Patisiran: Management of Infusion-Related Reactions

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CLINICAL DATA

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 hATTR-PN. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[1]

Global Open-Label Extension 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).[2]

APOLLO-B Study

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months.[3]

Management of IRRs in Patisiran Clinical Studies

In the APOLLO, Global OLE, and APOLLO-B studies, IRRs were managed according to protocol specifications[4–6]:

- In the event of an IRR, the infusion of patisiran could be stopped and the patient closely monitored until resolution of the reaction. Drugs that could be used to facilitate resolution and permit

resumption of patisiran administration included but were not limited to: paracetamol/acetaminophen (or equivalent), additional histamine H1/H2 receptor antagonists, NSAIDs, adrenaline, supplemental oxygen, IV fluids, and/or corticosteroids.

- Following the resolution of a mild or moderate IRR that required interruption of the patisiran infusion, resumption of administration could occur at the Investigator's discretion at a slower infusion rate (but not to exceed 3 hours) for that dose and for all subsequent doses of patisiran. If the infusion was delayed, the administration of the infusion was completed no more than 6 hours from the initial start of the infusion. In the case of a severe IRR, the study drug administration was not resumed for any patients until the case was discussed with the Medical Monitor.
- In the event of an IRR and following consultation with the Medical Monitor, the patient's steroid premedication could be increased based on the following recommended steps:

    1. If the IRR occurred while the patient received 10 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and did not resolve with slowing of the infusion rate, then the dose should be increased by multiples of 5 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and/or 5 mg oral dexamethasone or equivalent the night before the IV infusion.
    2. Increased dose of premedication steroids should NOT exceed the combination of 20 mg IV dexamethasone or equivalent on the day of infusion and 8 mg oral dexamethasone or equivalent taken the night before the infusion.
    3. If the IRR occurred while the patient received less than 10 mg IV dexamethasone or equivalent, then the patient should return to the prior dose of IV dexamethasone or equivalent that did not result in an IRR.

The patient's infusion site was assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient remained at the study site for 1 hour following completion of dosing for observation and completion of assessments.[4–6]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the ONPATTRO Prescribing Information[7]:

- DOSAGE AND ADMINISTRATION Section 2.2 Required Premedication
- WARNINGS AND PRECAUTIONS Section 5.1 Infusion-Related Reactions

ABBREVIATIONS

6-MWT = 6-minute walk test; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; H1 = histamine 1; H2 = histamine 2; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IRR = infusion-related reaction; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; NSAID = non-steroidal anti-inflammatory drug; OLE = open-label extension; wtATTR = wild-type transthyretin amyloidosis.

Updated 19 March 2026

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