[9] It accounts for 1-2% of paediatric end-stage kidney disease[9] but higher values are reported in specific populations with a high rate of consanguinity.[13]

The UK-based National Renal Rare Disease Registry (RaDaR) suggests there were 96 patients across English and Scottish hospitals who have hyperoxaluria as of 2018.[14] Assuming 80% of cases of PH are PH1,[11] there are approximately 76 patients in England and Scotland who suffer from PH1.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for PH1 centres on minimising calcium oxalate deposition and the maintenance of renal function.[15] A number of treatment options for preventing kidney stones benefit all patients with PH1, these include:[15]

- Drinking large amount of fluid
- Oral potassium citrate to inhibit calcium in the urine
- Drugs such as thiazides to decrease calcium in the urine
- Avoiding significant intake of vitamin C or D (they promote stone formation)
- Supplementation of dietary calcium

Treatment for kidney stones may involve shock wave lithotripsy, percutaneous nephrolithotomy, and/or ureteroscopy.

Combined liver-kidney transplantation is an option whether pre-emptive or after development of end-stage kidney damage.[16,17] Depending on response to other treatments and the disease severity, options may include combined liver-kidney transplant; sequential liver-kidney transplant; an isolated kidney transplant, or an isolated liver transplant. Transplantation requires life-long immune suppression and carries significant mortality risk.[15,18]

CURRENT TREATMENT OPTIONS

Currently, only pyridoxine (vitamin B6) is known to reduce the body's production of oxalate, although other dietary recommendations have been advocated to prevent kidney stones. Although only 10-30% of people with PH1 respond to the treatment, it has been recommended all recently diagnosed people have a three-month trial.[15]

PLACE OF TECHNOLOGY

Aside from vitamin B6 supplementation which works only for a subset of patients, no approved therapeutics exist. There is therefore a significant unmet need for an efficacious and durable treatment to stop liver oxalate production and prevent disease progression without the need for liver transplant.[3]

If licensed, lumasiran may provide the first pharmacological treatment option for patients with PH1 who do not currently have any approved treatment.

CLINICAL TRIAL INFORMATION

Trial	**ILLUMINATE-A; NCT03681184; children and adults aged 6-64 years; lumasiran; phase III**
Sponsor	Alnylam Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (incl UK), USA and other countries
Design	Randomised, parallel group assignment, quadruple masking
Participants	n=30 (estimated enrolment); aged 6-64 years; confirmation of PH1 disease; meet 24 hr urine oxalate excretion requirements; if taking vitamin B6, must have been on stable regimen for at least 90 days
Schedule	Subjects are randomised into two arms: • **Experimental:** Subjects receive a multiple dose of lumasiran by subcutaneous injection. A dose of 3mg/kg once monthly was given for three consecutive months, then once every three months thereafter.[b] • **Placebo comparator:** Subjects receive sterile normal saline (0.9% NaCl).
Follow-up	Six month double blind (placebo) treatment period (primary efficacy analysis at this timepoint). Followed be 3 months blinded extension (all patients on active treatment). Followed by 51 month open-label extension period.[c]
Primary Outcomes	Percent change in 24-hour urinary oxalate excretion from baseline to month 6 [Time frame: 6 months]
Secondary Outcomes	• Absolute change in 24-hour urinary oxalate corrected for body surface area (BSA) from baseline to month 6 [Time frame: 6 months] • Change in 24-hour urinary oxalate:creatinine ratio (value/upper limit of normal [ULN]) from baseline to month 6 [Time frame: 6 months] • Proportion of patients with 24-hour urinary oxalate level below 1.5 x ULN at month 6 [Time frame: 6 months] • Proportion of patients with 24-hour urinary oxalate level below ULN at month 6 [Time frame: 6 months] • Change in estimated glomerular filtration rate (eGFR) from baseline to month 6 [Time frame: 6 months] • Frequency of adverse events [Time frame: from treatment initiation to study completion (approximately 6 years)] • Seriousness of adverse events [Time frame: from treatment initiation to study completion (approximately 6 years)]

[b] Information provided by Alnylam Pharmaceuticals.

Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Estimated primary completion date Dec 2019. Estimated study completion date May 2024

Trial	**NCT03350451; children and adults aged 6 years and older; lumasiran; phase II extension**
Sponsor	Alnylam Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[19]
Location	EU countries (incl UK) and another country
Design	Single group assignment, open label
Participants	n=20 (planned); patients aged 6 years and older; enrolment within 12 months of completion of study lumasiran; if taking vitamin B6, willing to remain on stable regimen for study duration
Schedule	Lumasiran given by subcutaneous injection. Dosing was at 1mg/kg monthly.[c]
Follow-up	Extension phase up to 2 years follow-up.[d]
Primary Outcomes	Safety will be demonstrated by incidence of Adverse Events [Time frame: up to 850 days]
Secondary Outcomes	• Change in urinary oxalate excretion over time [Time frame: up to 834 days] • Change in estimated glomerular filtration rate (eGFR) over time [Time frame: through day 834] • Change in measured creatinine clearance (mCrCl) over time [Time frame: through day 834]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary and study completion date Sept 2021

Trial	**NCT02706886; children and adults aged 6-64 years; lumasiran; phase I/II**
Sponsor	Alnylam Pharmaceuticals
Status	Completed
Source of Information	Trial registry[20]
Location	EU (incl UK), USA and other countries
Design	Randomised, parallel group assignment, single masking
Participants	n=52 (actual enrolment); aged 6-64 years; confirmation of PH1 disease; meet 24 hr urine oxalate excretion requirements; estimated GFR of >45 mL/min/1.73m^2; if taking vitamin B6, must have been on stable regimen for at least 60 days
Schedule	Subjects are randomised into two arms:

[c] Information provided by Alnylam Pharmaceuticals
[d] Information provided by Alnylam Pharmaceuticals

	• **Experimental:** Subjects receive lumasiran as a single or multiple dose by subcutaneous injection. Dosing specifics were not reported on the trial registry. • **Placebo comparator:** Subjects receive sterile normal saline (0.9% NaCl). Dosing specifics were not reported on the trial registry.
Follow-up	Part A: Single Ascending Dose (SAD) phase – up to 405 days Part B: Multiple Ascending Dose (MAD) phase – up to 546 days Extension phase - up to 2 years follow-up
Primary Outcomes	Safety will be demonstrated by the proportion of subjects experiencing Adverse Events [Time frame: Part A (SAD phase): Up to 405 days; Part B (MAD phase): Up to 546 days]

Secondary Outcomes	• Profile of pharmacokinetics (PK) of lumasiran [Time frame: Part A (SAD phase): Up to 2 days; Part B (MAD phase): Up to 169 days]
	  ○ Cmax
	• Profile of pharmacokinetics (PK) of lumasiran [Time frame: Part A (SAD phase): Up to 2 days; Part B (MAD phase): Up to 169 days]
	  ○ tmax
	• Profile of pharmacokinetics (PK) of lumasiran [Time frame: Part A (SAD phase): Up to 2 days; Part B (MAD phase): Up to 169 days]
	  ○ AUC
	• Profile of pharmacokinetics (PK) of lumasiran [Time frame: Part A (SAD phase): Up to 2 days; Part B (MAD phase): Up to 169 days]
	  ○ t½
	• The effect of ALN-GO1 on plasma glycolate concentration [Time frame: Part A (SAD phase): Up to 405 days; Part B (MAD phase): Up to 546 days]
	• The effect of ALN-GO1 on urinary glycolate excretion [Time frame: Part B (MAD phase): Up to 546 days]
	• The effect of ALN-GO1 on urinary oxalate excretion [Time frame: Part B (MAD phase): Up to 546 days]

Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Previously reported as Jan 2019

ESTIMATED COST

The cost of lumasiran is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

- No relevant guidance identified.

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