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ADISINSIGHT REPORT

Givosiran: First Approval

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Abstract
Givosiran (Givlaari™) is an aminolevulinate synthase 1 (ALAS1)-directed small interfering RNA (siRNA) covalently linked to a ligand to enable specific delivery of the siRNA to hepatocytes. This results in downregulation of ALAS1 mRNA and prevents accumulation of neurotoxic δ-aminolevulinic acid and porphobilinogen levels that are associated with acute porphyria attacks. Givosiran is being developed by Alnylam Pharmaceuticals for the treatment of acute hepatic porphyria (AHP). In November 2019, givosiran was approved in the USA for the treatment of adults with AHP based on the positive results from the multinational, phase III ENVISION trial. In the EU, givosiran received a positive opinion in January 2020 for the treatment of AHP in adults and adolescents aged 12 years and older. This article summarizes the milestones in the development of givosiran leading to this first approval for the treatment of adults with AHP.

Givosiran (Givlaari™): Key Points

An aminolevulinate synthase 1-directed small interfering RNA therapy was developed by Alnylam Pharmaceuticals for the treatment of acute hepatic porphyria

Received its first approval on 20 Nov 2019 in the USA

Approved for the treatment of adults in acute hepatic porphyria

1 Introduction

Acute hepatic porphyria (AHP) are rare, serious and potentially life-threatening inherited metabolic disorders of haem biosynthesis resulting from autosomal dominant loss-of-function of the third [manifests as acute intermittent porphyria (AIP)], sixth [hereditary coproporhyria (HCP)] or seventh [variegate porphyria (VP)] enzyme in this pathway or, in very rare cases, from an autosomal recessive inheritance [1, 2]. These disorders result in the accumulation of the neurotoxic precursors δ-aminolevulinic acid (ALA) and porphobilinogen (PBG), which in turn, causes acute porphyria attacks that primarily manifest as neurovisceral symptoms such as abdominal pain (cardinal symptom), acute neuropathy and psychiatric symptoms [1, 2]. Most symptomatic patients have few attacks in their lifetime; however, up to 8% of patients will have more severe disease with recurrent attacks (i.e. ≥ 4 attacks/year) [3]. The most common AHP is AIP, which has an estimated prevalence of 5.4 per million individuals [4]. The disease significantly impacts on healthcare utilization and health-related quality of life for the patient and their caregiver, as observed in the prospective, international EXPLORE trial, which characterized the natural history and clinical management of AHP in patients experiencing recurrent attacks [5].

Currently, there is a paucity of treatment options for AHP, with intravenous hemin the only specific treatment recommended in the EU and USA for managing acute attacks and no approved prophylactic treatments to prevent acute attacks [2]. Along with its instability in aqueous solution, hemin treatment has several other limitations associated with repeated administration, including potential toxicities such as thrombophlebitis, tachyphylaxis, coagulation abnormalities and secondary iron overload [6]. Hence, there is an unmet need for additional treatments to manage acute porphyria attacks and reduce the long-term complications of these attacks. One such novel approach involves the use of a synthetic small interfering RNA (siRNA) therapy to target affected genes in the haem biosynthesis pathway [1, 2].

Enhanced material for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.11741715.

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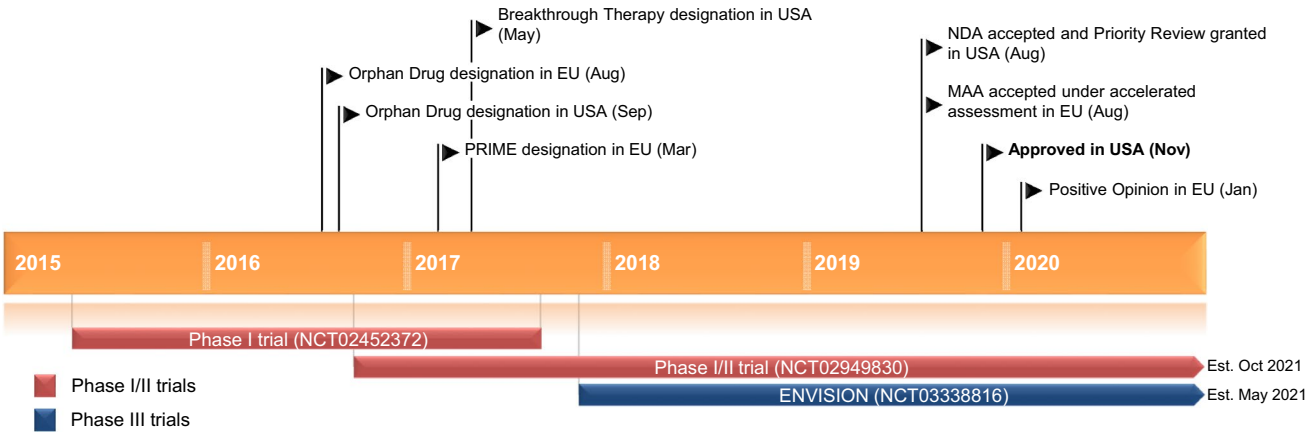

Key milestones in the development of givosiran for the treatment of acute hepatic porphyria. *MAA* Marketing Authorization Application, *NDA* New Drug Application, *PRIME* PRIority MEdicine

Givosiran (Givlaari™), an ALA synthase 1 (ALAS1)-directed siRNA, was developed by Alnylam Pharmaceuticals for the treatment of AHP. In November 2019, the US FDA approved givosiran for the treatment of adults with AHP [7, 8]. In the USA, the approved dosage of subcutaneous givosiran is 2.5 mg/kg once monthly; a missed dose should be administered as soon as possible, followed by monthly injections thereafter [8]. Prescribing information should be consulted regarding monitoring requirements and potential treatment interruption or discontinuation required for adverse reactions. In the EU, givosiran has orphan drug designation [9] and received a positive opinion on 30 January 2020 for the treatment of AHP in adults and adolescents aged 12 years and older [10].

1.1 Company Agreements

Before April 2019, Alnylam Pharmaceuticals entered into a licensing agreement with the Icahn School of Medicine at Mount Sinai (ISMMS) related to givosiran. ISMMS is a co-owner with Alnylam Pharmaceuticals of issued and pending patents associated with givosiran and has licensed their interest in these patents to Alnylam Pharmaceuticals. Under the terms of the agreement, ISMMS is entitled to receive payments from Alnylam Pharmaceuticals, including a milestone payment when givosiran entered phase III clinical studies, in addition to future royalty payments when givosiran is a marketed treatment for AHP [11].

In January 2019, Alnylam Pharmaceuticals entered into an agreement with Medison Pharma to commercialize RNA interference (RNAi) therapeutics, in Israel. Under the terms of agreement Medison Pharma has the rights to commercialize certain RNAi therapeutics developed by Alnylam Pharmaceuticals, including givosiran which is not currently approved for use in Israel [12].

In June 2005, Alnylam Pharmaceuticals entered into a licensing agreement with Garching Innovation (now known as Max Planck Innovation, the licensing arm of the Max Planck Institute). Licensing of this intellectual property helped to further establish the position of Alnylam Pharmaceuticals as the leading holder of patents, technology and know-how that underlie the discovery, development and commercialization of RNAi-based therapeutics [13].

2 Scientific Summary

2.1 Pharmacodynamics

Givosiran, a synthetic double-stranded siRNA, specifically targets *ALAS1* mRNA in hepatocytes, downregulating its elevated levels in the liver and thereby, reducing circulating levels of the neurotoxic intermediates ALA and PBG [2, 8]. The siRNA is covalently linked to a ligand containing three *N*-acetylgalactosamine (GalNAc) residues that target and bind with high affinity to asialoglycoprotein receptors (almost exclusively expressed on hepatocytes) [2]. Once internalized into hepatocytes, the RNA is cleaved by cellular enzymes to smaller ≈ 20-base pair fragments and then separated into single *ALAS1*-targeted RNA strands that bind to and silence *ALAS1* mRNA, thereby inhibiting both the translation and expression of the ALAS1 protein, leading to decreased systemic levels of neurotoxic ALA and PBG [2].

In preclinical studies in rodent and non-human primate models of AHP, subcutaneously administered givosiran was associated with rapid, dose-dependent reductions in *ALAS1* mRNA levels in liver, urine and serum samples [14], with corresponding reductions in urine and plasma ALA and PBG levels [14].

In a 3-part phase I trial (NCT02452372) in adults with AIP and chronic high excretion of PBG, single 0.035–2.5 mg/kg doses of givosiran resulted in rapid, dose-dependent reductions in urinary *ALAS1* mRNA, ALA and PBG levels, with mean maximum reductions from baseline with a 2.5 mg/kg dose of 86%, 91% and 96%, respectively [15]. There was significant ($p < 0.001$ for both) correlation between reductions in urinary *ALAS1* mRNA levels and urinary ALA and PBG levels. Following two once-monthly doses of givosiran 0.35 or 1.0 mg/kg, reductions in these levels were consistent to those observed after single doses. Reductions in urinary *ALAS1* mRNA, ALA and PBG levels, remained below baseline levels after both single and multiple doses of givosiran. In patients with AIP experiencing recurrent porphyria attacks, four once-monthly givosiran 2.5 or 5 mg/kg doses resulted in maximum reductions from baseline in *ALAS1* mRNA of 67 and 74%, respectively, with these reductions maintained until day 168 (i.e. the end of the trial). At both dosages, reductions in *ALAS1* mRNA levels were associated with corresponding reductions in ALA and PBG levels of > 90%, leading to normalization of these levels [15].

2.2 Pharmacokinetics

Subcutaneous givosiran exhibits dose-proportionality across the dose range of 0.35–2.5 mg/kg. Givosiran is rapidly absorbed after single and multiple once-monthly doses in patients with AHP, with maximum plasma concentrations of givosiran and its active metabolite AS(N-1)3′ givosiran attained in a median of 3 h and 7 h. Givosiran exhibits high, dose-dependent protein binding (90%; not evaluated for active metabolite), with reduced binding observed with increasing givosiran concentrations. Givosiran and AS(N-1)3′ givosiran distribute primarily to the liver after subcutaneous administration [8].

The half-life of both givosiran and AS(N-1)3′ givosiran is 6 h, with a mean apparent clearance of 35.1 L/h and 64.7 L/h. Givosiran is metabolized by nucleases to shorter length oligonucleotides and is not a substrate of cytochrome P450 enzymes. The primary route of elimination is in the urine, with 5–14% of a dose recovered in the urine as givosiran and 4–13% as AS(N-1)3′ givosiran [8].

No clinically relevant differences in the pharmacokinetics of givosiran were observed based on age, gender, race/ethnicity, renal impairment [estimated glomerular filtration (eGFR) rate ≥ 15 to < 89 mL/min/1.73 m^2] or mild hepatic impairment [bilirubin ≤ 1 × upper limit of normal (ULN) and AST > 1 × ULN, or bilirubin > 1 × ULN to 1.5 × ULN]. The effect of end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) and moderate to severe hepatic impairment on the pharmacokinetics of givosiran is unknown [8].

Concomitant use of givosiran with sensitive CYP1A2 (e.g. caffeine) and CYP2D6 (e.g. dextromethorphan) substrates increases the concentrations of these substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of givosiran with CYP1A2 and CYP2D6 substrates, for which minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, reduce the CYP1A2 and CYP2D6 substrate dosage in accordance with approved product labeling [8].

Features and properties of givosiran

Alternative names	ALN-AS1; Givlaari™
Class	Amides, amino sugars, drug conjugates, pyrrolidines, small interfering RNA
Mechanism of action	5 aminolevulinate synthase inhibitors; RNA interference
Route of administration	Subcutaneous injection
Pharmacodynamics	A double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference, reducing elevated levels of liver *ALAS1* mRNA and, thereby reducing circulating levels of the neurotoxic intermediates aminolevulinic acid and porphobilinogen; the active metabolite AS(N-1)3′ givosiran is equipotent to givosiran in plasma at the recommended dosage
Pharmacokinetics	Dose proportionality (once-monthly 0.35–2.5 mg/kg doses); t_{max} of givosiran and AS(N-1)3′ givosiran is 3 h and 7 h; givosiran and AS(N-1)3′ givosiran distribute primarily to the liver after subcutaneous administration; half-life of givosiran and AS(n-1)3′ givosiran is 6 h and 6 h; metabolized by nucleases to shorter length oligonucleotides; not a substrate of cytochrome P450 enzymes; primary route of elimination is in the urine
Adverse reactions	
Most frequent (≥ 15%)	Nausea, injection site reactions, rash (includes pruritus, eczema, erythema, rash, rash pruritic urticaria), serum creatinine increase [includes blood creatinine increased, glomerular filtration rate (GFR) decreased, chronic kidney disease (decreased estimated GFR)]
ATC codes	
WHO ATC code	A16A (other alimentary tract and metabolic products)
EphMRA ATC code	A16A (other alimentary tract and metabolic products)
Molecular formula	$C_{524}H_{651}F_{16}N_{173}Na_{43}O_{316}P_{43}S_6$

2.3 Therapeutic Trials

The randomized, double-blind, multinational, phase III ENVISION trial enrolled 94 patients with AHP (mean age 37.5 years); of the 94 patients, 89 had AIP, 2 had VP, 1 had HCP and 2 had no identified genetic mutation [16]. The study also has an ongoing open-label extension phase; 93 of the 94 patients enrolled in this phase [16]. ENVISION inclusion criteria included having a minimum of two porphyria attacks requiring hospitalization, urgent healthcare visits or intravenous hemin administration at home in the 6 months prior to study entry [8, 16]. Hemin use was permitted during the study for treatment of acute porphyria attacks. Treatment groups were well balanced with respect to the historical porphyria attack rate, hemin prophylaxis prior to study entry, use of opioid medications and patient-reported measures of pain symptoms between attacks [8].

In ENVISION, once-monthly subcutaneous givosiran 2.5 mg/kg ($n = 46$) was associated with a significant reduction from baseline to 6 months in the composite annualized attack rate (ARR) for porphyria attacks (those requiring hospitalization, urgent care or hemin administration at home) compared with placebo ($n = 43$) in patients with AIP (mean composite ARR 3.2 vs 12.5; between group rate ratio 0.26; 95% CI 0.16–0.41; $p < 0.0001$) [primary endpoint] [16]. At 6 months, the median composite ARR was reduced by 90% in givosiran recipients compared with placebo recipients (median composite ARR 10.7 vs 1.0) and there was a threefold increase in the percentage of patients who were attack free in the givosiran group (50 vs 16.3% of patients in the placebo group). At 6 months, mean ALA and PBG levels were reduced from baseline by 77% and 76%, respectively, in the givosiran group [16]. The mean number of days of hemin use was also significantly reduced in the givosiran group compared with the placebo group (4.7 vs 12.8 days; ratio 0.3; $p = 0.0002$); ratio adjusted for prior hemin prophylaxis status and historical attack rates, with a ratio of < 1 favouring givosiran [8].

2.4 Adverse Events

In ENVISION, patients received givosiran for a median of 5.5 months, with 47 of the 48 patients in the givosiran group receiving ≥ 5 months' treatment. The most common adverse reactions occurring at least 5% more frequently in patients receiving givosiran than in placebo recipients were nausea (27 vs 11%), injection site reactions (25 vs 0%), rash (17 vs 4%; included pruritus, eczema, erythema, rash, rash pruritic, urticaria), serum creatinine increase [15 vs 4%; includes blood creatinine increased, GFR decreased, chronic kidney disease (decreased eGFR)], transaminase elevations (13 vs 2%) and fatigue (10 vs 4%). One patient discontinued givosiran treatment because of transaminase elevations. In placebo-controlled and open-label studies ($n = 111$), adverse reactions observed at a lower frequency in givosiran recipients included an anaphylactic reaction (one patient; 0.9%) and hypersensitivity (one patient; 0.9%) [8].

As with all oligonucleotides, there is a potential for immunogenicity with givosiran treatment. In placebo-controlled and open-label clinical studies in patients with AHP ($n = 111$), one patient (0.9%) developed treatment-emergent anti-drug antibodies during givosiran treatment. No clinically significant differences in the efficacy, safety or pharmacological profile of givosiran were observed in this patient [8].

There are no available data on the use of givosiran in pregnant women to evaluate a givosiran-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcome. In animal studies, administration of subcutaneous givosiran to pregnant rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses that produced maternal toxicity. The benefits and risks of givosiran for the mother and potential adverse effects to the fetus should be considered when prescribing givosiran to pregnant women [8].

2.5 Ongoing Clinical Trials

The open-label extension phase of ENVISION (NCT03338816) is currently evaluating the long-term

Key clinical trials of givosiran (Alnylam Pharmaceuticals)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Givosiran	Acute intermittent porphyria	I	Completed	Sweden, UK, USA	NCT02452372; ALN-AS1-001
Givosiran	Acute intermittent porphyria	I/II	Ongoing	Sweden, UK, USA	NCT02949830; ALN-AS1-002
Givosiran vs placebo	Acute hepatic porphyria	III	Completed primary study; ongoing open-label extension	Multinational	NCT03338816; ALN-AS1-003; ENVISION

efficacy and safety of subcutaneous givosiran in patients with AHP, with an anticipated completion date of September 2021. In addition, an ongoing phase I/II study (NCT02949830) is evaluating the long-term efficacy and safety of givosiran in patients with AIP, with an estimated completion date of November 2019. An expanded access program (NCT04056481) for givosiran treatment in patients with AHP is also available.

3 Current Status

Givosiran received its first global approval on 20 November 2019 in the USA for the treatment of adults with AHP. Givosiran received a positive opinion from the European Medicines Agency on 30 January 2020 for the treatment of AHP in adults and adolescents aged 12 years and older.

Compliance with Ethical Standards

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