Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING SEPTEMBER 2018

Givosiran for acute hepatic porphyria (AHP)

NIHRIO ID	14974	**NICE ID**	9975
Developer/Company	Alnylam Pharmaceuticals Inc	**UKPS ID**	649697

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

SUMMARY

Givosiran as subcutaneous injection is in clinical development for the treatment of acute hepatic porphyria (AHP). AHP is a rare genetic condition in which patients lack certain enzymes needed to produce haem, a component of the blood pigment haemoglobin. As a result, substances for making haem accumulate in the body (particularly in the liver) and become toxic, causing attacks of severe abdominal pain, vomiting and nervous system disorders, such as seizures (fits), depression and anxiety. Some patients may also experience skin problems, with skin becoming oversensitive to light. AHP is life-threatening due to the possibility of paralysis and respiratory arrest during attacks and debilitating in the long term because of symptoms such as pain, nausea, seizures and skin blistering.

Givosiran is made of a short, synthetic strand of genetic material called 'small interfering RNA' (siRNA) that has been designed to interfere with the production of an enzyme involved in an early step in making haem. By blocking this early step of haem production in patients with AHP, givosiran is expected to prevent the next steps which produce substances that accumulate in the body and cause the symptoms of the disease.

PROPOSED INDICATION

Acute hepatic porphyria (AHP) in adult and adolescent patients[a]

TECHNOLOGY

DESCRIPTION

Givosiran (Givlaari; ALN-AS1) is a proprietary enhanced stabilisation chemistry (ESC)-stabilised conjugate composed of the liver-targeted ligand N-acetylgalactosamine (GalNAc) conjugated to small-interfering RNAs (siRNAs) directed against the liver-expressed enzyme aminolevulinic acid synthase 1 (delta-aminolevulinate synthase 1; ALAS1; ALAS-1) that can potentially be used in the treatment of AHPs. Upon subcutaneous administration (SC) of givosiran, the GalNAc moiety targets and binds with high affinity to asialoglycoprotein receptors (ASGPRs) expressed on hepatocytes. Once inside the cell, the siRNAs bind to and silence ALAS1 mRNA and inhibit both the translation and expression of the ALAS1 protein. This prevents delta-aminolevulinic acid (ALA) formation, decreases 5-ALA levels, and prevents the production of porphyrins and haems such as porphobilinogen (PBG).[1]

The recommended dose for givosiran is 2.5 mg/kg subcutaneous (SC) injection monthly.[a]

INNOVATION AND/OR ADVANTAGES

AHPs are a group of metabolic disorders caused by deficiencies of specific enzymes that are responsible for haemoglobulin biosynthesis within the liver, which leads to the accumulation of toxic intermediates, such as ALA and PBG. ALAS1, a liver-expressed, rate-limiting enzyme in the haem biosynthesis pathway, is responsible for the formation of ALA from succinyl-CoA and glycine.[1]

Monthly administration of givosiran has the potential to significantly lower induced liver ALAS1 levels in a sustained manner and thereby decrease neurotoxic haem intermediates ALA and PBG to near normal levels.[2] ESC enables the subcutaneous dosing of givosiran with increased efficacy, durability and a wide therapeutic index as compared to non-ESC GalNAc-siRNA conjugates.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Givosiran does not currently have Marketing Authorisation in the EU for any indication.

- Givosiran is a designated orphan drug in the EU in August 2016 for the treatment of AHP.[3]
- Givosiran was awarded PRIME status for AHP by the EMA in February 2017.[4]
- Givosiran is a designated orphan drug in the US in August 2016 for the treatment of AHP.[5]
- Givosiran was designated Breakthrough Therapy for AHP by the FDA in May 2017.[6]

[a] Information provided by Alnylam Pharmaceuticals Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

AHPs are a family of rare, serious and life-threatening metabolic disorders predominantly caused by a genetic mutation in 1 of the 8 enzymes responsible for haem synthesis. AHPs are comprised of four subtypes, each resulting from a genetic defect leading to deficiency in one of the enzymes of the haem biosynthesis pathway in the liver: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and ALA dehydratase-deficiency porphyrias (ADP). Certain triggers can impact the haem biosynthesis pathway and cause an increase of ALAS1. This increase results in the build-up of neurotoxic intermediates ALA and PBG throughout the body. ALA and PBG are harmful to nerve cells and thought to cause the attacks and chronic symptoms characteristic of AHPs. Symptoms of AHPs vary widely and usually first occur in the prime of patients' lives between the ages of 20 and 30.[7]

Symptoms may last days to weeks and usually improve slowly after the attack, including[8]:

- Severe abdominal pain
- Pain in the chest, legs or back
- Constipation or diarrhea
- Muscle pain, tingling, numbness, weakness or paralysis
- Red or brown urine
- Mental changes, such as anxiety, confusion, hallucinations, disorientation or paranoia
- Breathing problems
- Urination problems
- Rapid or irregular heartbeats (palpitations)
- High blood pressure
- Seizures

In addition to genetic risks, environmental factors may trigger the development of signs and symptoms in AHPs. Examples of triggers include exposures to sunlight, certain medications (including hormone drugs), recreation drugs, dieting or fasting, smoking, physical stress (including infections and illnesses), emotional stress, alcohol uses, and menses.[8]

CLINICAL NEED AND BURDEN OF DISEASE

A 3-year prospective study published in 2013 of newly diagnosed symptomatic patients with inherited porphyrias in 11 European countries reported an annual symptomatic acute porphyria of 0.2 per million (0.13 per million for AIP, 0.08 per million for VP and 0.02 per million for HCP). Estimates of prevalence vary widely and do not always distinguish between latent (never had symptoms) and overt (previous or currently symptomatic) disease. The European study estimated the prevalence of patients with overt acute porphyria (all types) as about 10 per million.[9,13]

As of 2016, AHPs were estimated to affect approximately 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 5,000 people.[3] As clinical features alone are not so specific and suitable either to confirm a diagnosis of acute porphyric attack or to distinguish between the different forms of acute porphyrias, the knowledge and the correct interpretation of the appropriate tests are mandatory for accurately diagnosing and managing these diseases. A delayed diagnosis and an inappropriate treatment of an acute porphyric attack may be fatal. [10]

Symptomatic AHP patients have decreased quality of life (QoL), an increased incidence of anxiety and depression, impaired physical functioning, and a negative disease impact on employment.[11] Individual needs assessments and counselling for these patients are critical to identify prodromal symptoms and plan for early intervention to treat their acute attacks. As well, referrals to social work, psychology, and pain management may be beneficial for these patients.[12]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Misdiagnosis of AHPs is common, as symptoms can often resemble those of other conditions such as irritable bowel syndrome (IBS), appendicitis, fibromyalgia, and endometriosis. Consequently, patients afflicted with AHPs are often misdiagnosed or remain undiagnosed for up to 15 years. These delays in diagnosis may lead to unnecessary surgeries and increased disease burden such as paralysis, hypertension, chronic kidney disease, or hepatocellular carcinoma.[7]

In the dominant AHPs (AIP, HCP, and VP), acute attacks are always accompanied by an increase in urinary excretion of ALA, PBG and porphyrin. Measurement of urine PBG and porphyrin are the first-line tests in a patient with a suspected acute attack of porphyria and normal results in an acutely unwell patient excludes acute porphyria as a cause of those symptoms. In VP and HCP, urine PBG excretion may return to normal within days to weeks, so the increase can be missed if sample collection is delayed, although urine porphyrin elevation persists for longer. In lead toxicity or the very rare ADP, urine porphyrin and ALA excretion are increased without a significant increase in PBG. Further investigation of a newly presenting symptomatic patient requires analysis of plasma and faecal porphyrins to determine the type of acute porphyria.[13,14]

Great care must be taken when prescribing for patients with AHPs, as certain drugs can induce acute porphyric crises. Since AHPs are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs. Where there is no safe alternative, drug treatment for serious or life-threatening conditions should not be withheld from patients with AHPs. Where possible, the clinical situation should be discussed with a porphyria specialist for advice on how to proceed and monitor the patient. Haem argenate is administered by short intravenous infusion as haem replacement in moderate, severe, or unremitting acute porphyria crises.[15]

CURRENT TREATMENT OPTIONS

- Haem argenate is indicated for the treatment of acute attacks of hepatic porphyria (AIP, HCP, and VP). The recommended daily dose for adult is 3 mg/kg once daily for four days, diluted in 100 ml of 0.9% sodium chloride in a glass bottle and infused intravenously over at least 30 minutes into a large antebrachial or central vein using an inline filter. The dose should not exceed 250 mg (1 ampoule) per day.[16,17] Exceptionally, the course of the treatment may be repeated under strict biochemical surveillance if there is inadequate response after the first course of treatment.[16]

PLACE OF TECHNOLOGY

If licensed, givosiran may offer an additional treatment option for the prevention of acute attacks and chronic symptoms in patients with confirmed AHP[b]

CLINICAL TRIAL INFORMATION

Trial	ENVISION, NCT03338816, ALN-AS1-003; givosiran vs placebo; phase III extension
Sponsor	Alnylam Pharmaceuticals Ltd
Status	Ongoing
Source of Information	Trial registry[18]
Location	12 EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, double-blind, parallel assignment
Participants	n=74 (planned); ≥ 12 years of age; AHP; elevated urinary or plasma PBG or ALA values within the past year; active disease (at least 2 documents porphyria attacks within the last 6 months); willing to discontinue or not initiate the use of prophylactic hemin
Schedule	Randomised to givosiran by SC injection or placebo; dosing regimen was not reported on the trial registry.
Follow-up	Not reported
Primary Outcomes	• The annualised rate of porphyria attacks in patients with AIP [Time frame: at 6 months]
Secondary Outcomes	• The pharmacodynamic (PD) effect of givosiran on urine levels of delta- ALA in patients with AIP [Time frame: at 3 and 6 months] • The PD effect of givosiran on urine levels of PBG in patients with AIP [Time frame: at 6 months] • Annualised rate of hemin administrations in AIP patients [Time frame: through month 6] • Annualised rate of porphyria attacks in patients with AHP [Time frame: through month 6] • Pain as measured by the Brief Pain Inventory-Short Form numeric rating scale, a 0 to 10 point scale with 10 rated as worst pain [Time frame: through month 6] • Nausea as measured by the numeric rating scale, a 0 to 10 point scale with 10 rated as worst nausea [Time frame: through month 6] • Fatigue as measured by the Brief Fatigue Inventory-Short Form numeric rating scale, a 0 to 10 point scale with 10 rated as worst fatigue [Time frame: through month 6] • Change from baseline in the Physical Component Summary of the 12-Item Short Form Survey (SF-12) [Time frame: through month 6]
Key Results	-
Adverse effects (AEs)	-

[b] Information provided by Alnylam Pharmaceuticals Ltd on UK PharmaScan

Expected reporting date	Estimated primary study completion date February 2019; estimated study completion date September 2021.

ADDITIONAL INFORMATION

Alnylam Pharmaceuticals Ltd

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (All Ages). E01/S/a.

OTHER GUIDANCE

- No other guidance identified.

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