Givosiran: Renal Effects

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for GIVLAARI® (givosiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- In the 6-month double-blind period of the ENVISION study, 15% of patients (7/48) treated with givosiran and 7% of patients (3/46) on placebo had renally-related AEs, the majority of which were an increase in serum creatinine level or a reduction in eGFR.[1]
- In the 30-month OLE of the ENVISION study, renal AEs were reported in 25% of patients (12/48) in the continuous givosiran group and 20% of patients (9/46) in the placebo crossover group. Worsening of chronic renal failure was reported as a SAE considered related to givosiran in 1 patient.[2]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database regarding renal effects did not identify any new safety concerns. Renal effects remain an important potential risk and will continue to be closely monitored through routine pharmacovigilance activities.[3]

INDEX

CLINICAL DATA

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 (N=94) 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.[1,4]

Patients were eligible to enroll in the study with an eGFR greater than 30 mL/min/1.73m^2.[4] At baseline, 25% of patients had medical history relating to renal impairment, and 34% of the patients had an eGFR of less than 60 mL/min/1.73m^2.[1]

In the ENVISION study at 6 months, 15% of patients (7/48) treated with givosiran and 7% of patients (3/46) on placebo had renally-related AEs, the majority of which were an increase in serum creatinine level or a reduction in eGFR. In the givosiran group, 10% of patients (5/48) had either the onset or worsening of chronic kidney disease, and 2% of patients (1/46) in the placebo group had worsening nephropathy, all of which were associated with an increased creatinine level and a decreased eGFR. Worsening chronic kidney

disease was reported as a SAE in 4% of patients (2/48) receiving givosiran and no patients receiving placebo.[1,5]

Renal biopsies from the patients who experienced these SAEs were consistent with underlying renal disease and showed no signs of an adverse drug effect. No patients discontinued either givosiran or placebo due to a renal AE. An analysis of renal measures showed that increases in the serum creatinine level and corresponding decreases in the eGFR were noted early during givosiran treatment; both findings were reversible over time without any dose modifications. Stratification of patients according to the baseline category of eGFR did not show an increased percentage of renal impairment in any group.[1]

ENVISION Open-Label Extension Study

Upon completion of the ENVISION 6-month double-blind period, eligible patients continued in the optional 30-month OLE study evaluating the long-term efficacy and safety of givosiran in patients (n=93). In the OLE, patients were initially assigned to givosiran 2.5 mg/kg monthly (n=56) or givosiran 1.25 mg/kg monthly (n=37) for a treatment period of at least 6 months. After such time, a protocol amendment was enacted to increase the dose of all patients receiving the 1.25 mg/kg monthly dose to the 2.5 mg/kg monthly dose.[2]

At 30 months into the OLE (for a total of 36 months in ENVISION), renal AEs were reported in 25% of patients (12/48) in the continuous givosiran group and 20% of patients (9/46) in the placebo crossover group. Worsening of chronic renal failure was reported as a SAE considered related to givosiran in 1 patient. No renal AEs led to a discontinuation of treatment. Small decreases in eGFR observed soon after initiation of givosiran treatment generally stabilized by Months 12 to 26. Mean changes in eGFR remained stable in most patients during the OLE.[2]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database regarding renal effects did not identify any new safety concerns. The majority of reported cases presented limited information regarding patients' medical history, concomitant medications, time to onset of the reporting events, and event details, precluding meaningful medical causality assessment. The cases with sufficient information were consistent with the already known ADR profile for givosiran and/or were confounded by patients' medical history and underlying disease, as AHP is known to be associated with increased risk of CKD.[3]

Renal effects remain an important potential risk and will continue to be closely monitored through routine pharmacovigilance activities.[3]

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The WARNINGS AND PRECAUTIONS section provides the following information[6]:

Renal Toxicity

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI. In the placebo-controlled study, 15% of the patients in the GIVLAARI arm experienced a renally-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment with GIVLAARI as clinically indicated.

The PATIENT COUNSELING INFORMATION section provides the following information[6]:

Renal Toxicity: *Inform patients that increases in serum creatinine and decreases in eGFR have been reported and that laboratory testing will be conducted as clinically indicated.*

ABBREVIATIONS

ADR = adverse drug reaction; AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; OLE = open-label extension; SAE = serious adverse event.

REFERENCES

1. Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med*. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1913147
2. Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. *J Hepatol*. 2023;79(5):1150-1158. doi:10.1016/j.jhep.2023.06.013
3. Alnylam Pharmaceuticals. Data on file. MED-ALL-AS1-2400049.
4. Protocol for: Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. N Engl J Med. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1913147.
5. Supplement to: Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med*. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1807838
6. GIVLAARI (givosiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.