Transition between Patisiran and Vutrisiran

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 AMVUTTRA® (vutrisiran) is provided here, and 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

- Patients who received patisiran during the 18-month treatment period of the HELIOS-A study were transitioned to vutrisiran during the RTE period (patisiran/vutrisiran group).[1]
  - At Month 18 of the RTE period, a consistent clinical effect was observed across key endpoints, including mNIS+7, Norfolk QOL-DN, 10-MWT, R-ODS, and mBMI, when compared to the HELIOS-A study baseline following the transition from patisiran to vutrisiran.[1]
  - A sustained TTR reduction was observed in patients who received patisiran during the 18-month treatment period and were transitioned to vutrisiran during the RTE (patisiran/vutrisiran group). The TTR reduction observed in patients in the patisiran/vutrisiran group was comparable with the TTR reduction observed in patients who received vutrisiran during both the 18-month treatment period and the RTE (vutrisiran/vutrisiran group).[1]
  - Through Month 18 of the RTE period, the majority of AEs were mild or moderate in severity. No deaths were considered related to study drug by the investigators.[1]
- Studies evaluating the transition of patients from vutrisiran to patisiran have not been conducted to date.[2,3]

INDEX

TRANSITION FROM PATISIRAN TO VUTRISIRAN

HELIOS-A Study

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[1,4]

Exclusion Criteria

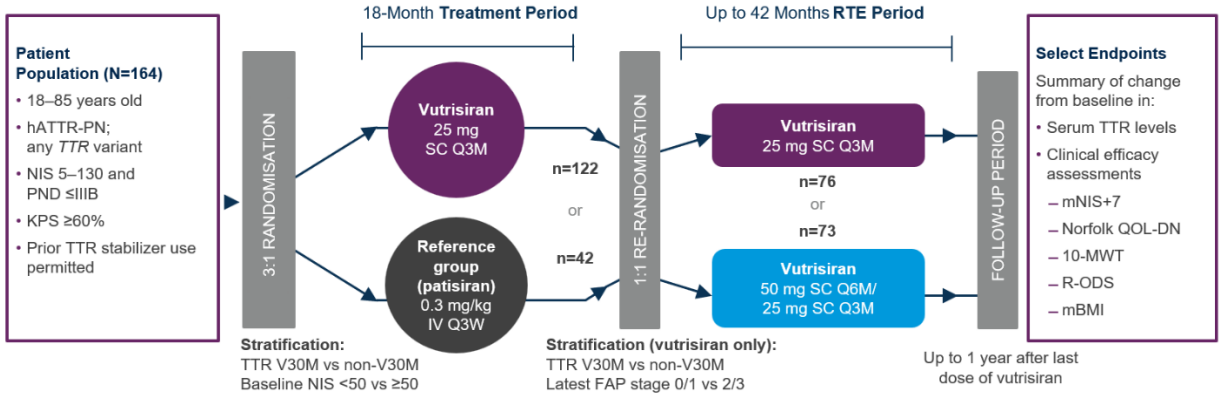
Patients were excluded from the study if they had received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR.[5]

HELIOS-A RTE Study

After the 18-month treatment period of HELIOS-A was completed, eligible patients (N=149), including those on patisiran as a reference group, entered the RTE and were randomized 1:1 to receive either vutrisiran 25 mg every 3 months (n=76) or vutrisiran 50 mg every 6 months (n=73) by subcutaneous injection for up to 42 months (**Figure 1**).[1] Patients in the patisiran reference arm were administered the last dose of patisiran in Week 81 and received the first dose of vutrisiran on Day 1 of the RTE period, which was 3 weeks after Week 81.[5]

During the RTE period, a protocol amendment was enacted to transition patients on vutrisiran 50 mg every 6 months to vutrisiran 25 mg every 3 months due to the pharmacodynamics of serum TTR recovery seen at the end of the 6-month dosing interval for patients on vutrisiran 50 mg every 6 months.[1]

Figure 1. HELIOS-A RTE Study Design.[1]

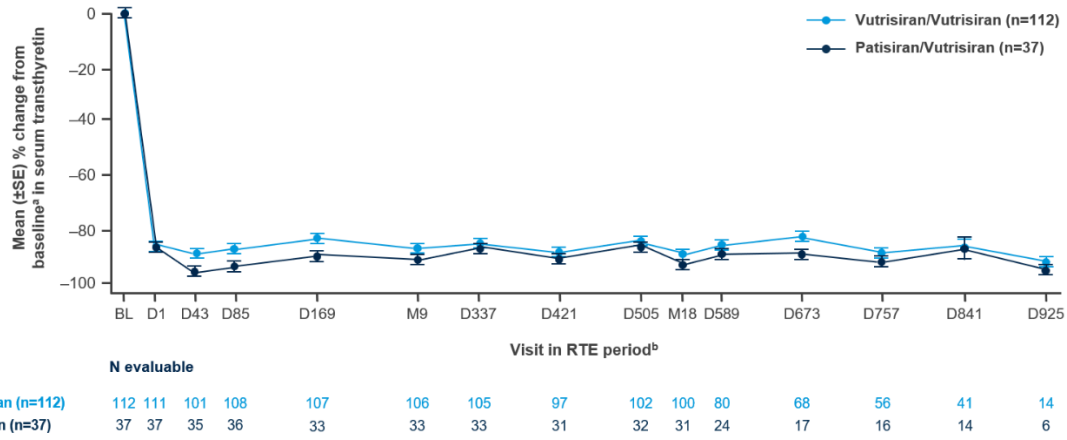


Abbreviations: 10-MWT = 10-meter walk test; FAP = familial amyloid polyneuropathy; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; KPS = Karnofsky Performance Status; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PND = polyneuropathy disability; Q3M = every 3 months; Q6M, every 6 months; Q3W = every 3 weeks; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SC = subcutaneous; TTR = transthyretin.
From Cauquil et al.[1]

Serum TTR Level

A sustained TTR reduction was observed in patients who received patisiran during the 18-month treatment period and were transitioned to vutrisiran during the RTE (patisiran/vutrisiran group). The TTR reduction observed in patients in the patisiran/vutrisiran group was comparable with the TTR reduction observed in patients who received vutrisiran during both the 18-month treatment period and the RTE (vutrisiran/vutrisiran group) (**Figure 2**).[1]

Figure 2. Mean (±SE) Percent Change from Baseline in Serum TTR During the RTE.[1]



Abbreviations: BL = baseline; D = day; M = month; RTE = randomized treatment extension; SE = standard error; TTR = transthyretin.
[a]Baseline is defined as the same as the 18-month treatment period, which is the mean of all non-missing measurements before the first dose in the 18-month treatment period.
[b]As of a data cut of February 23, 2024.
From Cauquil et al.[1]

Clinical Efficacy Endpoints

At Month 18 of the RTE period, a consistent clinical effect was observed across key endpoints compared to the HELIOS-A study baseline following the transition from patisiran to vutrisiran (**Table 1**).[1]

Table 1. Change from Baseline for Select Clinical Efficacy Endpoints in Patients Who Switched From Patisiran to Vutrisiran During the RTE.[1]

Endpoint, mean (SD)	n	Treatment Period Month 18 Patisiran (n=42)	n	RTE Month 18 Patisiran/Vutrisiran (n=37)
mNIS +7	36	1.59 (21.50)	32	3.73 (20.79)
Norfolk QOL-DN	38	-0.6 (19.3)	32	1.8 (19.3)
10-MWT, m/s	38	-0.043 (0.276)	32	-0.092 (0.250)
R-ODS	38	-1.2 (5.9)	32	-3.0 (6.2)
mBMI[a]	38	6.9 (91.8)	29	26.8 (113.2)

Abbreviations: 10-MWT = 10-meter walk test; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SD = standard deviation.
Baseline is defined as the last non-missing measurement before the first dose in the 18-month treatment period.
[a]mBMI is defined as [weight in kilograms divided by square of height in meters] × albumin level in grams per liter.

Safety Results

The mean treatment duration in the vutrisiran total group (N=149, PY=308.3) was 24.4 months (range: 0.7-33.0 months). The majority of AEs reported were mild or moderate in severity (**Table 2**). The most common AEs reported in ≥10% of patients in the total vutrisiran group were COVID-19 (28.9%), urinary tract infection (15.4%), and fall (12.8%). None of the deaths were considered related to study drug by investigators. The safety profile of vutrisiran was consistent with that observed previously in the treatment period of the HELIOS-A study.[1]

Table 2. Safety of Vutrisiran During the RTE.[1]

At least one event, n (%)	Total Vutrisiran (N=149; PY 308.3)
Any AE	137 (91.9)
SAEs[a]	54 (36.2)
Severe AEs	46 (30.9)
AEs leading to treatment discontinuation	11 (7.4)
AEs leading to stopping study participation	11 (7.4)
Death	13 (8.7)

Abbreviations: AE = adverse event; PY = patient-years; RTE = randomized treatment extension; SAE = serious adverse event.

[a]SAEs reported in ≥2 patients were cellulitis (5 patients); pneumonia (4 patients); cardiac failure and osteoarthritis (3 patients each); atrial fibrillation, cardiac arrest, cardiac failure acute, cardiac failure congestive, sudden cardiac death, sudden death, abdominal pain, COVID-19, septic shock, urinary tract infection, cerebrovascular accident, syncope, dyspnea, respiratory failure, and orthostatic hypotension (2 patients each)

TRANSITION FROM VUTRISIRAN TO PATISIRAN

Studies evaluating the transition of patients from vutrisiran to patisiran have not been conducted to date.

APOLLO Study

APOLLO was a multicenter, international, randomized (2:1), 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=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.[2]

Exclusion Criteria

Patients were excluded from the study if they had received an investigational agent or device within 30 days of anticipated study drug administration or within 5 half-lives of the investigational drug(s), whichever was longer.[6]

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. After the 12-month double-blind treatment period, all patients received patisiran in an OLE period.[3]

Exclusion Criteria

Patients were excluded from the study if they had received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR.[7]

ABBREVIATIONS

6-MWT = 6-minute walk test; 10-MWT = 10-meter walk test; AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; BL = baseline; D = day; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; KPS = Karnofsky Performance Status; M = month; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; OLE = open-label extension;

PND = polyneuropathy disability; PY = patient-years; Q3M = every 3 months; Q6M = every 6 months; Q3W = every 3 weeks; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SAE = serious adverse event; SC = subcutaneous; SD = standard deviation; SE = standard error; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

Updated 05 March 2025

REFERENCES

1. Cauquil C, Adams D, Polydefkis M, et al. HELIOS-A: 18-month randomised treatment extension analysis of vutrisiran in patients with hereditary transthyretin amyloidosis with polyneuropathy. Presented at: Société Francophone du Nerf Périphérique (SFNP); January 31-February 1, 2025; Paris, France.
2. 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
3. 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, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26. doi:10.1080/13506129.2022.2091985
5. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2300015.
6. 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
7. 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