

Patisiran: Immunogenicity

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SUMMARY

- In the placebo-controlled and open-label clinical studies (Phase 2 OLE, APOLLO, and Global OLE studies), 7 out of 194 (3.6%) patients developed ADAs during treatment with patisiran.¹ There was no evidence of an effect of ADAs on clinical efficacy, safety, or the PK or PD profiles of patisiran.^{1,2}
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify safety concerns regarding ADAs related to the use of patisiran.³
- ADA testing for patisiran is not commercially available.

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RELEVANT INFORMATION

Patisiran Formulation

Patisiran is a double-stranded siRNA administered via IV infusion and formulated as a LNP for targeted delivery to hepatocytes. The LNP components protect the siRNA from enzymatic degradation and provide stability during circulation, allowing the siRNA to reach the target tissue for intracellular delivery.⁴

ADA Testing Availability

ADA testing for patisiran is not commercially available.

CLINICAL DATA

Phase 2 Study

The Phase 2 study was a multicenter, international, open-label, multiple-dose escalation study in patients with hATTR-PN. Cohorts of 3 patients received 2 doses of patisiran, with each dose administered as an IV infusion.⁴

- Cohorts 1–3 (n=10) received 2 doses of patisiran 0.01 mg/kg (n=4), 0.05 mg/kg (n=3), and 0.15 mg/kg every 4 weeks (n=3), respectively.
- Cohorts 4 and 5 (n=7) both received 2 doses of patisiran 0.3 mg/kg every 4 weeks.
- Cohorts 6–9 (n=12) all received 2 doses of patisiran 0.3 mg/kg every 3 weeks.

ADAs

During the Phase 2 study, 2 out of 29 (6.9%) patients, both in the patisiran 0.3 mg/kg every 3 weeks dose group, had treatment-emergent ADAs. One patient was confirmed ADA positive on Day 56 (titer, 40) and tested negative for ADAs at all other times. The second patient was confirmed ADA positive on Days 7 (titer, 80), 56 (titer, 320), and 208 (titer, 320) and tested ADA negative at all other points. Nadir TTR reduction in these 2 patients (75% and 95.4%) was similar to the previously reported maximum mean TTR reduction for all patients (82.9% – 86.7%).⁴

Phase 2 OLE Study

The Phase 2 OLE study (N=27) was a multicenter, international study in patients with hATTR-PN. Patients who previously received and tolerated patisiran in the Phase 2 study were eligible to enroll in the Phase 2 OLE study. Patients received IV patisiran 0.3 mg/kg every 3 weeks for approximately 2 years.⁴

ADAs

During the Phase 2 OLE, 1 out of 27 (3.7%) patients tested ADA positive, with a low titer (80) at screening and on Days 21 and 84, after having previously developed ADAs during the Phase 2 study. There was no impact of ADAs on the TTR reduction in this patient.⁴

APOLLO Study

APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, phase 3 study designed to assess the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with the hATTR-PN. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.⁵

ADAs

During the APOLLO study, 5 out of 145 (3.4%) patients in the patisiran group and 1 out of 77 (1.3%) patients in the placebo group developed treatment-emergent ADAs. The 5 patisiran-treated patients tested positive for ADAs in Week 3, with 2 patients also testing positive in Week 18. ADA positivity was transient, as all samples tested negative at subsequent visits throughout the study. ADA titer ranged from 40 to 160.²

Global OLE Study

The Global OLE study (N=211) was a multicenter, international study designed to evaluate the long-term safety and efficacy of IV patisiran in patients with hATTR-PN. Patients with hATTR-PN who completed the patisiran Phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue IV patisiran 0.3 mg/kg every 3 weeks for up to 5 years. The study enrolled 25 patients from the patisiran Phase 2 OLE study (Phase 2 OLE-patisiran group), 137 patients from the APOLLO-patisiran arm (APOLLO-patisiran group), and 49 patients from the APOLLO-placebo arm (APOLLO-placebo group).⁶

ADAs

During the 5-year Global OLE, 2 out of 211 (1.0%) patients treated with patisiran were confirmed positive for ADA results: 1 (2.5%) in the APOLLO-placebo group, 1 (0.8%) in the APOLLO-patisiran group, and none in the Phase 2 OLE group. ADA titers were low (80 and 40, respectively) and did not have any effect on safety (no infusion-related reactions, anaphylactic reactions, or hypersensitivity reactions).⁷

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify safety concerns regarding ADAs related to the use of patisiran.³

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The **ADVERSE REACTIONS** section provides the following information¹:

Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ONPATTRO in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies to ONPATTRO were evaluated by measuring antibodies specific to PEG2000-C-DMG, a lipid component exposed on the surface of ONPATTRO. In the placebo-controlled and open-label clinical studies, 7 of 194 (3.6%) patients with hATTR amyloidosis developed anti-drug antibodies during treatment with ONPATTRO. One additional patient had pre-existing anti-drug antibodies. There was no evidence of an effect of anti-drug antibodies on clinical efficacy, safety, or the pharmacokinetic or pharmacodynamic profiles of ONPATTRO. Although these data do not demonstrate an impact of anti-drug antibody development on the efficacy or safety of ONPATTRO in these patients, the available data are too limited to make definitive conclusions.

ABBREVIATIONS

ADA = anti-drug antibody; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; LNP = lipid nanoparticle; mNIS+7 = modified Neuropathy Impairment Score +7; PD = pharmacodynamics; PK = pharmacokinetics; OLE = open-label extension; siRNA = small interfering ribonucleic acid; TTR = transthyretin.

Updated 22 September 2025

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