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Newcastle University

Health Technology Briefing
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Nedosiran for primary hyperoxaluria

Company/Developer	Novo Nordisk Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28146	NICE TSID: 11777	UKPS ID: 665857

Licensing and Market Availability Plans

Currently in phase II and III clinical trials.

Summary

Nedosiran is currently in development for the treatment of primary hyperoxaluria (PH). PH is a group of rare genetic metabolic disorders that are characterized by the build-up of a substance known as oxalate in the kidneys and other organs of the body. This is due to low functional levels of a specific enzyme that normally prevents oxalate build-up. Excess oxalate binds to calcium that forms a hard compound (calcium oxalate) which can cause kidney and urinary stones. Recurrent stone formation and calcium oxalate in the kidney can cause chronic kidney disease (CKD) which can deteriorate kidney function and lead to kidney failure, and this can lead to oxalate build-up in other organs. The symptoms and severity of PH may vary greatly from one person to another. PH is an inherited disease. There is currently no cure for PH. Treatment focuses on protecting the kidneys to prevent kidney stones from developing, which includes drinking lots of liquid, low-oxalate diet and treatment with vitamin B6 as this can reduce oxalate build-up.

Nedosiran is an RNA interference (RNAi) agent (which are small molecules that inhibit expression of genes) designed to inhibit production of the hepatic lactate dehydrogenase (LDH) enzyme – an enzyme (protein) that catalyses the final step in the metabolism pathway that can lead to oxalate overproduction in patients with PH. There is currently only one EU-approved therapy for PH type 1, and none for PH type 2 and 3. This is the first RNAi candidate explored for all types of PH. Nedosiran will be administered as a subcutaneous (SC) injection. If approved, Nedosiran will provide a novel treatment option for PH.

Proposed Indication

Treatment of primary hyperoxaluria (PH).[1-3]

Technology

Description

Nedosiran (DCR-PHXC) is an RNAi agent that inhibits hepatic lactate dehydrogenase (LDH), the enzyme responsible for the common, final step of oxalate production in all three genetic subtypes of PH. Nedosiran is composed of nedosiran sodium (a synthetic, double-stranded RNAi oligonucleotide conjugated to N-acetyl-d-galactosamine amino sugar residues). The N-acetyl-d-galactosamine amino sugar residues ensure preferential uptake by hepatocytes via the asialoglycoprotein receptor. After hepatocyte internalization and release into the cytoplasm, nedosiran exploits the endogenous RNAi regulatory mechanism to degrade the lactate dehydrogenase-A (*LDHA*) gene mRNA which encodes LDH, thereby reducing production of the LDHA protein, which is an isoform of LDH.[4,5] Consequently, the activity of hepatic LDH is reduced.[5]

Nedosiran is in clinical development for the treatment of all PH types. In the phase II (NCT03847909) and phase III trial (NCT04042402), nedosiran was administered in multiple fixed doses via SC injection, and in the phase II (NCT04580420) trial, it will be administered monthly via SC injection based on age and weight.[1-3]

Key Innovation

Novel therapeutic strategies focus on RNA interference (RNAi) to decrease the levels of enzymes involved in the glyoxylate metabolic pathway and so reduce oxalate production.[5] The only approved RNAi medicinal product is lumasiran, which is the first treatment to be licensed for PH but is indicated only for PH1 due to its mechanism of action.[5,6]

Nedosiran is the only RNAi drug candidate explored in all PH types.[7] In a phase I trial (NCT03392896), nedosiran demonstrated favourable safety and tolerability in patients with PH1 and PH2.[5] In the phase III long term extension trial (NCT04042402), nedosiran showed an acceptable safety profile also in the interim analysis for PH1 and PH2. It also showed sustained reduction of urinary oxalate (Uox) excretion which are encouraging signs of potential long-term safety and clinical benefit of a multidose regimen of nedosiran.[8] If approved, nedosiran will provide an alternative treatment option for patients with PH.

Regulatory & Development Status

Nedosiran does not currently have marketing authorisation in the EU/UK for any indication.

Nedosiran has the following regulatory designations/awards:

- An Orphan Drug in the EU in 2018 for PH.[9]
- An Orphan Drug in the USA in 2018 for PH.[10]
- A Breakthrough Therapy by the US FDA for PH1 in July 2019.[11]
- A Rare Pediatric Disease by the US FDA for PH in June 2020.[12]

Patient Group

Disease Area and Clinical Need

PH is a group of rare genetic metabolic disorders that are characterized by the accumulation of a substance known as oxalate in the kidneys and other organ systems of the body.[13] PH encompasses 3 related but genetically distinct subtypes, PH types 1, 2 and 3 (PH1, PH2, and PH3), each characterized by a specific enzyme deficiency, resulting in increased levels of intrahepatocellular (meaning present within liver cells) glyoxylate. Nearly all intrahepatocellular glyoxylate undergoes conversion to oxalate by LDH, a homotetrameric enzyme encoded by the LDHA gene.[5] In the kidneys, excess oxalate binds with calcium to form a hard compound (calcium oxalate) that is the main component of kidney and urinary stones. Common symptoms include the formation of stones throughout the urinary tract (urolithiasis) and kidneys (nephrolithiasis) and progressively increased levels of calcium in the kidneys (nephrocalcinosis). Chronic, recurrent stone formation and the accumulation of calcium oxalate in kidney tissue can cause chronic kidney disease (CKD), which can ultimately progress to kidney failure. Eventually, kidney function can deteriorate to the point where oxalate begins to accumulate in other organ systems. The symptoms and severity of PH may vary greatly from one person to another. CKD and kidney failure may already be present when a diagnosis of PH is first made. PH is inherited in an autosomal recessive pattern.[13]

PH1 is the most severe and most common of the three types of PH. It is estimated to account for 70 to 80% of all diagnosed PH patients. PH2 is thought to account for approximately 10% of PH cases. PH affects males and females in equal numbers.[13] Around 120 people in the UK have hyperoxaluria as of October 2021, according to the National Registry of Rare Kidney Diseases (RaDaR).[14] PH1 is very rare with an estimated prevalence of 0.05 in 10,000 people in the EU.[6] No data regarding the prevalence of PH2 exist.[15]

Recommended Treatment Options

There is currently no cure for PH. Treatment focuses on protecting the kidneys to try to stop kidney stones from developing. It is important that people with PH drink plenty of liquid – at least three litres a day. This increases urine production and helps the body to get rid of more diluted waste products, leaving less to build up in the kidneys. Vitamin B6 (pyridoxine) could potentially be helpful in reducing oxalate build-up in some patients with PH1. Occasionally PH is only diagnosed after kidney failure has occurred. Treatment for kidney failure may need dialysis and/or transplantation. A kidney transplant by itself is not a permanent cure. This is because PH can redevelop in the transplanted kidney. To overcome this, a combined liver and kidney transplant may be recommended. This corrects the way the body handles oxalate.[16]

Standard care for PH1 depends on a person's kidney function. In people with no kidney impairment, treatment includes supportive measures such as following a low oxalate diet, hyperhydration, using crystallisation inhibitors and pyridoxine supplementation, if appropriate. In people with more advanced stages of kidney impairment, dialysis may be started to slow the build-up of oxalate around the body or replace lost kidney function. In people with end-stage kidney disease, a liver transplant (with or without a kidney transplant) may be needed to eliminate the source of excess oxalate production. Treatment of kidney stones may be needed at all stages of disease.[17]

Currently the only EU approved drug for PH1 is lumasiran, however it is not recommended, within its marketing authorisation, for treating PH1 by NICE.[6,17]

Clinical Trial Information

Trial	**PHYOX3**; NCT04042402; EudraCT-2018-003099-10; An Open-Label Roll-Over Study to Evaluate the Long-Term Safety and Efficacy of DCR-PHXC

	Solution for Injection (Subcutaneous Use) in Patients With Primary Hyperoxaluria **Phase III –** Enrolling by invitation **Location(s) –** 5 countries in EU; UK, USA, Australia, Canada and Asia **Primary completion date –** December 2023
Trial Design	Single group assignment, open label
Population	N = 50 (estimated); Participant successfully completed a Dicerna Pharmaceuticals, Inc. study of nedosiran or participant is the sibling of a participant who successfully completed a Dicerna Pharmaceuticals, Inc. study of DCR PHXC; 6 years and older.
Intervention(s)	Nedosiran monthly SC injection
Comparator(s)	No comparator
Outcome(s)	**Primary outcome:** • The annual rate of decline in estimated glomerular filtration rate (eGFR) [Time Frame: Annual change from baseline] See trial record for full list of other outcomes.
Results (efficacy)	Total exposure (based on 15 participants) to monthly dosing of nedosiran has exceeded 3 years based on the cumulative duration of patient participation in the trial. Seven participants have had exposure to at least 3 monthly doses of nedosiran. Six out of the 7 participants who have had exposure to at least 3 monthly doses of nedosiran showed normalization or near-normalization of Uox excretion (defined as < 0.46 mmol/24 hr/1.73 m2 and ≥ 0.46-0.60 mmol/24 hr/1.73 m2, respectively) on at least 2 visits after the first dose.[8]
Results (safety)	Treatment-emergent adverse events (AEs) were observed in 11 participants. Seven participants experienced 33 AEs considered related to study drug: administration-site events (n=18), blood chemistry findings (6), pain (2), dysuria (1), nasal congestion (1), edema (1), and erectile dysfunction (1). Three AEs were uncoded at this time. None of the participants experienced injection-site reactions (defined as occurring 4 hr or more after injection). All drug-related AEs were mild. There were no drug-related serious AEs.[8]

Trial	**PHYOX7; NCT04580420; EudraCT-2020-002826-97;** A Phase 2 Open-Label Study to Evaluate the Safety and Efficacy of DCR-PHXC in Patients With Primary Hyperoxaluria Type 1 or 2 and Severe Renal Impairment, With or Without Dialysis **Phase II –** Recruiting **Location(s) –** 1 country in EU; UK and USA **Primary completion date –** November 2022
Trial Design	Sequential assignment, open label

Population	N = 12 (estimated); Documented diagnosis of PH1 or PH2, confirmed by genotyping; all ages.
Intervention(s)	Nedosiran monthly SC injection based on age and weight
Comparator(s)	No comparator
Outcome(s)	**Primary outcome:** • Safety: Incidence of Events [Time Frame: 180 days] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**PHYOX2; NCT03847909; EudraCT-2018-003098-91;** A Phase 2 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of DCR-PHXC Solution for Injection (Subcutaneous Use) in Patients With Primary Hyperoxaluria **Phase II –** Completed **Location(s) –** 7 countries in EU; UK, USA, Australia, Canada and Asia **Study completion date –** June 2021
Trial Design	Randomized, parallel assignment, quadruple-masked
Population	N = 35 (actual); Documented diagnosis of PH1 or PH2, confirmed by genotyping; 6 years and older.
Intervention(s)	Nedosiran SC injection
Comparator(s)	Sterile Normal Saline (0.9% NaCl) SC injection, administered at same injection volume as nedosiran
Outcome(s)	**Primary outcome:** • Area under the curve (AUC) of percent change from baseline in 24-hour urinary oxalate excretion between Day 90 and Day 180 [Time Frame: 3 months (Last 3 months of the 6 month treatment period)] See trial record for full list of other outcomes.
Results (efficacy)	Of the 35 patients randomized (23 nedosiran and 12 placebo; 29 with PH1 and 6 with PH2), 34 participants had at least one efficacy assessment after Day 90 (modified intent-to-treat population; mITT). Baseline mean estimated glomerular filtration rate (eGFR; a measure of kidney function) was 89.5 mL/min/1.73 m2 (SD=37.5) for participants given nedosiran and 82.0 mL/min/1.73 m2 (SD=30.0) for participants given placebo. Baseline mean Uox values were approximately 1.33 mmol/day (SD=0.47) and 1.96 mmol/day (SD=0.71) for the nedosiran and placebo groups, respectively. The primary endpoint of the study was met, with nedosiran resulting in a statistically significant reduction in Uox ($p<0.0001$). In

	the overall trial, nedosiran resulted in a 57.5% greater daily average reduction over Day 90 to Day 180 compared to placebo.[7]
Results (safety)	The most common AEs in the trial were mild, self-resolving injection-site reactions (2 patients given nedosiran and zero given placebo). There were three reported kidney stone AEs in participants given nedosiran (13%) and five in participants given placebo (42%). Of the 35 participants enrolled in the trial, two discontinued, with one withdrawing from the study due to declining renal function (a participant who was receiving placebo) and one discontinuing due to self-resolving, benign palpitations considered to be unrelated to study drug by external experts.[7]

Estimated Cost

The cost of nedosiran is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Lumasiran for treating primary hyperoxaluria type 1 (GID-TA10660). Expected date of issue September 2022.

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

- Cochat P, Hulton SA, Acquaviva C et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. May 2012.[18]

Additional Information

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