Givosiran: Renal Effects

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SUMMARY

- In the 48-month Phase 1/2 OLE, renal AEs were reported in 31% of patients (5/16), all of which were mild or moderate in severity. None of the renal AEs resulted in treatment interruption or discontinuation.[1]
- 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.[2]
- 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.[3]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving renal effects related to the use of givosiran. Renal effects remain an important potential risk and continue to be closely monitored through routine pharmacovigilance activities.[4]

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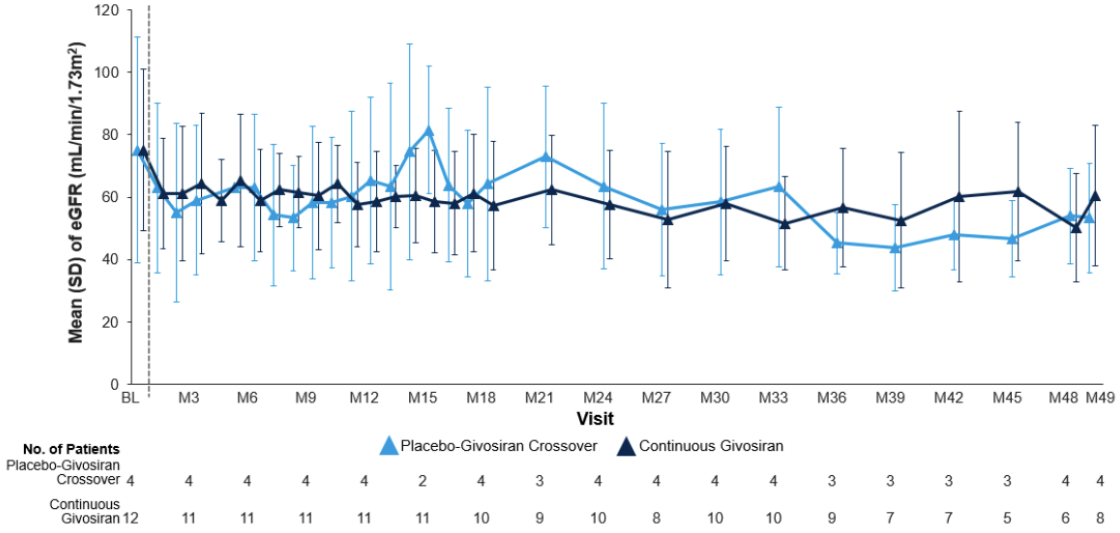
CLINICAL DATA

Phase 1/2 Open Label Extension Study

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. 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]

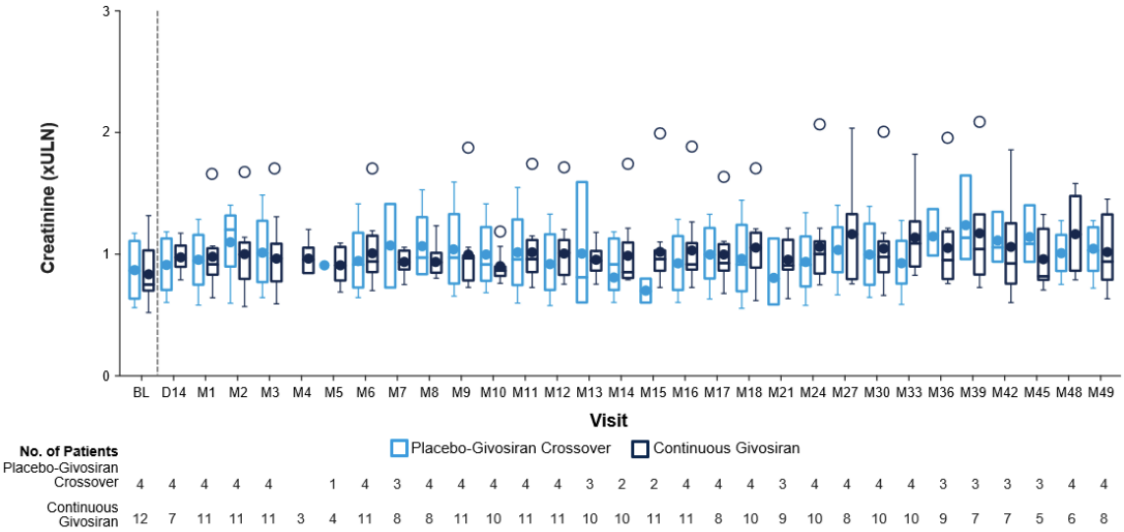
By the end of the study at 48 months, renal AEs were reported in 31% of patients (5/16). All the AEs were mild or moderate in severity, and none were serious or resulted in treatment interruption or discontinuation. Two patients with a medical history of renal impairment (eGFR 30-44 mL/min/1.73m^2 at study entry) had AEs of renal impairment that were moderate in severity. The mean values for eGFR and serum creatinine were generally stable over the course of the study, with intermittent fluctuations observed over time (**Figures 1 and 2**).[1,5]

Figure 1. Mean (SD) eGFR Over Time in the Phase 1/2 OLE.[5,a]



Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; OLE = open-label extension; SD = standard deviation.
[a]Baseline is defined as the derived baseline value in the Phase 1 study. The dotted line indicates the gap in time between baseline of the Phase 1 study and the first visit in the OLE study.
From Sardh et al.[5]

Figure 2. Creatinine Levels Relative to ULN by Visit in the Phase 1/2 OLE.[5,a]



Abbreviations: BL = baseline; D = day; M = month; OLE = open-label extension; ULN = upper limit of the normal.
[a]Baseline is defined as the derived baseline value in the Phase 1 study. The dotted line indicates the gap in time between baseline of the Phase 1 study and the first visit in the OLE study.
From Sardh et al.[5]

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.[2]

Patients were eligible to enroll in the study with an eGFR greater than 30 mL/min/1.73m^2.[6] 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.[2]

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.[2,7]

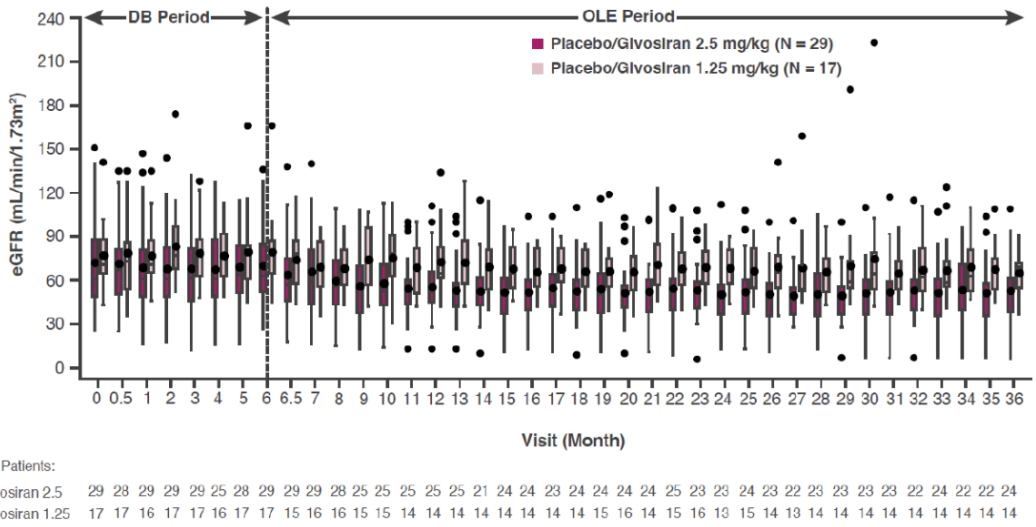
Renal biopsies from the patients who experienced these SAEs were consistent with underlying renal disease and showed no signs of an adverse drug effect. No patients discontinued either givosiran or placebo due to a renal AE. An analysis of renal measures showed that increases in the serum creatinine 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.[2]

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.[3]

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 (**Figure 3**).[3,8]

Figure 3. eGFR Over Time in the ENVISION OLE.[8,a]



Abbreviations: DB = double-blind; eGFR = estimated glomerular filtration rate; OLE = open-label extension.
[a]Boxplots present median (horizontal line), interquartile range (top and bottom edges of the box), and range with outliers excluded (whiskers; third quartile + 1.5 * interquartile range). Outliers are represented as single data points.
From Kuter et al.[8]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving renal effects related to the use of givosiran. 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 chronic kidney disease.[4]

Renal effects remain an important potential risk and continues to be closely monitored through routine pharmacovigilance activities.[4]

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The **WARNINGS AND PRECAUTIONS** section provides the following information[9]:

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[9]:

Advise patients of the potential risks of GIVLAARI treatment:

- ***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; BL = baseline; D = day; DB = double-blind; eGFR = estimated glomerular filtration rate; M = month; OLE = open-label extension; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of the normal.

Updated 02 April 2026

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7. 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
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