Vutrisiran: Randomized Treatment Extension Period of the HELIOS-A Study

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SUMMARY

- Vutrisiran is a transthyretin-directed small interfering RNA indicated for the treatment of the polyneuropathy of hATTR in adults. The recommended dosage of vutrisiran is 25 mg administered by subcutaneous injection once every 3 months.[1]
- After the 18-month treatment period of the HELIOS-A study, all eligible patients entered the RTE period and were randomized 1:1 to either vutrisiran 25 mg every 3 months or vutrisiran 50 mg every 6 months for up to an additional 42 months.[2]
  - At Month 9, non-inferiority of vutrisiran 50 mg every 6 months compared with vutrisiran 25 mg every 3 months in serum TTR mean percent reduction was met. Some TTR recovery was noted at the end of the 6-month dosing interval.
  - From RTE baseline to Month 9, clinical efficacy endpoint results were generally comparable between vutrisiran 25 mg every 3 months and vutrisiran 50 mg every 6 months.
- Through Month 9 of the RTE period, a consistent effect was observed in serum TTR reduction and in clinical endpoints following the switch from patisiran to vutrisiran, irrespective of the vutrisiran dosing regimen.[2]
- During the RTE period, the safety profile was comparable between vutrisiran 25 mg every 3 months and vutrisiran 50 mg every 6 months.[2]
- Regulatory submissions for the vutrisiran 50 mg every 6 months dosing regimen will not be pursued due to the pharmacodynamics of serum TTR recovery seen at the end of the 6-month dosing interval.[3]

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STUDY DESIGN

HELIOS-A was a phase 3, global, randomized, open-label study designed to assess 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. After the 18-month treatment period was completed, eligible patients (N=149), including those on patisiran, 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.[2,4]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

At HELIOS-A RTE enrollment, the vutrisiran 25 mg every 3 months arm had more patients with early-onset V30M and FAP stage ≥II. The vutrisiran 50 mg every 6 months arm had more patients with non-V30M genotype, NYHA class III or IV, and NT-proBNP >3000 ng/L.[2]

Table 1. HELIOS-A RTE Baseline Demographics and Characteristics.[2]

Characteristic	Vutrisiran 25 mg Q3M (N=76)	Vutrisiran 50 mg Q6M (N=73)	Total (N=149)
Age at RTE randomization, years, median (range)	61.5 (33–83)	63.0 (33–83)	62.0 (33–83)
Female, n (%)	26 (34.2)	30 (41.1)	56 (37.6)
Race, n (%)			
White/Caucasian	47 (61.8)	58 (79.5)	105 (70.5)
Asian	17 (22.4)	10 (13.7)	27 (18.1)
Other[a]	12 (15.8)	5 (6.8)	17 (11.4)
Non-V30M, n (%)	38 (50.0)	42 (57.5)	80 (53.7)
Early-onset V30M (<50 years), n (%)	19 (25.0)	11 (15.1)	30 (20.1)
NIS <50, n (%)	48 (63.2)	46 (63.0)	94 (63.1)
FAP stage ≥II, n (%)	24 (31.6)	19 (26.0)	43 (28.9)
PND score ≥III, n (%)	22 (28.9)	17 (23.3)	39 (26.2)
NYHA class III or IV, n (%)	4 (5.3)	9 (12.3)	13 (8.7)
NT-proBNP >3000 ng/L, n (%)	3 (3.9)	7 (9.6)	10 (6.7)
Randomized to vutrisiran during 18-month treatment period	57 (75.0)	55 (75.3)	112 (75.2)
Randomized to patisiran during 18-month treatment period	19 (25.0)	18 (24.7)	37 (24.8)

Abbreviations: FAP = familial amyloid polyneuropathy; NIS = Neuropathy Impairment Score; 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; RTE = randomized treatment extension.
[a]Includes Black/African American, ≥2 races, and other races.

EFFICACY RESULTS

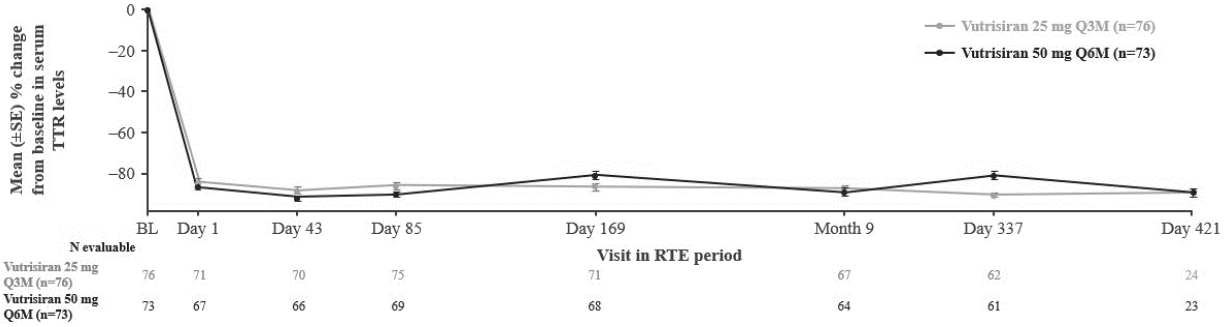
Vutrisiran 25 mg Q3M vs. Vutrisiran 50 mg Q6M

Serum TTR Level

At Month 9, the HL median TTR percent reduction was 89.87% in the vutrisiran 25 mg every 3 months arm and 90.38% in the vutrisiran 50 mg every 6 months arm. Non-inferiority of vutrisiran 50 mg every 6 months versus vutrisiran 25 mg every 3 months was established, based on mean serum TTR percent reduction with HL estimate of median difference of 0.50 (95% CI: -1.40, 2.75), in which the lower 95% CI limit was > -10%, the prespecified non-inferiority margin.[2]

There was a slight recovery of serum TTR noted at the end of the vutrisiran 50 mg every 6 months dosing interval, as shown in **Figure 1**.[2]

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



Abbreviations: BL = baseline; Q3M = every 3 months; Q6M = every 6 months; 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. Data >5 patients per treatment arm presented at given study visit.
Adapted from Obici et al.[2]

At Day 169, the percent of patients that achieved greater than an 80% reduction in trough TTR levels was 80.3% in the vutrisiran 25 mg every 3 months arm and 63.2% in the vutrisiran 50 mg every 6 months arm.[2]

Clinical Efficacy Endpoints

At Month 9, clinical efficacy endpoint results were comparable between vutrisiran 25 mg every 3 months and vutrisiran 50 mg every 6 months (**Table 2**).[2]

Table 2. Change from RTE Baseline to RTE Month 9 for Selected Clinical Efficacy Endpoints.[2]

Endpoint	Vutrisiran 25 mg Q3M (N=66)	Vutrisiran 50 mg Q6M (N=64)
mNIS+7, mean (SE)	-0.21 (1.82)	0.88 (1.64)
Norfolk QOL-DN, mean (SE)	1.1 (2.0)	4.5 (1.8)
10-MWT, m/s, mean (SE)	-0.061 (0.023)	-0.069 (0.022)
mBMI[a], mean (SE)	8.5 (10.9)[b]	-4.1 (9.7)
R-ODS, mean (SE)	-1.1 (0.5)	-1.7 (0.6)[c]
NT-proBNP, ng/L, median[d] (range)	1.95 (-6606.27, 3653.42)[e]	-1.95 (-1322.25, 3986.71)[c]

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; SE= standard error.
Footnotes: RTE baseline is defined as the last non-missing derived value before the first dose in the RTE period.
[a]mBMI is defined as [weight in kilograms divided by square of height in meters] x albumin level in grams per liter.
[b]n=64. [c]n=65. [d]Medians presented due to large variations. [e]n=67.

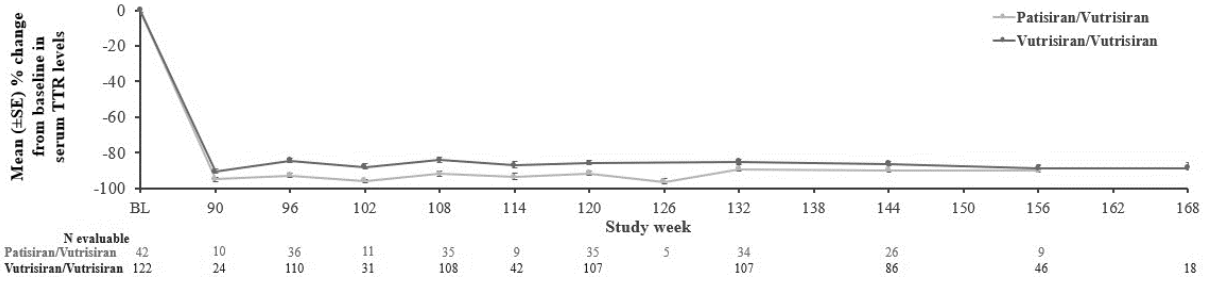
Switch from Patisiran to Vutrisiran

Serum TTR Level

As previously reported, serum TTR reduction with vutrisiran was non-inferior to patisiran in the reference arm over the 18-month treatment period in HELIOS-A.[2,4]

After the 18-month treatment period, all eligible patients, including those on patisiran, entered the RTE and were randomized 1:1 to receive either vutrisiran 25 mg every 3 months or vutrisiran 50 mg every 6 months for up to an additional 42 months.[2] Through the RTE period, the serum TTR reduction in patients who received patisiran during the 18-month treatment period and switched 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 2**.[2]

Figure 2. 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 randomized treatment extension period).
[a]Vutrisiran data shown during the RTE is pooled 25 mg Q3M and 50 mg Q6M.

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 switch from patisiran to vutrisiran during the RTE, irrespective of the vutrisiran dosing regimen (**Table 3**).[2]

Table 3. 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

AEs reported in the RTE period in the vutrisiran 25 mg every 3 months arm and the vutrisiran 50 mg every 6 months arm are summarized below in **Table 4.** The median exposure to vutrisiran during the RTE study was 13.2 months (range 2.4–16.9 months) in the vutrisiran 25 mg every 3 months arm and 13.0 months (range 0.7–16.5 months) in the vutrisiran 50 mg every 6 months arm. The most common AEs reported in ≥10% of patients in either vutrisiran arm were COVID-19, fall, and urinary tract infection. The majority of AEs were mild or moderate in severity.[2]

Table 4. 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; NYHA = New York Heart Association; PND = polyneuropathy disability; Q3M = every 3 months; Q6M = every 6 months.
Data cutoff October 7, 2022.
Footnotes: 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 were identified in either vutrisiran arm, including regarding cardiac, hepatic, or renal events.[2]

During the RTE period, there were 5 deaths (6.8%) reported in the vutrisiran 50 mg every 6 months arm and 1 death (1.3%) 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]

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; ALT = alanine transaminase; AST = aspartate transferase; mBMI = modified body mass index; CI = confidence interval; CV = cardiovascular; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; HL = Hodges-Lehmann; IV = intravenous; 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; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; Q3M, every 3 months; Q6M, every 6 months; RTE, randomized treatment extension; R-ODS = Rasch-built Overall Disability Scale; SAE = serious adverse event; SE, standard error; TTR = transthyretin.

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