Givosiran: Hepatic Effects

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SUMMARY

- The Phase 1/2 OLE study was an extension of the Phase 1 clinical study evaluating the safety and tolerability of givosiran in patients (N=16) with AIP for up to 48 months.[1]
  - By the end of the study at 48 months, hepatic AEs were reported in 7 patients (44%), most of which were mild or moderate in severity and resolved during treatment with givosiran.[1]
- The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP.[2]
  - At baseline, 37% of patients had coexisting illnesses of increased aminotransferase levels, and 28% had liver disease.[2]
  - During the 6-month double-blind period, an ALT level > 3x ULN was reported in 7 patients (15%) in the givosiran group and 1 patient (2%) in the placebo group.[2]
  - Upon completion of the 6-month double-blind period, all eligible patients received givosiran in the ENVISION OLE study. At 36 months, hepatic AEs were reported in 18 (19%) patients treated with givosiran.[3]
  - ALT elevation generally occurred 3 to 6 months after givosiran treatment initiation and resolved over time.[2,3]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety signals regarding givosiran and hepatic effects.[4]

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BACKGROUND

Elevated serum transaminase levels have been observed in some patients with AHP during an acute attack.[5,6] In EXPLORE, a prospective natural history study of 112 patients with AHP and recurrent attacks, 16% of patients were found to have liver transaminase elevations (>ULN and <3x ULN) at baseline.[7] Furthermore, in ENVISION, a study of 94 patients diagnosed with AHP that assessed the efficacy and safety of givosiran treatment vs placebo, 37% and 28% of patients had coexisting illnesses of increased aminotransferase levels and liver disease at baseline, respectively.[2]

CLINICAL DATA

Phase 1 Study

The Phase 1 study was a multicenter, randomized, placebo-controlled, 3-part study (n=23 in Parts A and B; n=17 in Part C) designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of givosiran in patients with AIP.[8]

In the Phase 1 study, there were 2 AEs of elevated ALT and 2 AEs of elevated AST in patients receiving givosiran. ALT increases occurred in 1 patient who received a single dose of 0.35 mg/kg in Part A and in 1 patient who received 2.5 mg/kg quarterly in Part C. AST increases occurred in 1 patient who received a single dose of 0.35 mg/kg in Part A and in 1 patient who received 2.5 mg/kg quarterly in Part C.[9]

Phase 1/2 Open Label Extension

The Phase 1/2 OLE study was an extension of the Phase 1 clinical study evaluating the safety and tolerability of givosiran in patients (N=16) with AIP for up to 48 months. Eligible patients who completed Part C of the Phase 1 study were enrolled in the Phase 1/2 OLE study. Upon study entry, patients received givosiran 2.5 mg/kg once monthly or 5.0 mg/kg once monthly or every 3 months. All patients enrolled in the OLE were transitioned to receive subcutaneous injections of givosiran 2.5 mg/kg once a month.[1]

By the end of the study at 48 months, hepatic AEs were reported in 7 patients (44%), most of which were mild or moderate in severity and resolved during treatment with givosiran. None of the hepatic AEs were serious and did not result in dose interruptions, changes in dose, or treatment discontinuation.[1]

Elevations in liver transaminases were reported in 10 patients (63%). Two patients had transient ALT or AST elevations >3x ULN and ≤5x ULN without a change in total bilirubin. All transaminase elevations resolved with continued givosiran treatment, and there were no Hy's law cases (hepatocellular injury indicted by ALT or AST elevation ≥3x ULN and increased total bilirubin ≥2x ULN. Mean values of ALT, AST, ALP, bilirubin, and GGT were generally stable over the course of the study.[1]

ENVISION Study

The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrolled patients were randomized on a 1:1 basis to receive subcutaneous injections of givosiran 2.5 mg/kg (n=48) or placebo (n=46) once a month for 6 months, followed by an optional 30-month OLE. The primary endpoint was the annualized rate of composite porphyria attacks among patients with AIP at 6 months.[2]

At baseline, 37% (n=35/94) of patients had coexisting illnesses of increased aminotransferase levels, and 28% (n=26/94) had liver disease. A summary of serum aminotransferase elevations at baseline and during the 6-month double-blind period is summarized in **Table 1**.[2]

Table 1. Serum Aminotransferase Elevations in Patients with AHP. [10]

n (%)	Placebo (n=46)	Givosiran (n=48)
Baseline		
ALT elevation > ULN and ≤ 3xULN at baseline[a]	2 (4)	10 (21)
AST elevation > ULN and ≤ 3xULN at baseline[a]	3 (7)	9 (19)
ALT or AST elevation >ULN and ≤ 3xULN at baseline[a]	3 (7)	13 (27)
6-month double-blind period		
ALT elevation > ULN and ≤ 3xULN	9 (20)	19 (40)
ALT elevation > 3xULN to ≤ 5xULN	1 (2)	5 (10)
ALT elevation > 5xULN to ≤ 10xULN	0	2 (4)
ALT elevation > 10xULN	0	0
ALT or AST > 3xULN with concurrent total bilirubin > 2xULN	0	0

Abbreviations: AHP = acute hepatic porphyria; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
[a]Defined as highest value of serum ALT or AST at screening.

An ALT level >3x ULN was reported in 7 patients (15%) in the givosiran group and 1 (2%) in the placebo group. These increases occurred after the first 3 to 5 months of givosiran and placebo treatment. Six patients continued givosiran with resolution of ALT elevation. Of the 6 patients, 1 patient experienced increase in ALT levels of 5.4x ULN, that met the protocol's dose interruption rules (ALT >5x ULN) and resumed dosing at 1.25 mg/kg. A summary of hepatic AEs is provided in **Table 2**.[2]

One patient discontinued givosiran treatment due to an SAE of increase in ALT levels of 9.9x ULN, that met the protocol's stopping rules for permanent discontinuation (>8x ULN). The event resolved and the patient withdrew from the study at the end of the DB period.[2]

Table 2. Summary of Hepatic Adverse Events in Patients with AHP.[10]

n (%)	Placebo (n=46)	Givosiran (n=48)
Any hepatic adverse event[a]	1 (2)	6 (13)
Investigations system organ class	1 (2)	6 (13)
Alanine aminotransferase increased	1 (2)	4 (8)
Aspartate aminotransferase increased	1 (2)	3 (6)
Blood bilirubin increased	1 (2)	0
Gamma-glutamyltransferase increased	0	1 (2)
Hepatic enzyme increased	0	1 (2)
Liver function test abnormal	0	1 (2)

Abbreviations: AHP = acute hepatic porphyria; MedDRA = Medical Dictionary for Regulatory Activities
[a]Hepatic adverse events include all adverse events selected according to MedDRA terms in the Drug-related hepatic disorders Standardized MedDRA Query, both narrow and broad terms.

ENVISION OLE Period

Upon completion of dosing in the ENVISION double-blind period, all eligible patients (99%; n=93/94) continued in the ENVISION OLE, receiving monthly givosiran administration. In the OLE, patients were initially assigned to givosiran 2.5 mg/kg monthly or givosiran 1.25 mg/kg monthly for a treatment period of at least 6 months. A protocol amendment was enacted to increase the dose of all patients to 2.5 mg/kg monthly.[3]

By the end of the ENVISION study, hepatic AEs were reported in 18 patients (19%), 9 in the continuous givosiran group and 9 in the placebo crossover group. Overall, 10 patients (11%) treated with givosiran had ALT levels >3x ULN and 3 patients (3%) had ALT levels of >5x ULN. ALT elevation generally occurred 3 to 6 months after givosiran treatment initiation and resolved over time.[3]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety concerns regarding hepatic effects with the use of givosiran. There were no cases suggestive of significant DILI attributable to givosiran. Cases were consistent with the known ADR profile for givosiran and/or were confounded by patients' underlying disease, medical history, or concurrent illnesses.[4]

Hepatic effects remain an important potential risk and will continue to be closely monitored through routine pharmacovigilance activities.[4]

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the GIVLAARI Prescribing Information[11]:

- WARNINGS AND PRECAUTIONS Section 5.2 Hepatic Toxicity
- ADVERSE REACTIONS Section 6.1 Clinical Trial Experience
- DOSAGE AND ADMINISTRATION Section 2.1 Recommended Dosage
- PATIENT COUNSELING INFORMATION Section 17 Hepatic Toxicity

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ABBREVIATIONS

ADR = adverse drug reaction; AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = double-blind; DILI = drug-induced liver injury; GGT = gamma-glutamyl transpeptidase; LFT = liver function test; MedDRA = Medical Dictionary for Regulatory Activities; OLE = open label extension; SAE = serious adverse event; ULN = upper limit of normal.

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