Transition between Patisiran and Vutrisiran

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SUMMARY

- In the HELIOS-A study, patients were excluded from the study if they had received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR.[1]
- After the 18-month treatment period of the HELIOS-A study, all eligible patients, including those on patisiran as a reference group, entered the RTE and received either vutrisiran 25 mg every 3 months or vutrisiran 50 mg every 6 months for up to additional 42 months.[2]
  - Through 9 months of the HELIOS-A RTE period, a consistent effect was observed in serum TTR reduction and in clinical endpoints following transition from patisiran to vutrisiran, irrespective of the vutrisiran dosing regimen.[2]
  - The safety profiles reported in the RTE period in the vutrisiran 25 mg every 3 months arm and the vutrisiran 50 mg every 6 months arm were comparable, of which the majority of AEs were mild or moderate in severity.[2]
  - The decision was made not to further advance the vutrisiran 50 mg every 6 months dosing regimen due to the pharmacodynamics of serum TTR recovery seen at the end of the 6-month dosing interval.[2]
- Studies evaluating the transition of patients from vutrisiran to patisiran have not been conducted to date.
  - In the APOLLO study, 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.[3]
  - In the APOLLO-B study, patients were excluded from the study if they had received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR.[4]

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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 the polyneuropathy of hATTR. 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 the mNIS+7 at 9 months.[5]

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.[1]

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.[2]

Patients in the patisiran reference arm transitioned to either vutrisiran 25 mg every 3 months or vutrisiran 50 mg every 6 months at Month 18. The last dose of patisiran was administered in Week 81. Patients in the patisiran reference arm received the first dose of vutrisiran on Day 1 of the RTE period, which was 3 weeks after Week 81.[1]

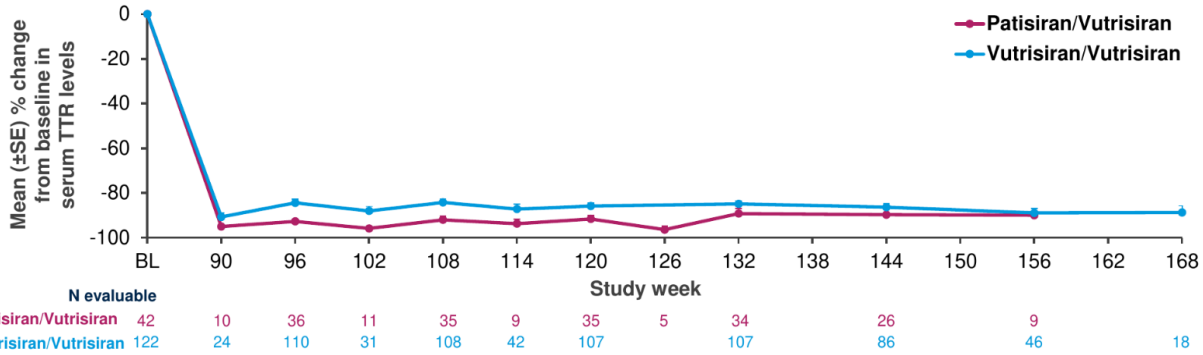
The decision was made not to further advance the vutrisiran 50 mg every 6 months dosing regimen due to the pharmacodynamics of serum TTR recovery seen at the end of the 6-month dosing interval.[2]

Efficacy Results: Transition from Patisiran to Vutrisiran

Serum TTR Level

Serum TTR reduction with vutrisiran was non-inferior to patisiran in the reference arm over the 18-month treatment period in HELIOS-A.[5] Through the RTE period, the serum TTR reduction in patients who received patisiran during the 18-month treatment period and transitioned to vutrisiran during the RTE period (patisiran/vutrisiran) was comparable to patients who had been on vutrisiran for the entire study (vutrisiran/vutrisiran), as shown in **Figure 1**.[2]

Figure 1. Change from HELIOS-A Baseline in Serum TTR during the RTE.[2,a]



Abbreviations: RTE = randomized treatment extension; SE = standard error; TTR = transthyretin.

Footnotes: Baseline is defined as the same as the 18-month treatment period, which is the mean of all non-missing measurements before first dose of 18-month treatment period. Presented data ≥5 patients per treatment arm at given study visit. Assessments at Week 84 were all in the 18-month treatment period, taken before the first dose of the extension treatment period, except 1 patient, whose assessment was taken during the legacy treatment period. Figure includes patients who switched to vutrisiran after Week 84 (legacy or RTE extension period).

[a]Vutrisiran data shown during the RTE is pooled 25 mg Q3M and 50 mg Q6M.

From Obici et al.[2]

Clinical Efficacy Endpoints

At Month 9 of the RTE period, a consistent clinical effect was observed compared with the HELIOS-A study baseline across key endpoints following transition from patisiran to vutrisiran during the RTE, irrespective of the vutrisiran dosing regimen (**Table 1**).[2]

Table 1. Change from HELIOS-A Baseline for Selected Clinical Efficacy Endpoints: Patisiran to Vutrisiran (25 mg Q3M and 50 mg Q6M Results Pooled).[2]

Endpoint, median (range)	n	Month 9 (Patisiran)	n	Month 18[a] (Patisiran)	n	RTE Month 9 (Vutrisiran)
mNIS+7	40	-1.25 (-47.0, 62.9)	36	1.00 (-30.4, 106.1)	30	-1.06 (-44.9, 28.6)
Norfolk QOL-DN	40	-4.5 (-26, 54)	38	-2.0 (-49, 58)	30	-2.0 (-29, 59)
10-MWT, m/s	40	-0.039 (-0.50, 0.38)	38	-0.034 (-0.95, 0.45)	30	-0.076 (-0.46, 0.25)
mBMI[b]	38	-2.7 (-369, 169)	38	-3.0 (-284, 179)	29	27.1 (-335, 222)
R-ODS	40	-0.5 (-21, 10)	38	0.0 (-18, 8)	30	-1.0 (-15, 16)
NT-proBNP, ng/L	38	3.98 (-1180, 8723)	38	-6.47 (-1911, 4741)	29	7.95 (-2057, 1823)

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; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; Q3M = every 3 months; Q6M, every 6 months; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension.
Footnotes: N=42 at baseline for all assessments. Baseline is defined as the last non-missing measurement before the first dose in the 18-month treatment period. Scores indicate the mean of 2 non-missing assessments planned to be performed ≥24 hours to ≤7 days apart at baseline, Month 9, and Month 18 visits during the 18-month treatment period; and a single assessment performed at RTE Month 9 visit after component imputation. [a]Patients switched from patisiran to vutrisiran after the 18-month timepoint.
[b]mBMI is defined as [weight in kilograms divided by square of height in meters] x albumin level in grams per liter.

Safety Results

The safety profiles reported in the RTE period in the vutrisiran 25 mg every 3 months arm and the vutrisiran 50 mg every 6 months arm were comparable (**Table 2**). The majority of AEs were mild or moderate in severity.[2]

Table 2. Safety Profile of Vutrisiran 25 mg Q3M and 50 mg Q6M during the RTE Period.[2]

At least one event, n (%)	Vutrisiran 25 mg Q3M (N=76)	Vutrisiran 50 mg Q6M (N=73)	Total (N=149)
AEs	58 (76.3)	63 (86.3)	121 (81.2)
Serious AEs	18 (23.7)	18 (24.7)	36 (24.2)
Severe AEs	12 (15.8)	17 (23.3)	29 (19.5)
AEs leading to treatment discontinuation[a]	1 (1.3)	5 (6.8)	6 (4.0)
Deaths[b]	0	5 (6.8)	5 (3.4)
Deaths after stopping study participation	1 (1.3)	0	1 (0.7)

Abbreviations: AE = adverse event; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; Q3M = every 3 months; Q6M = every 6 months.
Footnotes: Data cutoff October 7, 2022. AEs during the RTE period included AE with onset or worsening in severity after first dose of the RTE through last dose + 84 days (vutrisiran 25 mg Q3M) or + 168 days (vutrisiran 50 mg Q6M), or AE considered treatment related at any time after first dose of the RTE.
[a]Includes 1 patient in the vutrisiran 25 mg Q3M arm with end-stage endometrial neoplasm and the 5 deaths in the vutrisiran 50 mg Q6M arm.
[b]In the vutrisiran 50 mg Q6M arm, 3 deaths were adjudicated as CV deaths (2 sudden deaths; 1 presumed CV death) in patients with cardiac amyloidosis, chronic heart failure, and advanced cardiac disease (NYHA class III; elevated NT-proBNP levels [>2000 ng/L]). 2 deaths were adjudicated as non-CV deaths (1 patient with advanced hATTR [PND score IIIB] and fatal pneumonia, and 1 patient with a fatal reaction to chemotherapy for acute myeloid leukemia). Excludes 1 death due to endometrial neoplasm in the vutrisiran 25 mg Q3M arm that occurred after the patient stopped study participation.

During the RTE period, 1 SAE related to treatment was reported in the vutrisiran 50 mg every 6 months arm; a patient with non-alcoholic fatty liver disease and gallstones experienced an elevated ALT and AST with normal bilirubin. The SAE resolved without treatment or disruption of vutrisiran. No new safety signals regarding cardiac, hepatic, or renal events were reported in either vutrisiran arm.[2]

During the RTE period, there were 5 (6.8%) deaths reported in the vutrisiran 50 mg every 6 months arm and 1 (1.3%) death in the vutrisiran 25 mg every 3 months arm, none of which were considered related to vutrisiran. All patients who died had multiple risk factors for poor prognosis.[2]

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 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 polyneuropathy of hATTR. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[6]

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.[3]

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 with cardiomyopathy, 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 open-label extension period.[7]

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.[4]

ABBREVIATIONS

6-MWT = 6-minute walk test; 10-MWT = 10-meter walk test; AE = adverse event; ALT = alanine transaminase; AST = aspartate transferase; ATTR = transthyretin amyloidosis; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; IV = intravenous; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NYHA = New York Heart Association; PND = polyneuropathy disability; Q3M = every 3 months; Q6M = every 6 months; RNA = ribonucleic acid; RTE = randomized treatment extension; R-ODS = Rasch-built Overall Disability Scale; SAE = serious adverse event; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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