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

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SUMMARY

- HELIOS-A was a phase 3, global, randomized, open-label study designed to assess 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.[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; thus, a protocol amendment was initiated to transition all patients on vutrisiran 50 mg every 6 months to vutrisiran 25 mg every 3 months.[2]
- From RTE baseline to Months 9 and 18, treatment with vutrisiran demonstrated sustained clinical efficacy in select endpoints including mNIS+7, Norfolk QOL-DN, 10-MWT, R-ODS, and mBMI.[2]
- At Month 18 of the RTE period, a consistent effect was observed in serum TTR reduction and in clinical efficacy endpoints following the switch from patisiran to vutrisiran.[2]
- During the RTE period, the majority of AEs reported with vutrisiran were mild or moderate in severity.[2]

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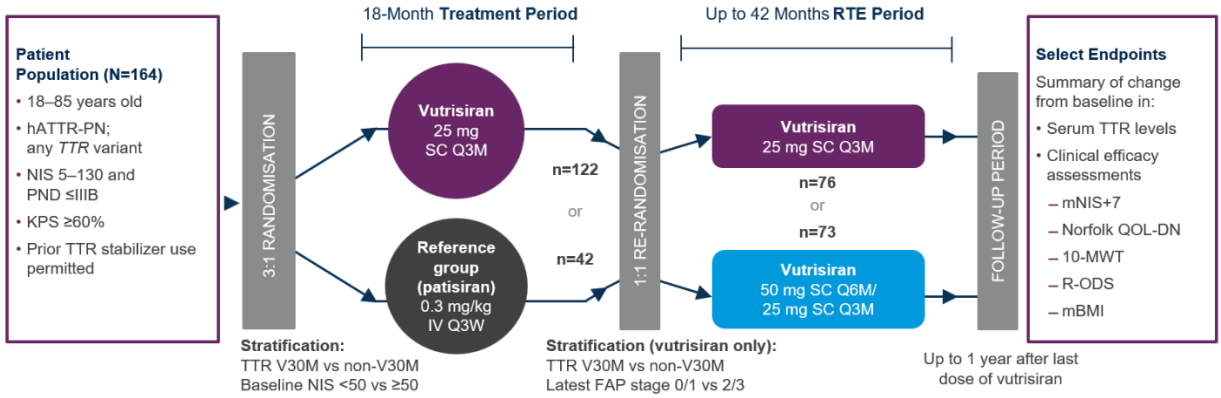
STUDY DESIGN

HELIOS-A was a phase 3, global, randomized, open-label study designed to assess the efficacy and safety of vutrisiran in patients with 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. After the 18-month treatment period was completed, all eligible patients, including those on patisiran, entered the RTE and were randomized 1:1 to receive either vutrisiran 25 mg every months or vutrisiran 50 mg every 6 months by subcutaneous injection (**Figure 1**).[1,2]

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.[2]

Figure 1. HELIOS-A RTE Study Design.[2]



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; Q3W = every 3 weeks; Q6M = every 6 months; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SC = subcutaneous; TTR = transthyretin.
From Cauquil et al.[2]

At data cutoff (February 23, 2024), 64 patients (43%) continued with vutrisiran treatment; 67 patients (45%) completed vutrisiran treatment; and 18 patients (12%) discontinued vutrisiran treatment due to: death (n=12), physician decision (n=3), lost to follow-up (n=2), or an AE (n=1).[2]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

The baseline demographics and disease characteristics of the total vutrisiran group at HELIOS-A RTE enrollment is summarized in **Table 1.**[2]

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

Characteristic	Total Vutrisiran (n=149)
Male, n (%)	93 (62.4)
Age, years, median (range)	62.0 (33.0-83.0)
Age at hATTR symptom onset <50 years, n (%)	54 (36.2)
TTR genotype: V30M, n (%)	69 (46.3)
TTR genotype: non-V30M, n (%)	80 (53.7)
Early-onset V30M, n (%)	30 (20.1)
Previous TTR stabilizer use, n (%)	98 (65.8)
NIS <50, n (%)	94 (63.1)
FAP stage ≥II, n (%)	42 (28.2)
PND score ≥III, n (%)	39 (26.2)
NYHA class III or IV, n (%)	13 (8.7)
NT-proBNP >3000 ng/L, n (%)	10 (6.7)
mBMI, median (range)	1057.7 (615, 1843)

Abbreviations: FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; mBMI = modified body mass index; 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; TTR = transthyretin.

EFFICACY RESULTS

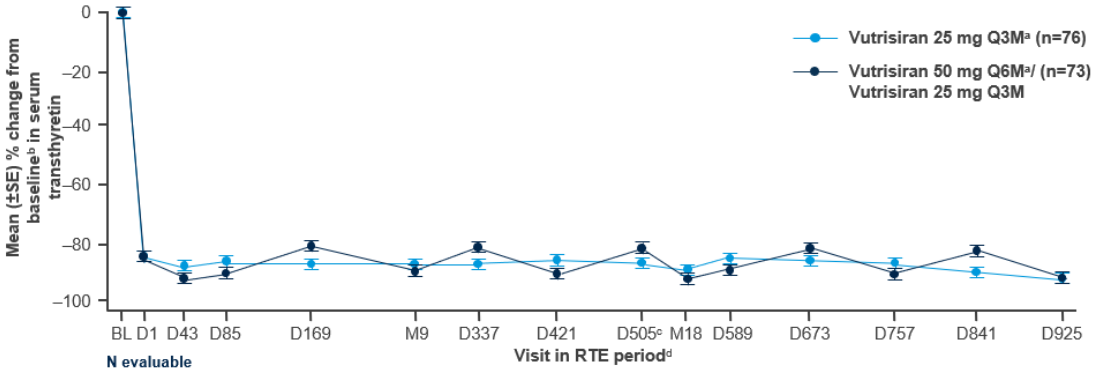
Vutrisiran 25 mg Q3M vs. Vutrisiran 50 mg Q6M

Serum TTR Level

At Month 9, the H-L median TTR reduction was 89.73% in the vutrisiran 25 mg every 3 months arm (n=76) and 90.37% in the vutrisiran 50 mg every 6 months arm (n=73). Non-inferiority of vutrisiran 50 mg every 6 months versus vutrisiran 25 mg every 3 months was established at Month 9 based on mean serum TTR percent reduction. The H-L median difference between the two arms was 0.58 (95% CI: -1.28, 2.92), in which the lower 95% CI limit was >-10%, the prespecified non-inferiority margin.[2]

Recovery of serum TTR was noted at the end of the vutrisiran 50 mg every 6 months dosing interval; thus, a protocol amendment was initiated to transition all patients on vutrisiran 50 mg every 6 months to vutrisiran 25 mg every 3 months. The mean percent change in serum TTR from baseline during the RTE period is shown in **Figure 2**.[2]

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



Abbreviations: BL = baseline; D = day; M = month; RTE = randomized treatment extension; SE = standard error; TTR = transthyretin.
[a]The vutrisiran 25 mg Q3M and the vutrisiran 50 mg Q6M represent the randomization treatment assignment at the beginning of the RTE period.
[b]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 of the 18-month treatment period.
[c]The first patient transitioned from vutrisiran 50 mg Q6M to 25 mg Q3M at this timepoint.
[d]As of a data cut of February 23, 2024.
From Cauquil et al.[2]

Total Vutrisiran Group

Clinical Efficacy Endpoints

The clinical efficacy endpoint results at Months 9 and 18 of the RTE period among the total vutrisiran group are presented in **Table 2.**[2]

Table 2. Mean Change from RTE Baseline in Clinical Efficacy Endpoints at Months 9 and 18.[2,a]

Endpoint, mean (SE), n	Month 9 RTE Total Vutrisiran Group (N=149)	Month 18 RTE Total Vutrisiran Group (N=149)
mNIS+7	0.34 (1.19), n=137	5.44 (1.39), n=130
Norfolk QOL-DN	2.4 (1.3), n=137	5.2 (1.5), n=131
10-MWT	-0.063 (0.016), n=137	-0.087 (0.018), n=131
R-ODS	-1.3 (0.4), n=137	-2.3 (0.4), n=132
mBMI[b]	0.2 (7.2), n=135	-10.3 (8.4), n=128

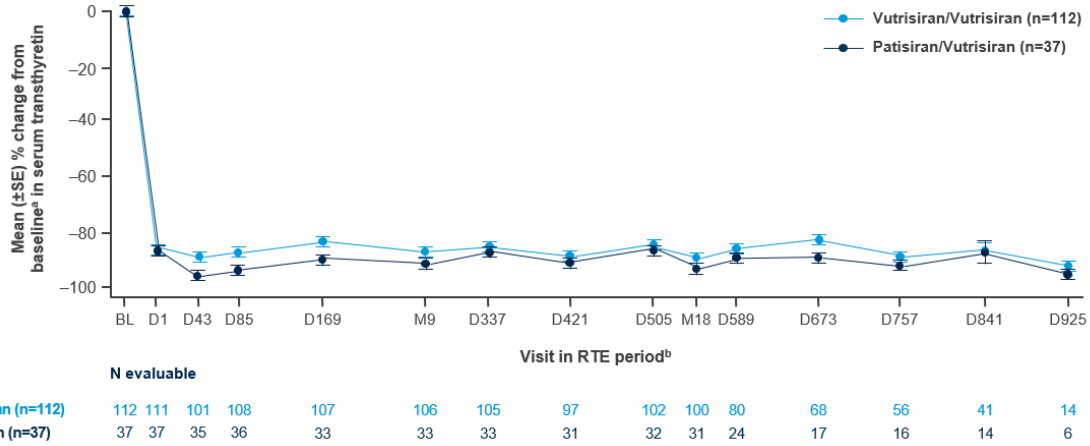
Abbreviations: 10-MWT = 10-meter walk test; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life- Diabetic Neuropathy; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SE = standard error.
[a]RTE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

Switch from Patisiran to Vutrisiran

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). The TTR reduction observed in patients in the patisiran/vutrisiran group was comparable to the TTR reduction observed in patients who received vutrisiran during both the 18-month treatment period and the RTE (vutrisiran/vutrisiran) (**Figure 3**).[2]

Figure 3. Mean (±SE) Percent Change from Baseline in Serum TTR During the RTE.[2]



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.[2]

Clinical Efficacy Endpoints

At Month 18 of the RTE period, a consistent clinical effect was observed across key endpoints compared with the HELIOS-A study baseline following switch from patisiran to vutrisiran (**Table 3**).[2]

Table 3. Change from Baseline for Select Clinical Efficacy Endpoints for Patients Who Switched From Patisiran to Vutrisiran During the RTE.[2]

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.
Footnotes: 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] x albumin level in grams per liter.

SAFETY RESULTS

The mean treatment duration in the total vutrisiran group was 24.4 months (range: 0.7-33.0 months). The majority of AEs reported were mild or moderate in severity (**Table 4**). 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.[2]

Table 4. Safety of Vutrisiran During the RTE.[2]

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).

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; BL = baseline; CI = confidence interval; D = day; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; H-L = Hodges-Lehmann; IV = intravenous; 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; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; PY = patient-years; Q3M = every 3 months; Q6M = every 6 months; RTE = randomized treatment extension; R-ODS = Rasch-built Overall Disability Scale; SAE = serious adverse event; SD = standard deviation; SE = standard error; TTR = transthyretin.

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REFERENCES

1. 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
2. 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.