Patisiran: Premedications

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 ONPATTRO® (patisiran) 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 APOLLO, Global OLE, and APOLLO-B studies, all patients received the following premedications at least 60 minutes before each infusion to reduce the likelihood of IRRs[1–3]:
  - IV dexamethasone (10 mg) or equivalent
  - Oral paracetamol/acetaminophen (500 mg) or equivalent
  - IV H1 blocker (e.g., diphenhydramine 50 mg)
  - IV H2 blocker (e.g., ranitidine 50 mg, famotidine 20 mg)
- During the APOLLO and Global OLE studies, modifications to the premedication regimen were allowed after consultation with the Medical Monitor either due to a patient's inability to tolerate one or more of the premedications or due to the occurrence of IRRs unresponsive to slowing of the infusion rate. Oral premedication equivalents were permitted.[1,2]
- During the APOLLO-B study, lowering the dose of the steroid premedication was allowed after consultation with the Medical Monitor either due to a patient's inability to tolerate the steroid premedication regimen or a patient's ability to tolerate their double-blind study drug infusions well with their steroid premedication regimen. Oral premedication equivalents were permitted.[3]

INDEX

APOLLO – Global OLE – APOLLO-B – Label Information – Abbreviations – References

APOLLO

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.[4]

Premedication Regimen

In APOLLO, to reduce the likelihood of IRRs, patients received the following premedications or equivalents at least 60 minutes before each infusion[1]:

- IV dexamethasone (10 mg) or equivalent
- Oral paracetamol/acetaminophen (500 mg) or equivalent
- IV H1 blocker (e.g., diphenhydramine 50 mg)
- IV H2 blocker (e.g., ranitidine 50 mg, famotidine 20 mg)

Modifications to the Steroid Premedication

Modifications to the premedication regimen were allowed after consultation with the Medical Monitor either due to a patient's inability to tolerate one or more of the premedications or due to the occurrence of IRRs unresponsive to slowing of the infusion rate[1]:

- If a patient had difficulty tolerating the steroid premedication (e.g., patient developed uncontrolled hyperglycemia, altered mental status, or other complication), then lowering the dose of the steroid premedication may be allowed after consultation with the Medical Monitor based on the following required steps[1]:
  - If the current steroid dosage is 10 mg IV dexamethasone or equivalent, then the dosage may be lowered in increments no greater than 2.5 mg IV dexamethasone or equivalent.
  - After each incremental lowering below 10 mg IV dexamethasone or equivalent, the patient must receive three consecutive IV doses of patisiran without IRR and continued signs or symptoms of steroid intolerance before further reductions in steroid premedication.
  - The steroid premedication dosage should not be reduced below 5 mg IV dexamethasone or equivalent.
- In the event of an IRR and following consultation with the Medical Monitor, the patient's steroid premedication could have been 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.
  - Increased dose of steroid premedication 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.
  - 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.

GLOBAL OLE

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).[5]

Premedication Regimen

In the Global OLE, all patients received premedication in order to reduce the risk of IRR. The premedication regimen used in Global OLE was identical to that in APOLLO (listed above). Oral premedication equivalents were permitted, but had to be administered in the presence of a healthcare professional.[2]

Home Infusion

Patients who had received at least 3 consecutive doses of patisiran on the study at the clinic site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion were eligible to have patisiran administered at home by a healthcare professional, where allowed by applicable country and local regulations. Home administration of patisiran was performed by a healthcare professional trained on the protocol and administration of premedications and patisiran infusion.[2]

If a patient received patisiran through home infusion, premedications were prepared by the site pharmacy and administered at home to the patient per study protocol. There is no modified premedication regimen specific to patients who receive home infusions of patisiran.[2]

APOLLO-B

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. After the 12-month double-blind treatment period, all patients received patisiran in an OLE period.[6]

Premedication Regimen

In APOLLO-B, all patients received premedication in order to reduce the risk of IRR. The premedication regimen used in APOLLO-B was identical to the regimen in APOLLO (listed above). Oral premedication equivalents were permitted, but had to be administered in the presence of a healthcare professional.[3]

Modifications to the Steroid Premedication

Modifications to the premedication regimen may be made after consultation with the Medical Monitor for either of the two following reasons as specified in the protocol[3]:

- If a patient is having difficulty tolerating the steroid premedication regimen (e.g., patient developed uncontrolled hyperglycemia, altered mental status, or other complication), then lowering the dose of the steroid premedication may be allowed after consultation with the Medical Monitor.
- For patients who are tolerating their double-blind study drug infusions well with their current steroid premedication regimen (i.e., no IRRs during the past 3 or more infusions), the steroid dose may be reduced in 2.5 mg increments to a minimum dose of 5 mg IV dexamethasone or equivalent.
    - At the start of the open-label period, patients must receive dexamethasone 10 mg or the equivalent as their steroid premedication. Patients taking more than 10 mg of dexamethasone at the end of the double-blind period should take the higher dose. The steroid dose then may be tapered as described above if the patient is tolerating infusions. However, if a patient's steroid premedication had been decreased in the double-blind period due to their inability to tolerate

the premedication regimen as described above, continuation of the reduced dose regimen (as it had been in the double-blind period) may be permitted after consultation with the Medical Monitor.

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The **DOSAGE AND ADMINISTRATION** section provides the following information[7]:

Required Premedication

All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs). Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:

- *Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)*
- *Oral acetaminophen (500 mg)*
- *Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)*
- *Intravenous H2 blocker (e.g., famotidine 20 mg, or equivalent)*

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs.

The **WARNINGS AND PRECAUTIONS** section provides the following information[7]:

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs led to infusion interruption in 5% of patients. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies. Across clinical studies, the most common symptoms (reported in greater than 2% of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache. Severe hypotension and syncope have been reported as symptoms of IRRs in the expanded access program and postmarketing setting.

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs.

ABBREVIATIONS

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

Updated 20 October 2025

REFERENCES

1. Protocol for: Adams D, González-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153
2. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-1800584.
3. Protocol for: Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
4. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153
5. Adams, Polydefkis, González-Duarte, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol*. 2021;20(1):49-59. doi:10.1016/S1474-4422(20)30368-9
6. Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
7. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.