Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

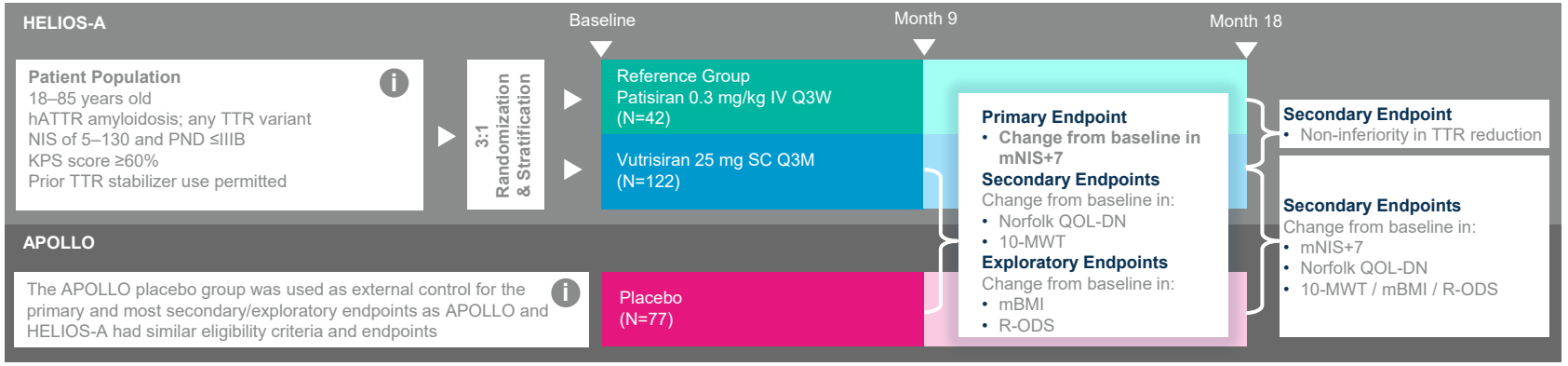
hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, rapidly progressive, debilitating, and fatal disease caused by transthyretin (*TTR*) gene variants, that has a heterogeneous clinical presentation including sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces serum TTR levels by reducing synthesis of variant and wild-type TTR and is given by Q3M SC injection

Patisiran is an RNAi therapeutic encapsulated in a lipid nanoparticle that directs it to the liver following Q3W IV administration and utilizes the same RNAi approach as vutrisiran to target variant and wild-type TTR synthesis

The HELIOS-A study aimed to assess the effect of vutrisiran in patients with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)



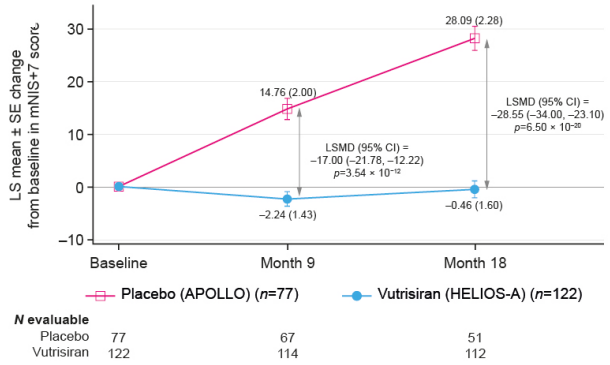
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neuropathy Impairment (mNIS+7)



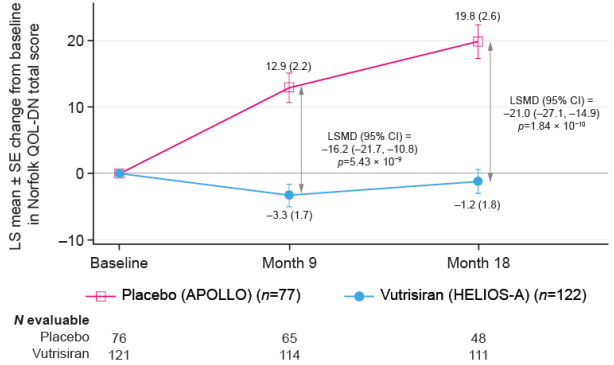
N evaluable

	Baseline	Month 9	Month 18
Placebo	77	67	51
Vutrisiran	122	114	112

Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

QOL (Norfolk QOL-DN)



N evaluable

	Baseline	Month 9	Month 18
Placebo	76	65	48
Vutrisiran	121	114	111

Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

Other Efficacy Endpoints

Vutrisiran met all other secondary efficacy endpoints

- Gait speed (10-MWT)
- Nutritional status (mBMI)
- Disability (R-ODS)

Patisiran efficacy was also reported

Pharmacodynamic Endpoints

TTR reduction with vutrisiran Q3M was rapid, sustained, and statistically non-inferior to within-study patisiran Q3W

- Peak and trough serum TTR reduction
- Serum TTR reduction

Safety Assessments

Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths

- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, rapidly progressive, debilitating, and fatal disease caused by transthyretin (*TTR*) gene variants, that has a heterogeneous clinical presentation including sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces serum TTR levels by reducing synthesis of variant and wild-type TTR and is given

Patisiran is an RNAi therapeutic encapsulated in a directs it to the liver following Q3W IV administrati RNAi approach as vutrisiran to target variant and

The HELIOS-A study aimed to assess the effect o with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)

Author Information

David Adams[a], Ivailo L. Tournev[b,c], Mark S. Taylor[d], Teresa Coelho[e], Violaine Planté-Bordeneuve[f], John L. Berk[g], Alejandra González-Duarte[h], Julian D. Gillmore[i], Soon-Chai Low[j], Yoshiki Sekijima[k], Laura Obici[l], Chongshu Chen[m], Prajakta Badri[m], Seth M. Arum[m], John Vest[m] , and Michael Polydefkis[n], and The HELIOS-A Collaborators

[a]Neurology Department, CHU Bicêtre, APHP, Université Paris-Saclay, Le Kremlin Bicêtre Cedex, France;
[b]Department of Neurology, Clinic of Nervous Diseases, University Hospital Aleksandrovska, Medical University – Sofia, Bulgaria;
[c]Department of Cognitive Sciences, New Bulgarian University, Sofia, Bulgaria;
[d]Department of Clinical Immunology and Allergy, Westmead Hospital and Westmead Clinical School, University of Sydney, Sydney, NSW, Australia;
[e]Hospital de Santo António, Centro Hospitalar Universitário do Porto, Porto, Portugal;
[f]Neurology – Amyloid Network, CHU Henri Mondor, APHP, University Paris Est – Créteil, Créteil, France;
[g]Boston Medical Center, Boston University, Boston, Massachusetts, USA;
[h]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México D.F., México;
[i]National Amyloidosis Centre, University College London, Royal Free Hospital, London, UK;
[j]Department of Medicine, Division of Neurology, University Malaya Medical Centre, Kuala Lumpur, Malaysia;
[k]Department of Medicine (Neurology & Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan;
[l]Amyloidosis Research and Treatment Centre, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy;
[m]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA;
[n]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abbreviations

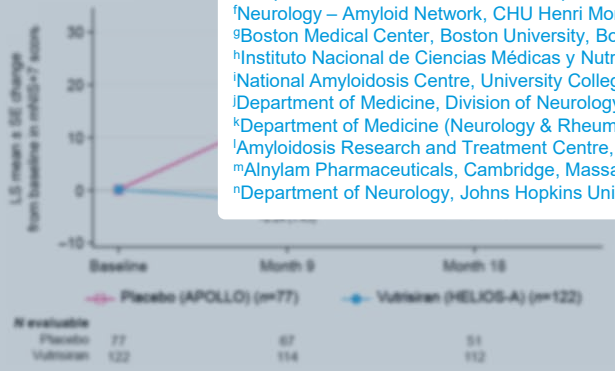
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

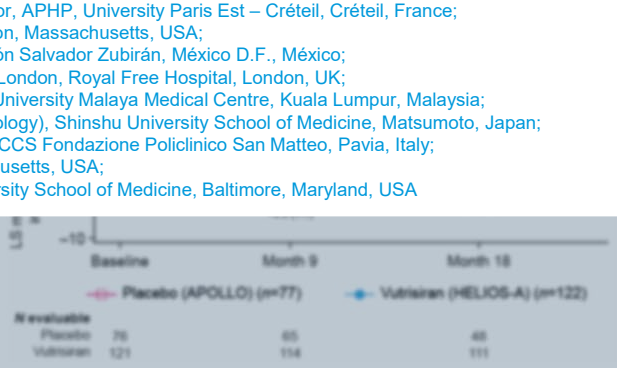
The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neurop



Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components



Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

dpoints
r secondary efficacy endpoints
T)
nBMI)
also reported

c Endpoints
trisiran Q3M was rapid, sustained, and statistically non-inferior to within-study patisiran Q3W
- Peak and trough serum TTR reduction
- Serum TTR reduction

Safety Assessments
Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths
- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

hATTR amyloidosis, also known as ATTRv amyloi… progressive, debilitating, and fatal disease caused … gene variants, that has a heterogeneous clinical p… sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces seru… synthesis of variant and wild-type TTR and is giver…

Patisiran is an RNAi therapeutic encapsulated in a… directs it to the liver following Q3W IV administrati… RNAi approach as vutrisiran to target variant and …

The HELIOS-A study aimed to assess the effect o… with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)

Month 18

…ary Endpoint
…hange from baseline in …NIS+7

…ondary Endpoints
…nge from baseline in:
…rfolk QOL-DN
…-MWT

…loratory Endpoints
…nge from baseline in:
…BMI
…CDS

Secondary Endpoint
- Non-inferiority in TTR reduction

Secondary Endpoints
Change from baseline in:
- mNIS+7
- Norfolk QOL-DN
- 10-MWT / mBMI / R-CODS

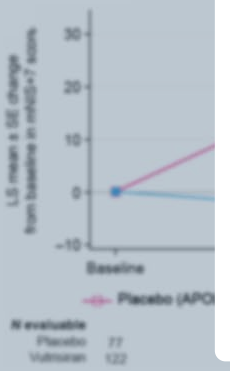
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neurop…



Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

…dpoints
…r secondary efficacy endpoints
…T)
…nBMI)
…also reported

…c Endpoints
…trisiran Q3M was rapid, sustained, and statistically …tudy patisiran Q3W …rum TTR reduction …on

Safety Assessments
Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths
- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-220005… | July 2022 |

INTRODUCTION

- hATTR amyloidosis, also known as ATTRv (v for variant) amyloidosis, is a rare, rapidly progressive, debilitating, and fatal disease caused by TTR gene variants.[1–4]
  - Misfolded TTR accumulates as amyloid deposits in multiple organs and tissues,[5–8] resulting in a heterogeneous clinical presentation including sensory, motor, and autonomic polyneuropathy, and cardiomyopathy.[2,9–11]
- Vutrisiran is an RNAi therapeutic that reduces serum TTR levels by reducing synthesis of variant and wild-type TTR.[12–13]
  - The vutrisiran siRNA–GalNAc conjugate features an ESC design for increased potency and high metabolic stability allowing for Q3M SC injection.
- Patisiran is an RNAi therapeutic encapsulated in a lipid nanoparticle that directs it to the liver following IV administration and utilizes the same RNAi approach as vutrisiran to target TTR synthesis.[14–17]
  - Patisiran was approved based on the pivotal phase 3, randomized, double-blind, placebo-controlled, 18-month APOLLO study.[15]
  - Patisiran approved in more than 30 countries for the treatment of hATTR amyloidosis with polyneuropathy[18,19]

1. Hawkins et al. *Ann Med* 2015;47:625-638; 2. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528-540; 3. Hanna *Curr Heart Fail Rep* 2014;11:50-57; 4. Adams et al. *Neurology* 2015;85:675-682; 5. Kelly JW. *Structure* 1997;5:595-600; 6 . Klimtchuk et al. *Proc Natl Acad Sci USA* 2018;115:E6428-E6436; 7. Koike and Katsuno *Biomedicines* 2019;7:11; 8. Mangione et al. *J Biol Chem* 2018;293:14192-14199; 9. Shin and Robinson-Papp *Mt Sinai J Med* 2012;79:733-748; 10. Conceição et al. *J Peripher Nerv Syst* 2016;21:5-9; 11. Adams et al. *Nat Rev Neurol* 2019;15:387-404; 12. Nair et al. *J Am Chem Soc* 2014;136:16958-16961; 13. Habtemariam et al. *Clin Pharmacol Ther* 2021;109:372-382; 14. Coelho et al. *N Engl J Med* 2013;369:819-829; 15. Adams et al. *N Engl J Med* 2018;379:11-21; 16. Adams et al. *BMC Neurol* 2017;17:181; 17. Solomon et al. *Circulation*. 2019;139:431-443. 18. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use. 19. European Medicines Agency. Summary of product characteristics: Onpattro 2 mg/mL concentrate for solution for infusion. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf

Abbreviations

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

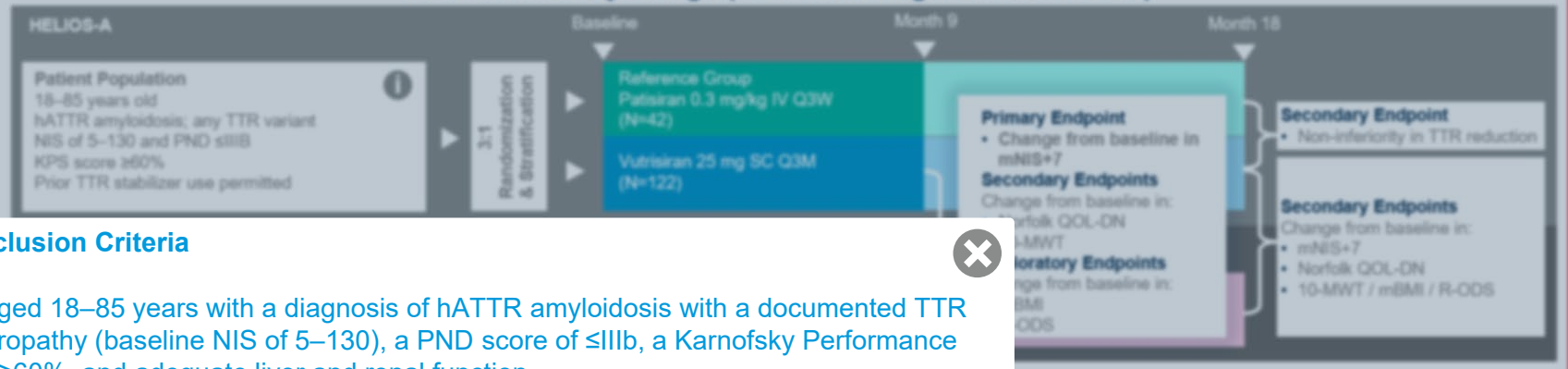
hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, rapidly progressive, debilitating, and fatal disease caused by transthyretin (*TTR*) gene variants, that has a heterogeneous clinical presentation including sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces serum TTR levels by reducing synthesis of variant and wild-type TTR and is given by Q3M SC injection

Patisiran is an RNAi therapeutic encapsulated in a lipid nanoparticle that directs it to the liver following Q3W IV administrati… RNAi approach as vutrisiran to target variant and

The HELIOS-A study aimed to assess the effect o… with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)



Inclusion and Exclusion Criteria

- Patients were aged 18–85 years with a diagnosis of hATTR amyloidosis with a documented TTR variant and neuropathy (baseline NIS of 5–130), a PND score of ≤IIIb, a Karnofsky Performance Status score of ≥60%, and adequate liver and renal function.
- Patients who had received previous gene-silencing therapy were excluded.
- Previous use of TTR stabilizers was permitted but patients must have completed a wash-out period (14 days for tafamidis; 3 days for diflunisal) prior to study drug dosing.
- Patients with prior liver transplantation or likely to undergo liver transplantation during the 18-month treatment period and those with a New York Heart Association heart failure class >II were excluded.

Abbreviations

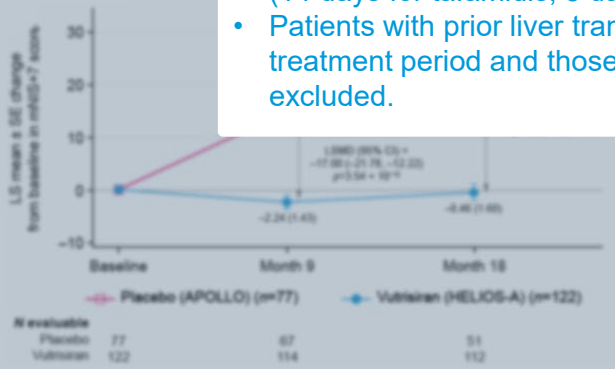
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

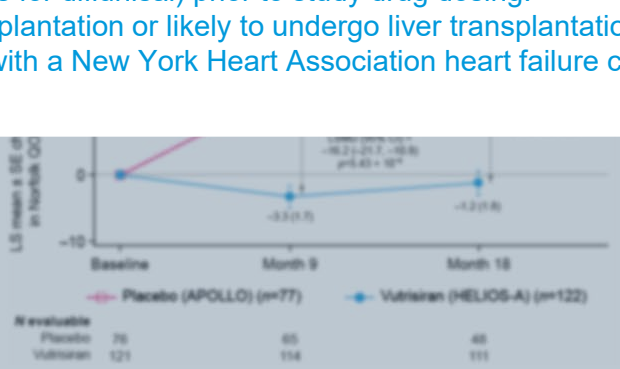
The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neurop…



Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components



Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

…dpoints
…r secondary efficacy endpoints
…T)
…mBMI)
…also reported

Pharmacodynamic Endpoints

TTR reduction with vutrisiran Q3M was rapid, sustained, and statistically non-inferior to within-study patisiran Q3W

- Peak and trough serum TTR reduction
- Serum TTR reduction

Safety Assessments

Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths

- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-220005g | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

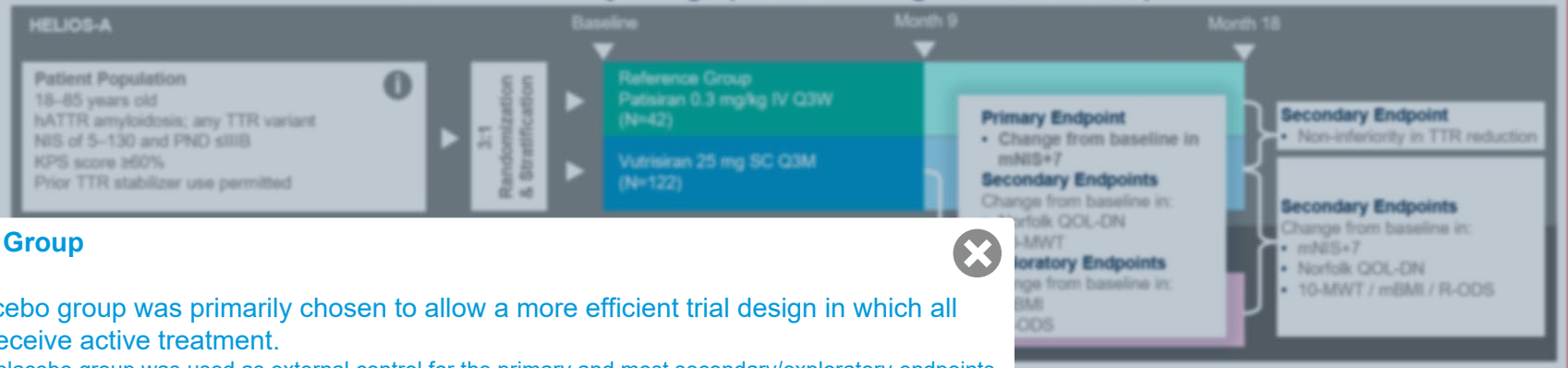
hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, rapidly progressive, debilitating, and fatal disease caused by transthyretin (*TTR*) gene variants, that has a heterogeneous clinical presentation including sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces serum TTR levels by reducing synthesis of variant and wild-type TTR and is given by Q3M SC injection

Patisiran is an RNAi therapeutic encapsulated in a lipid nanoparticle that directs it to the liver following Q3W IV administrati… RNAi approach as vutrisiran to target variant and

The HELIOS-A study aimed to assess the effect o… with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)



External Placebo Group

- An external placebo group was primarily chosen to allow a more efficient trial design in which all patients could receive active treatment.
  - The APOLLO placebo group was used as external control for the primary and most secondary/exploratory endpoints as the populations in HELIOS-A and APOLLO were expected to be similar due to APOLLO and HELIOS-A having similar eligibility criteria and endpoints
- Sensitivity analyses performed for change from baseline in mNIS+7 and Norfolk QOL-DN at Month 9 utilized a propensity score method to account for differences in patient baseline characteristics, including those between the HELIOS-A vutrisiran group and the external placebo group

Abbreviations

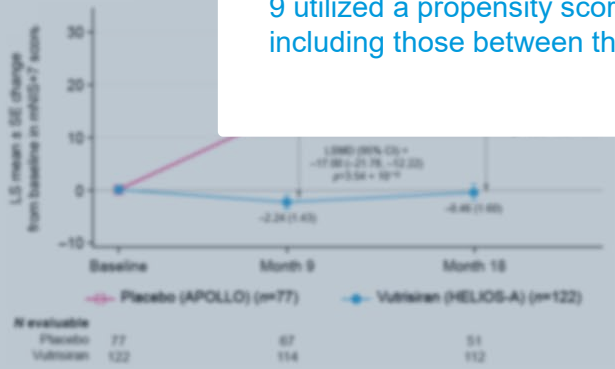
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

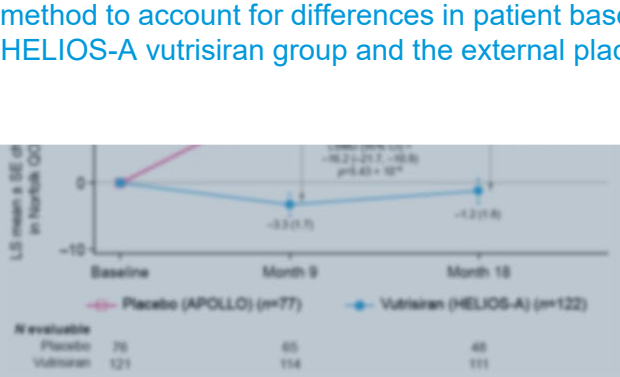
The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neurop…



Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components



Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

…dpoints
…r secondary efficacy endpoints
…T)
…mBMI)
…also reported

Pharmacodynamic Endpoints
TTR reduction with vutrisiran Q3M was rapid, sustained, and statistically non-inferior to within-study patisiran Q3W
- Peak and trough serum TTR reduction
- Serum TTR reduction

Safety Assessments
Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths
- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

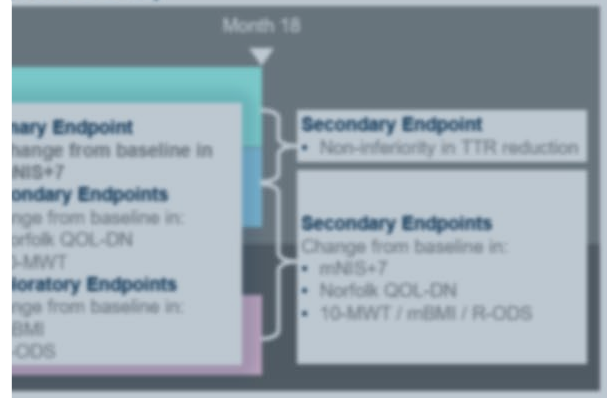
hATTR amyloidosis, also known as ATTRv amyloi
progressive, debilitating, and fatal disease caused
gene variants, that has a heterogeneous clinical p
sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces seru
synthesis of variant and wild-type TTR and is giver

Patisiran is an RNAi therapeutic encapsulated in a
directs it to the liver following Q3W IV administrati
RNAi approach as vutrisiran to target variant and

The HELIOS-A study aimed to assess the effect o
with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)



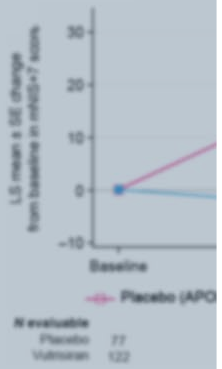
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neurop



Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

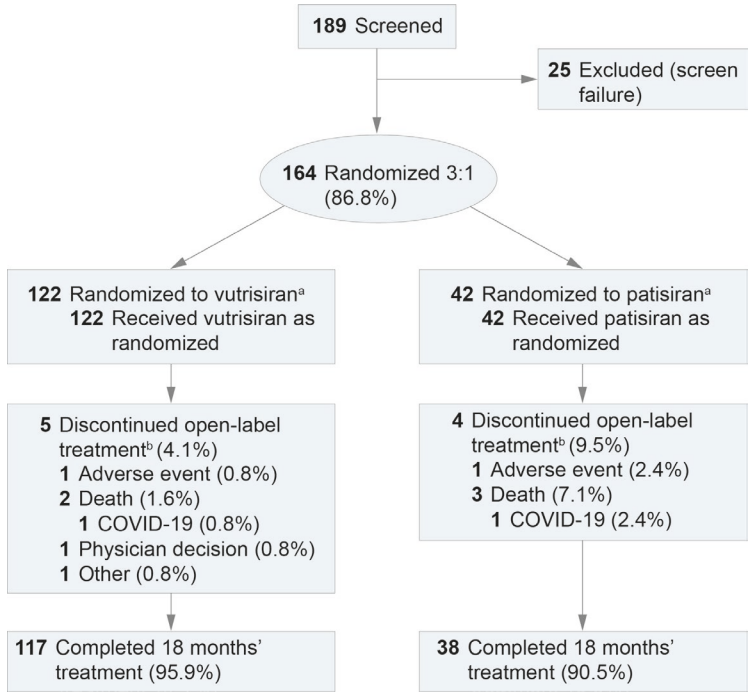
Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

dpoints
r secondary efficacy endpoints
(T)
nBMI)
also reported

c Endpoints
trisiran Q3M was rapid, sustained, and statistically
tudy patisiran Q3W
rum TTR reduction
on

nts
Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths
- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Patient Disposition



- Between February 2019 and March 2020, 164 patients were randomized, received treatment, and were included in the mITT population (vutrisiran, n=122; patisiran, n=42).
- In the vutrisiran and patisiran groups, 117 (95.9%) and 38 (90.5%) patients, respectively, completed the randomized 18-month treatment period.
- The primary reason for study discontinuation was death which occurred in 2/122 (1.6%) and 3/42 (7.1%) patients, respectively.

[a]Modified intent-to-treat population: all patients who were randomized and received at least one dose of study drug.
[b]Numbers of discontinuations to the end of 18 months. One patient in each treatment group discontinued due to suspected or confirmed diagnosis of COVID-19 or due to the impact of the global COVID-19 pandemic, reported in addition to primary reason for treatment discontinuation. There were two deaths due to COVID-19, one in each treatment arm.

Abbreviations

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary

Tra rial

Study Design

INTROD

hATTR amyloidosis, also known a
progressive, debilitating, and fata
gene variants, that has a heterog
sensory, motor and autonomic po

Vutrisiran is an RNAi therapeutic
synthesis of variant and wild-type

Patisiran is an RNAi therapeutic
directs it to the liver following Q3
RNAi approach as vutrisiran to ta

The HELIOS-A study aimed to as
with hATTR amyloidosis with poly

Month 18

Secondary Endpoint
- Non-inferiority in TTR reduction

Secondary Endpoints
Change from baseline in:
- mNIS+7
- Norfolk QOL-DN
- 10-MWT / mBMI / R-CODS

Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

components

QOL-DN score domains

acy endpoints

s rapid, sustained, and statistically

us AEs considered related to vutrisiran (one
ction). . There were no drug-related discontinuations

- Impact on doses due to COVID-19

Baseline Demographics and Clinical Characteristics

Characteristic	APOLLO	HELIOS-A		
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)	Total (n=164)
Median age, years (IQR)	63 (15)	60 (20)	60 (12)	60 (18)
Males, n (%)	58 (75.3)	79 (64.8)	27 (64.3)	106 (64.6)
Race, n (%)				
White/Caucasian	50 (64.9)	86 (70.5)	29 (69.0)	115 (70.1)
Asian	25 (32.5)	21 (17.2)	8 (19.0)	29 (17.7)
Black or African American	1 (1.3)	4 (3.3)	4 (9.5)	8 (4.9)
Other[a]	1 (1.3)	11 (9.0)	1 (2.4)	12 (7.3)
Median time since ATTRv amyloidosis diagnosis, years (IQR)	1.41 (3.04)	1.94 (4.34)	2.39 (3.01)	2.22 (4.15)
TTR genotype, n (%)				
V30M	40 (51.9)	54 (44.3)	20 (47.6)	74 (45.1)
Early-onset V30M (<50 years)	10 (13.0)	25 (20.5)	8 (19.0)	33 (20.1)
Non-V30M[b]	37 (48.1)	68 (55.7)	22 (52.4)	90 (54.9)
Previous tetramer stabilizer use, n (%)	41 (53.2)	75 (61.5)	33 (78.6)	108 (65.9)
Tafamidis	27 (35.1)	53 (43.4)	25 (59.5)	78 (47.6)
Diflunisal	14 (18.2)	22 (18.0)	8 (19.0)	30 (18.3)
Neuropathy Impairment Score, n (%)				
<50	35 (45.5)	78 (63.9)	27 (64.3)	105 (64.0)
≥50–<100	33 (42.9)	39 (32.0)	13 (31.0)	52 (31.7)
≥100	9 (11.7)	5 (4.1)	2 (4.8)	7 (4.3)
PND score,[c] n (%)				
I	20 (26.0)	44 (36.1)	15 (35.7)	59 (36.0)
II	23 (29.9)	50 (41.0)	17 (40.5)	67 (40.9)
IIIA	22 (28.6)	16 (13.1)	7 (16.7)	23 (14.0)
IIIB	11 (14.3)	12 (9.8)	3 (7.1)	15 (9.1)
NT-proBNP,[d] n (%)				
≤3000 ng/L	66 (85.7)	112 (91.8)	37 (88.1)	149 (90.9)
>3000 ng/L	9 (11.7)	10 (8.2)	5 (11.9)	15 (9.1)
Cardiac subpopulation,[e] n (%)	36 (46.8)	40 (32.8)	14 (33.3)	54 (32.9)

[a]Includes more than one race, vutrisiran *n*=1 (0.8%); other, vutrisiran *n*=10 (8.2%), patisiran *n*=1 (2.4%); missing, placebo *n*=1 (1.3%). [b]The non-V30M TTR genotype represents 25 different *TTR* mutations in HELIOS-A. [c]PND score I: preserved walking, sensory disturbances; II: impaired walking but can walk without stick or crutch; IIIA: walk with one stick or crutch; IIIB: walk with two sticks or crutches; 1 patient (1.3%) in APOLLO placebo group had a PND score IV defined as confined to wheelchair or bedridden. [d]NT-proBNP missing for 2 patients in APOLLO placebo group. [e]Cardiac subpopulation was defined as mITT population patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).

- The patient population enrolled included a wide range of disease severity and was representative of the global population with this disease.
- Baseline characteristics were similar across treatment groups in HELIOS-A and APOLLO placebo groups.
- Overall, the patient group was 64.6% male with a median (IQR) age of 60 years (18) and a median (IQR) time since hATTR amyloidosis diagnosis of 2.22 years (4.15); 45.1% of patients had the V30M TTR variant; patients with 26 different TTR variants were included in the HELIOS-A study.
- The HELIOS-A vutrisiran group had a greater proportion of patients with PND I/II and NIS <50 than the external placebo group (n=77), although the two populations had widely overlapping characteristics and were clinically comparable.

Abbreviations

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

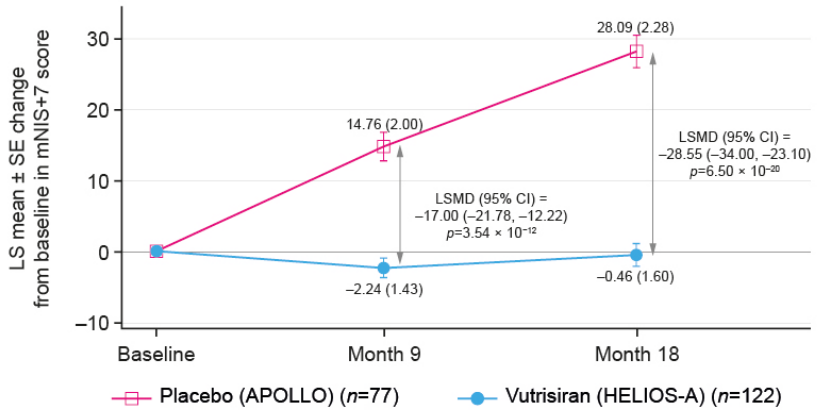
Abbreviations

Alnylam PHARMACEUTICALS

Efficacy and Safety of Vutrisiran for Patients with Hereditary

Neuropathy Impairment (mNIS+7)

LS mean change from baseline in mNIS+7 through 18 months (mITT population)[a]



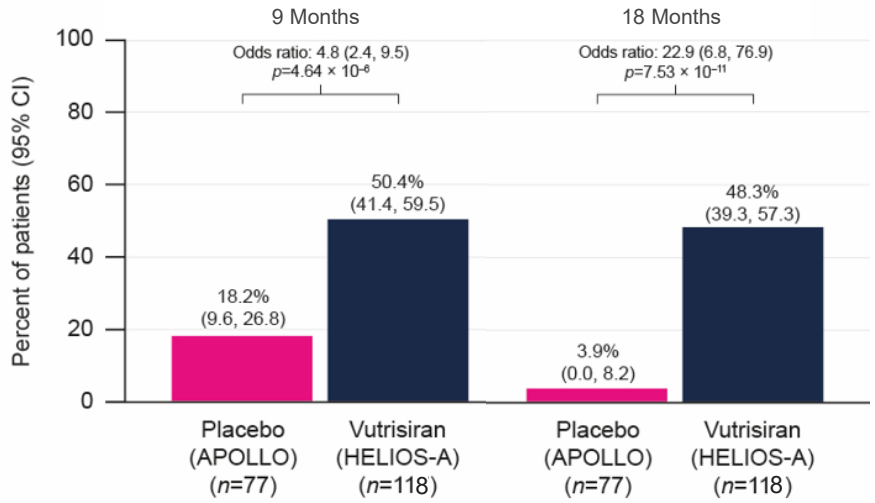
***N* evaluable**

Placebo	77	67	51
Vutrisiran	122	114	112

[a]Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0–304). At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in the external placebo group. Data at 9 months are from ANCOVA/multiple imputation model and data at 18 months are from the MMRM model.

- Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 versus the external placebo group (least-squares [LS] mean difference [95% CI]: –17.00 [–21.78, –12.22], p=3.54 × 10^{-12}), meeting the primary endpoint.
- The treatment effect of vutrisiran on mNIS+7 at Month 9 was validated by sensitivity analyses.
- Significant improvement in mNIS+7 with vutrisiran compared with the external placebo group was also observed at Month 18 (LS mean difference [95% CI]: –28.55 [–34.00, –23.10], p=6.50 × 10^{-20}).

Percentage of patients with an improvement[a] in mNIS+7 from baseline after 9 Months and 18 Months (mITT population)



[a]Improvement defined as patients with a decrease from baseline. Exploratory binary analysis; nominal p value. Patients with missing post-baseline values due to COVID-19 (including values on or after onset of a serious COVID-19 adverse event) were excluded from analysis. Assessments after initiation of local standard treatment for hereditary transthyretin-mediated amyloidosis were treated as missing.

- At Month 9, 50.4% of patients in the vutrisiran group showed improvement in mNIS+7 (decrease from baseline) versus 18.2% in the external placebo group.
- At Month 18, 48.3% of patients in the vutrisiran group showed improvement in mNIS+7 versus 3.9% in the external placebo group.

Abbreviations

Study Design

Results

Patients

Secondary Endpoint
- Non-inferiority in TTR reduction

Secondary Endpoints
Change from baseline in:
- mNIS+7
- Norfolk QOL-DN
- 10-MWT / mBMI / R-ODS

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

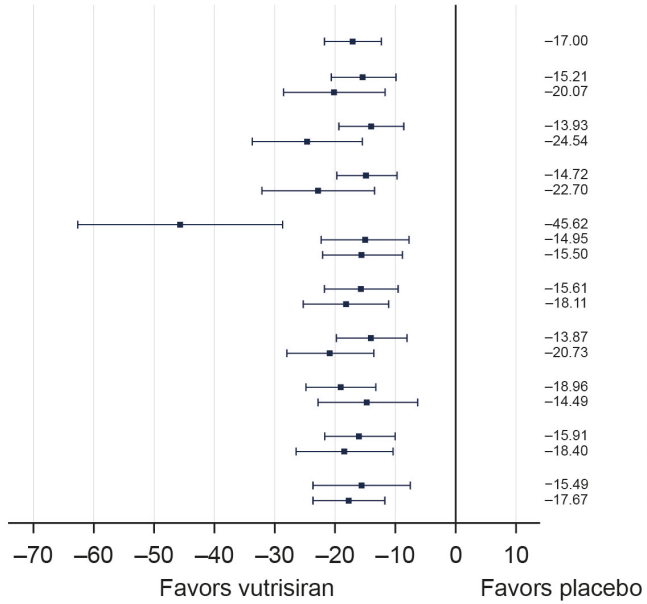
Efficacy and Safety of Vutrisiran for Patients with Hereditary

Neuropathy Impairment (mNIS+7)

Exploratory patient subgroup analysis of mNIS+7 (mITT population)

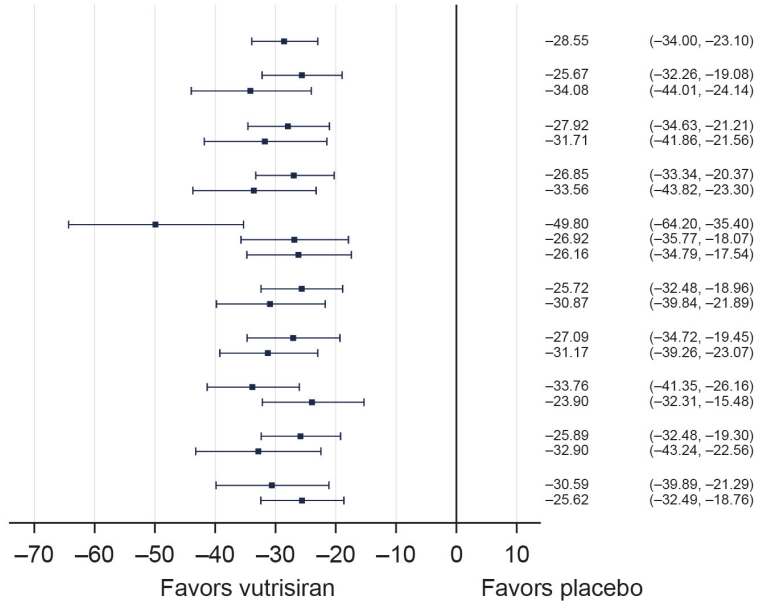
9 Months

Subgroup	LS mean difference	95% CI
Overall (*n*=199)	−17.00	(−21.78, −12.22)
Age		
<65 (*n*=111)	−15.21	(−20.55, −9.88)
≥65 (*n*=70)	−20.07	(−28.44, −11.71)
Sex		
M (*n*=127)	−13.93	(−19.33, −8.53)
F (*n*=54)	−24.54	(−33.77, −15.31)
Race		
White (*n*=124)	−14.72	(−19.77, −9.66)
All other races (*n*=57)	−22.70	(−32.12, −13.28)
Region		
North America (*n*=33)	−45.62	(−62.59, −28.65)
Western Europe (*n*=71)	−14.95	(−22.20, −7.70)
Rest of World (*n*=77)	−15.50	(−22.13, −8.88)
NIS		
<50 (*n*=104)	−15.61	(−21.79, −9.43)
≥50 (*n*=77)	−18.11	(−25.27, −10.95)
Genotype		
V30M (*n*=88)	−13.87	(−19.73, −8.01)
Non-V30M (*n*=93)	−20.73	(−27.99, −13.46)
Previous tetramer stabilizer use		
Y (*n*=108)	−18.96	(−24.77, −13.16)
N (*n*=73)	−14.49	(−22.69, −6.29)
FAP stage		
I (*n*=114)	−15.91	(−21.76, −10.05)
II & III (*n*=67)	−18.40	(−26.42, −10.37)
Cardiac population[a]		
Y (*n*=63)	−15.49	(−23.59, −7.38)
N (*n*=118)	−17.67	(−23.65, −11.68)



18 Months

Subgroup	LS mean difference	95% CI
Overall (*n*=163)	−28.55	(−34.00, −23.10)
Age		
<65 (*n*=101)	−25.67	(−32.26, −19.08)
≥65 (*n*=62)	−34.08	(−44.01, −24.14)
Sex		
M (*n*=111)	−27.92	(−34.63, −21.21)
F (*n*=52)	−31.71	(−41.86, −21.56)
Race		
White (*n*=115)	−26.85	(−33.34, −20.37)
All other races (*n*=48)	−33.56	(−43.82, −23.30)
Region		
North America (*n*=29)	−49.80	(−64.20, −35.40)
Western Europe (*n*=66)	−26.92	(−35.77, −18.07)
Rest of World (*n*=68)	−26.16	(−34.79, −17.54)
NIS		
<50 (*n*=97)	−25.72	(−32.48, −18.96)
≥50 (*n*=66)	−30.87	(−39.84, −21.89)
Genotype		
V30M (*n*=79)	−27.09	(−34.72, −19.45)
Non-V30M (*n*=84)	−31.17	(−39.26, −23.07)
Previous tetramer stabilizer use		
Y (*n*=95)	−33.76	(−41.35, −26.16)
N (*n*=68)	−23.90	(−32.31, −15.48)
FAP stage		
I (*n*=104)	−25.89	(−32.48, −19.30)
II & III (*n*=59)	−32.90	(−43.24, −22.56)
Cardiac population[b]		
Y (*n*=60)	−30.59	(−39.89, −21.29)
N (*n*=103)	−25.62	(−32.49, −18.76)



Forest plot showing the LS mean difference in mNIS+7 change from baseline to Month 9 and Month 18 between vutrisiran and external placebo group within subgroups. [a]Cardiac subpopulation defined in the Month 9 analysis. [b]Select echocardiogram parameters were re-read for the Month 18 analysis and the cardiac subpopulation was re-derived based on baseline LV wall thickness values after the re-read. As a result, in the Month 18 analysis the cardiac subpopulation status of 9 patients receiving vutrisiran was reclassified and 1 patient receiving patisiran was added to the cardiac subpopulation compared with the cardiac subpopulation defined in the Month 9 analysis.

- The treatment effect favoring vutrisiran at Months 9 and 18 was consistent across all prespecified patient subgroups and subcomponents of mNIS+7.

Abbreviations

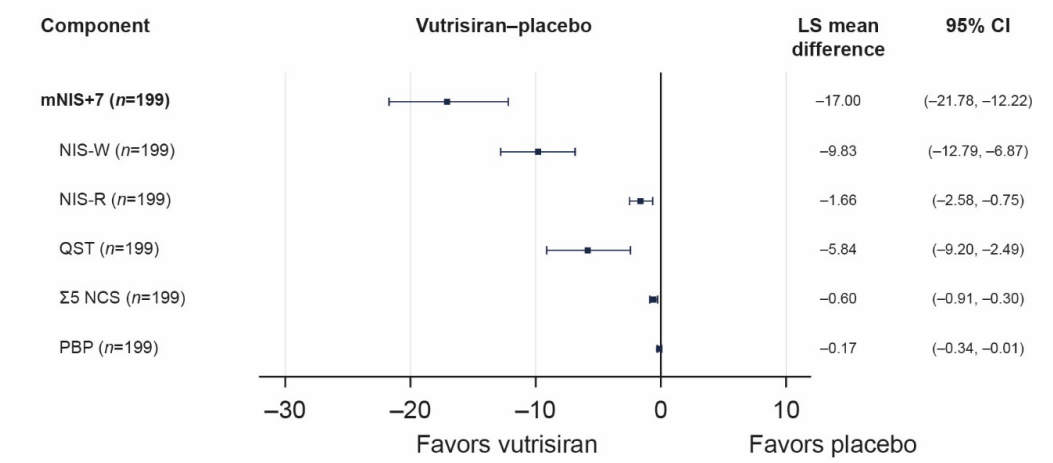
Alnylam

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

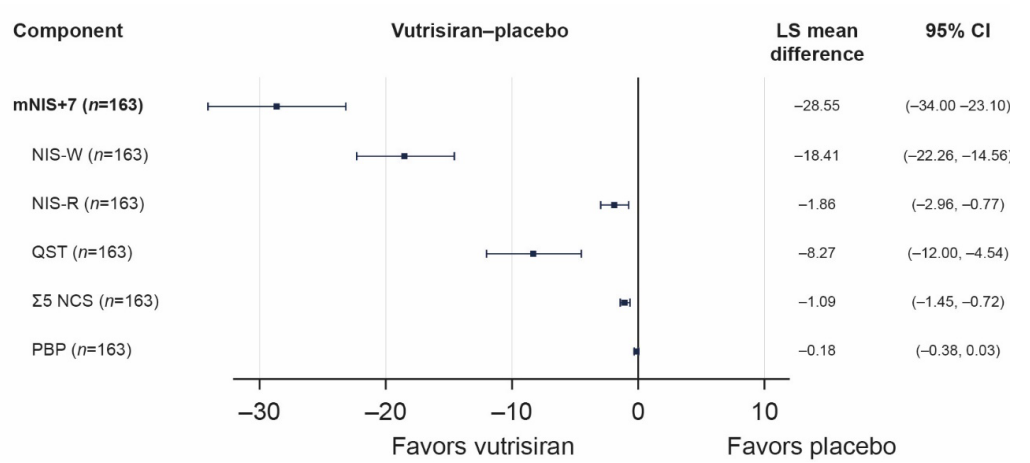
Neuropathy Impairment (mNIS+7)

Exploratory subcomponent analysis of mNIS+7 (mITT population)

9 Months



18 Months



Forest plot showing the LS mean difference between vutrisiran and external placebo group in change from baseline to Month 9 and Month 18 in mNIS+7 subcomponents.

- The treatment effect favoring vutrisiran at Months 9 and 18 was consistent across all prespecified patient subgroups and subcomponents of mNIS+7.

Abbreviations

Study Design

Results

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

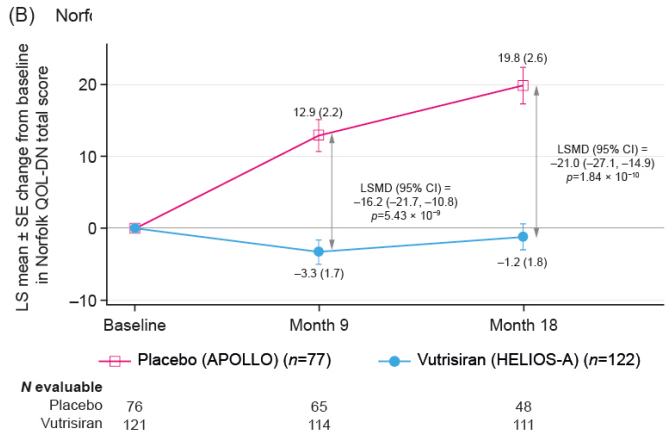
MED-US-TTRSC02-2200059 | July 2022 |

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

QOL (Norfolk QOL-DN)

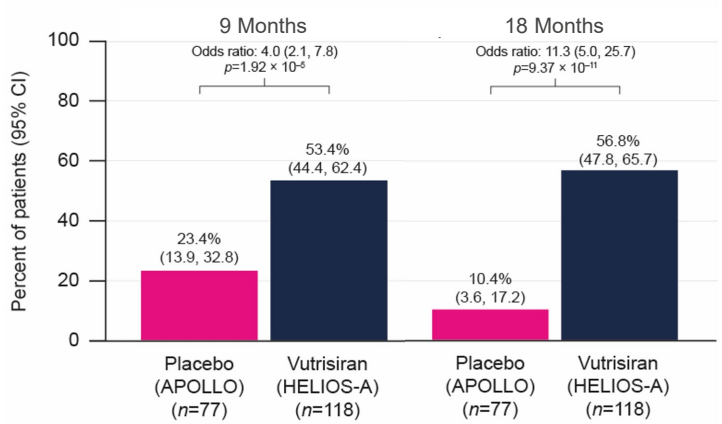
LS mean change from baseline in Norfolk QOL-DN with vutrisiran through 18 months (mITT population)



[a]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, –4 to 136). At baseline, the mean (±SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. Data at 9 months are from ANCOVA/multiple imputation model and data at 18 months are from the MMRM model.

- Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at
  - Month 9 (LS mean difference [95% CI]: –16.2 [–21.7, –10.8], p=5.43 × 10^{-9})
  - Month 18 (LS mean difference [95% CI]: –21.0 [–27.1, –14.9], p=1.84 × 10^{-10})

Percentage of patients with an improvement[a] in Norfolk QOL-DN from baseline after 9 Months and 18 Months (mITT population)



[a]Improvement defined as patients with a decrease from baseline. Exploratory binary analysis; nominal p value. Patients with missing post-baseline values due to COVID-19 (including values on or after onset of a serious COVID-19 adverse event) were excluded from analysis.

- At Month 9, 53.4% of patients in the vutrisiran group showed improvement (decrease from baseline) in Norfolk QOL-DN score versus 23.4% in the external placebo group.
- By Month 18, the percentage of patients showing improvement in Norfolk QOL-DN score was 56.8% vs 10.4% in the vutrisiran and external placebo groups, respectively.

Abbreviations

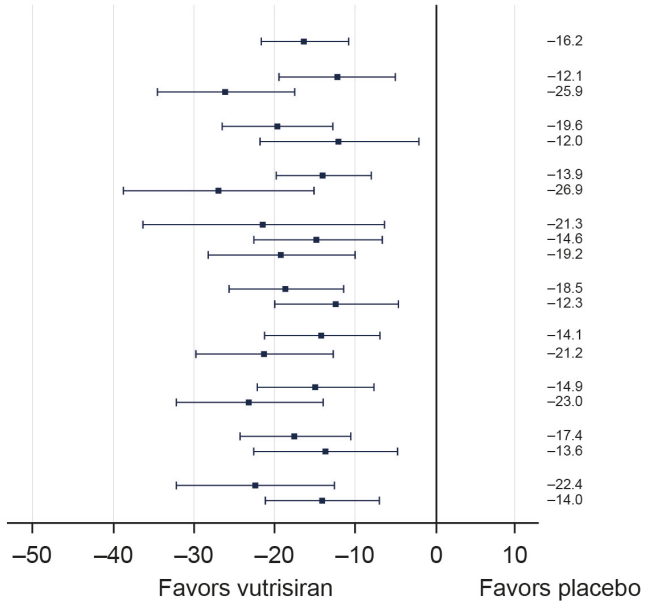
Efficacy and Safety of Vutrisiran for Patients with Hereditary

QOL (Norfolk QOL-DN)

Exploratory patient subgroup analysis of Norfolk QOL-DN (mITT population)

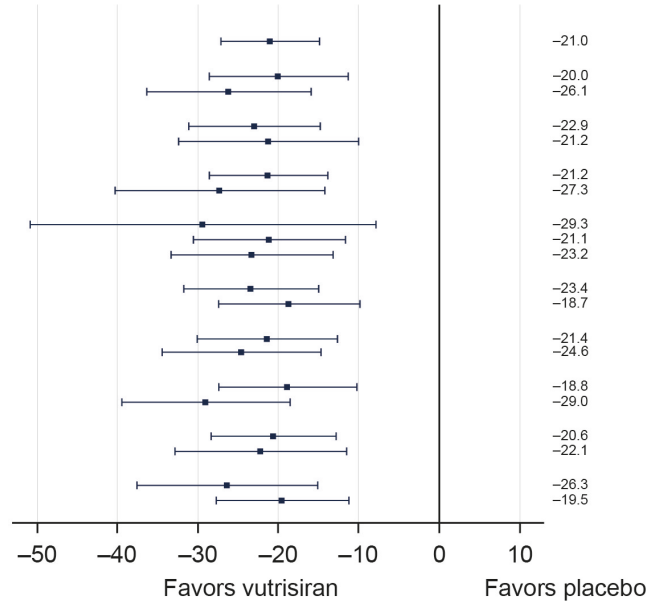
9 Months

Subgroup	LS mean difference	95% CI
Overall (*n*=197)	−16.2	(−21.7, −10.8)
Age		
<65 (*n*=111)	−12.1	(−19.3, −5.0)
≥65 (*n*=68)	−25.9	(−34.5, −17.4)
Sex		
M (*n*=125)	−19.6	(−26.4, −12.7)
F (*n*=54)	−12.0	(−21.8, −2.1)
Race		
White (*n*=122)	−13.9	(−19.8, −8.1)
All other races (*n*=57)	−26.9	(−38.7, −15.1)
Region		
North America (*n*=32)	−21.3	(−36.3, −6.3)
Western Europe (*n*=69)	−14.6	(−22.6, −6.6)
Rest of World (*n*=78)	−19.2	(−28.2, −10.1)
NIS		
<50 (*n*=104)	−18.5	(−25.5, −11.4)
≥50 (*n*=75)	−12.3	(−20.0, −4.6)
Genotype		
V30M (*n*=85)	−14.1	(−21.3, −6.9)
Non-V30M (*n*=94)	−21.2	(−29.7, −12.7)
Previous tetramer stabilizer use		
Y (*n*=107)	−14.9	(−22.1, −7.6)
N (*n*=72)	−23.0	(−32.1, −14.0)
FAP stage		
I (*n*=114)	−17.4	(−24.3, −10.5)
II & III (*n*=65)	−13.6	(−22.5, −4.7)
Cardiac population[a]		
Y (*n*=63)	−22.4	(−32.2, −12.5)
N (*n*=116)	−14.0	(−21.1, −7.0)



18 Months

Subgroup	LS mean difference	95% CI
Overall (*n*=159)	−21.0	(−27.1, −14.9)
Age		
<65 (*n*=99)	−20.0	(−28.6, −11.4)
≥65 (*n*=60)	−26.1	(−36.3, −15.9)
Sex		
M (*n*=107)	−22.9	(−33.1, −14.8)
F (*n*=52)	−21.2	(−32.3, −10.0)
Race		
White (*n*=111)	−21.2	(−28.6, −13.8)
All other races (*n* = 48)	−27.3	(−40.3, −14.2)
Region		
North America (*n*=28)	−29.3	(−50.8, −7.8)
Western Europe (*n*=63)	−21.1	(−30.5, −11.7)
Rest of World (*n*=68)	−23.2	(−33.3, −13.1)
NIS		
<50 (*n*=96)	−23.4	(−31.7, −15.0)
≥50 (*n*=63)	−18.7	(−27.5, −9.9)
Genotype		
V30M (*n*=75)	−21.4	(−30.1, −12.6)
Non-V30M (*n*=84)	−24.6	(−34.5, −14.7)
Previous tetramer stabilizer use		
Y (*n*=93)	−18.8	(−27.4, −10.2)
N (*n*=66)	−29.0	(−39.4, −18.5)
FAP stage		
I (*n*=103)	−20.6	(−28.4, −12.8)
II & III (*n*=56)	−22.1	(−32.8, −11.5)
Cardiac population[b]		
Y (*n*=58)	−26.3	(−37.5, −15.1)
N (*n*=101)	−19.5	(−27.7, −11.2)



Forest plot showing the LS mean difference in Norfolk QOL-DN change from baseline to (A) Month 9 and (B) Month 18 between vutrisiran and external placebo group within subgroups. [a]Cardiac subpopulation defined in the Month 9 analysis. [b]Select echocardiogram parameters were re-read for the Month 18 analysis and the cardiac subpopulation was re-derived based on baseline LV wall thickness values after the re-read. As a result, in the Month 18 analysis the cardiac subpopulation status of 9 patients receiving vutrisiran was reclassified and 1 patient receiving patisiran was added to the cardiac subpopulation compared with the cardiac subpopulation defined in the Month 9 analysis.

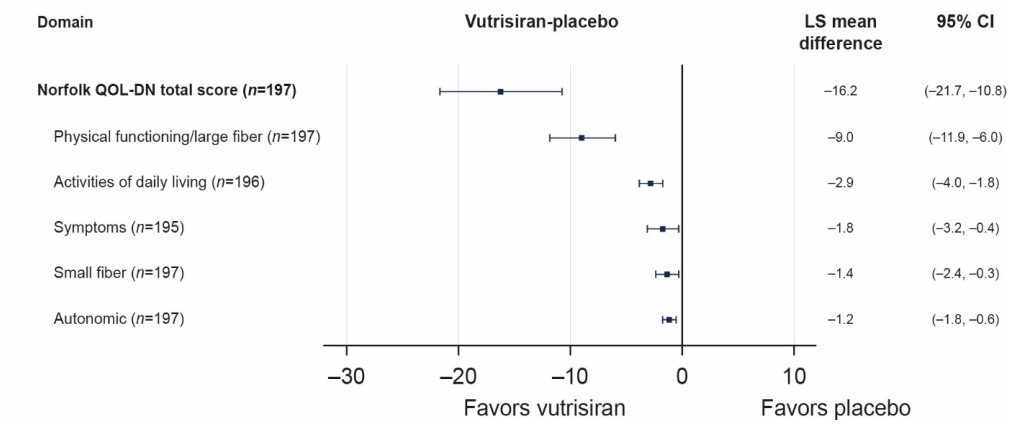
- The treatment effect for Norfolk QOL-DN at Months 9 and 18 was consistent across all prespecified subgroups and individual domains of the score.

Abbreviations

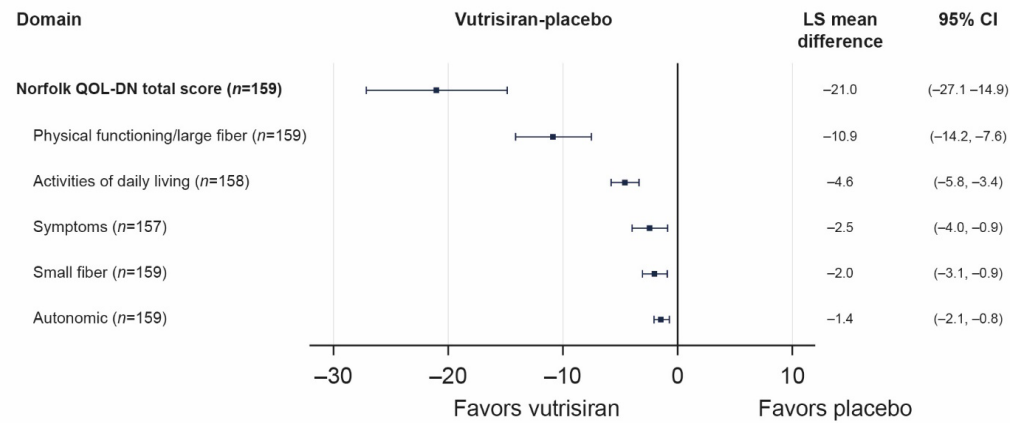
QOL (Norfolk QOL-DN)

Exploratory subdomain analysis of Norfolk QOL-DN (mITT population)

9 Months



18 Months



Forest plot showing the LS mean difference in Norfolk QOL-DN change from baseline to Month 9 and Month 18 between vutrisiran and external placebo group in individual domains.

- The treatment effect for Norfolk QOL-DN at Months 9 and 18 was consistent across all prespecified subgroups and individual domains of the score.

Abbreviations

Select Secondary and Exploratory Endpoints (mITT population)

Endpoints at Month 9[a]	APOLLO	HELIOS-A
	External placebo group (n=77)	Vutrisiran (n=122)
Norfolk QOL-DN		
Baseline	n=76	n=121
Mean (SD) score	55.5 (24.3)	47.1 (26.3)
Change from baseline to Month 9	n=65	n=114
LS mean change (SE)	12.9 (2.2)	−3.3 (1.7)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	−16.2 (−21.7, −10.8)	
p value	5.43×10^{-9}	
10-MWT (gait speed ms^{-1})		
Baseline	n=77	n=122
Mean (SD)	0.790 (0.319)	1.006 (0.393)
Change from baseline to Month 9	n=68	n=113
LS mean change (SE)	−0.133 (0.025)	−0.001 (0.019)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	0.131 (0.070, 0.193)	
p value	3.10×10.0^{-5}	
mBMI[b,c]		
Baseline	n=77	n=122
Mean (SD)	989.9 (214.2)	1057.5 (234.0)
Change from baseline to Month 9	n=68	n=112
LS mean change (SE)	−60.2 (10.1)	7.6 (7.9)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	67.8 (43.0, 92.6)	
p value	8.46×10^{-8}	
R-ODS[b]		
Baseline	n=76	n=122
Mean (SD)	29.8 (10.8)	34.1 (11.0)
Change from baseline to Month 9	n=66	n=113
LS mean change (SE)	−4.9 (0.7)	−0.6 (0.5)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	4.3 (2.7, 6.0)	
p value	3.26×10^{-7}	

Endpoints at Month 18[d]	APOLLO	HELIOS-A
	External placebo group (n=77)	Vutrisiran (n=122)
mNIS+7		
Baseline	n=77	n=122
Mean (SD)	74.6 (37.0)	60.6 (36.0)
Change from baseline to Month 18	n=51	n=112
LS mean change (SE)	28.1 (2.3)	−0.46 (1.6)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	−28.6 (−34.0, −23.1)	
p value	6.50×10^{-20}	
Norfolk QOL-DN		
Change from baseline to Month 18	n=48	n=111
LS mean change (SE)	19.8 (2.6)	−1.2 (1.8)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	−21.0 (−27.1, −14.9)	
p value	1.84×10^{-10}	
10-MWT (gait speed ms^{-1})		
Change from baseline to Month 18	n=55	n=112
LS mean change (SE)	−0.264 (0.036)	−0.024 (0.025)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	0.239 (0.154, 0.325)	
p value	1.21×10^{-7}	
mBMI[c]		
Change from baseline to Month 18	n=52	n=113
LS mean change (SE)	−115.7 (13.4)	25.0 (9.5)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	140.7 (108.4, 172.9)	
p value	4.16×10^{-15}	
R-ODS		
Change from baseline to Month 18	n=54	n=113
LS mean change (SE)	−9.9 (0.8)	−1.5 (0.6)
Vutrisiran vs APOLLO placebo		
LS mean difference (95% CI)	8.4 (6.5, 10.4)	
p value	3.54×10^{-15}	

[a]Data from the analysis of covariance/multiple imputation model. [b]Exploratory efficacy endpoints. [c]mBMI is defined as [weight in kilograms divided by square of height in meters] x albumin level in grams per liter. [d]Data from the mixed-effects model for repeated measures.

Abbreviations

Significant improvements with vutrisiran treatment compared with the external placebo group were observed for all other secondary endpoints, including 10-MWT at Months 9 and 18, mBMI at Month 18, and R-ODS at Month 18

Change from Baseline for Primary and Secondary Efficacy Endpoints for the Patisiran mITT Population

Endpoint	HELIOS-A Patisiran
mNIS+7	
Mean change from baseline at Month 9 (SD) (n=37)	−1.41 (17.23)
Mean change from baseline at Month 18 (SD) (n=36)	1.59 (21.50)
Norfolk QOL-DN	
Mean change from baseline at Month 9 (SD) (n=38)	0.1 (18.0)
Mean change from baseline at Month 18 (SD) (n=38)	−0.6 (19.3)
10-MWT	
Mean change from baseline at Month 9, ms^{-1} (SD) (n=37)	−0.039 (0.205)
Mean change from baseline at Month 18, ms^{-1} (SD) (n=38)	−0.043 (0.276)
mBMI[a]	
Mean change from baseline at Month 9 (SD) (n=36)	−6.2 (106.0)
Mean change from baseline at Month 18 (SD) (n=38)	6.9 (91.8)
R-ODS	
Mean change from baseline at Month 9 (SD) (n=38)	−1.8 (6.5)
Mean change from baseline at Month 18 (SD) (n=38)	−1.2 (5.9)
Serum TTR	
Mean percent change from baseline through Month 9 (SD) (n=42)	−73.3 (16.8)
Mean percent change from baseline through Month 18 (SD) (n=42)	−75.1 (14.9)

[a]mBMI is defined as [weight in kilograms divided by square of height in meters] × albumin level in grams per liter.

The mean changes from baseline for primary and secondary efficacy endpoints in the within-study patisiran group were similar to those in the vutrisiran group.

Abbreviations

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Safety Summary

Summary of Adverse Events

At least one event, n (%)	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Summary of AEs[a]			
Any AE	75 (97.4)	119 (97.5)	41 (97.6)
Serious AEs	31 (40.3)	32 (26.2)	18 (42.9)
Severe AEs	28 (36.4)	19 (15.6)	16 (38.1)
AEs leading to treatment discontinuation	11 (14.3)	3 (2.5)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)
AEs occurring in ≥10% in vutrisiran-treated patients[a]			
Fall	22 (28.6)	22 (18.0)	6 (14.3)
Pain in extremity	8 (10.4)	18 (14.8)	3 (7.1)
Diarrhea	29 (37.7)	17 (13.9)	7 (16.7)
Edema peripheral	17 (22.1)	16 (13.1)	4 (9.5)
Urinary tract infection	14 (18.2)	16 (13.1)	8 (19.0)
Arthralgia	0	13 (10.7)	4 (9.5)
Dizziness	11 (14.3)	13 (10.7)	0

[a]Safety reported in the safety population during the 18-month treatment period.

- During the 18-month treatment period, AEs were reported in 119 (97.5%) patients in the vutrisiran group, with the majority mild or moderate in severity.
  - Three (2.5%) patients in the vutrisiran group discontinued treatment, and also stopped study participation, due to AEs by Month 18 (two of which were due to death).
  - AEs leading to discontinuation included acute cardiac failure, COVID-19 pneumonia, and iliac artery occlusion (each n=1; 0.8%), none of which were considered related to vutrisiran.
  - Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection).
  - AEs occurring in ≥10% of patients receiving vutrisiran included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness; all of which, except from pain in extremity and arthralgia, occurred at a similar or lower rate than in the external placebo group.
  - There were no cardiac AEs related to vutrisiran in the safety population.
- Five patients (4.1%) who received vutrisiran reported mild and transient ISRs.
  - In total, 5/836 (0.6%) injections led to ISRs.
  - IRRs, which are reported with patisiran due to its different mode of administration, occurred in 10 (23.8%) patients who received patisiran.
- There were no safety signals regarding liver function tests, hematology, or renal function related to vutrisiran.
- A total of 4 (3.3%) vutrisiran-treated patients developed ADAs.
  - ADA titers were low and transient with no evidence of an effect on clinical efficacy, safety, or pharmacodynamic parameters of vutrisiran.

Abbreviations

Study Design

Results

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

Safety Summary

Summary of Deaths in the Safety Population[a]

Primary cause of death[a]		Demographics and disease characteristics at baseline					
		Age	Sex	*TTR* variant	PND score	NT-proBNP (pg/mL)	Medical history of CV disease
Vutrisiran (2/122; 1.6%)							
Patient 1	Multilobar pneumonia with severe respiratory failure secondary to COVID-19 infection	85	Male	V30M (late onset)[b]	IIIA	1589	Heart failure Cardiac amyloidosis Pacemaker implant Second-degree AV heart block
Patient 2	Occlusion of common internal and external iliac artery	68	Male	T60A	IIIA	7588	Atrial fibrillation Stroke Heart failure relating to cardiac amyloidosis Cardiac amyloidosis
Patisiran (3/42; 7.1%)							
Patient 1	Sudden death likely cardiac arrhythmia	81	Male	F64L	II	1994	Coronary angioplasty Hypertension Atrial fibrillation
Patient 2	COVID-19 pneumonia	56	Male	E89Q	IIIA	1868	Cardiac amyloidosis Heart failure relating to cardiac amyloidosis Pacemaker implant Second-degree AV heart block
Patient 3	Triple-vessel coronary artery disease	63	Male	I107V	IIIA	1320	Hypertension Cardiac amyloidosis Heart failure relating to cardiac amyloidosis

[a]Data reported during 18-month treatment period. [b]Onset of V30M hereditary transthyretin-mediated amyloidosis at 50 years or older.

- There were two (1.6%) deaths in the vutrisiran group and three (7.1%) deaths in the patisiran group, none of which were considered drug related.
- One death in each group was due to COVID-19.
- The non-COVID deaths, one in the vutrisiran group and two in the patisiran group, were seen in patients with non-V30M TTR variants who had medical histories of cardiac disease.

Abbreviations

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Impact on Doses Due to COVID-19 (Safety Population)

	HELIOS-A	
	Vutrisiran (n=122)	Patisiran (n=42)
Total administered doses	836	1065
Missed dose,[a] n (%)	1 (0.1)	27 (2.5)
Delayed dose,[a,b] n (%)	18 (2.2)	3 (0.3)
Patients with missed or delayed doses[a], n (%)	17 (13.9)	18 (42.9)

[a]Data were study coordinator-reported and only introduced in June 2020 following a protocol update during the pandemic. [b]Dose administered outside of window originally intended before window expansion defined in protocol amendment 2.

- The study took place during the COVID-19 pandemic.
- Five patients in the vutrisiran group missed efficacy assessments due to COVID-19:
  - Two at both 9 and 18 months.
  - Two at 9 months (who remained on study until 18 months)
  - One at 18 months.
- In addition, 1/836 (0.1%) and 27/1065 (2.5%) doses were missed, and 18/836 (2.2%) and 3/1065 (0.3%) doses were delayed due to COVID-19 in the vutrisiran and patisiran groups, respectively.

Abbreviations

Study Design

INTRODUCTION

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)

Month 18

Secondary Endpoint
- Non-inferiority in TTR reduction

Secondary Endpoints
Change from baseline in:
- mNIS+7
- Norfolk QOL-DN
- 10-MWT / mBMI / R-ODS

Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

Safety Assessments
Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths
- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

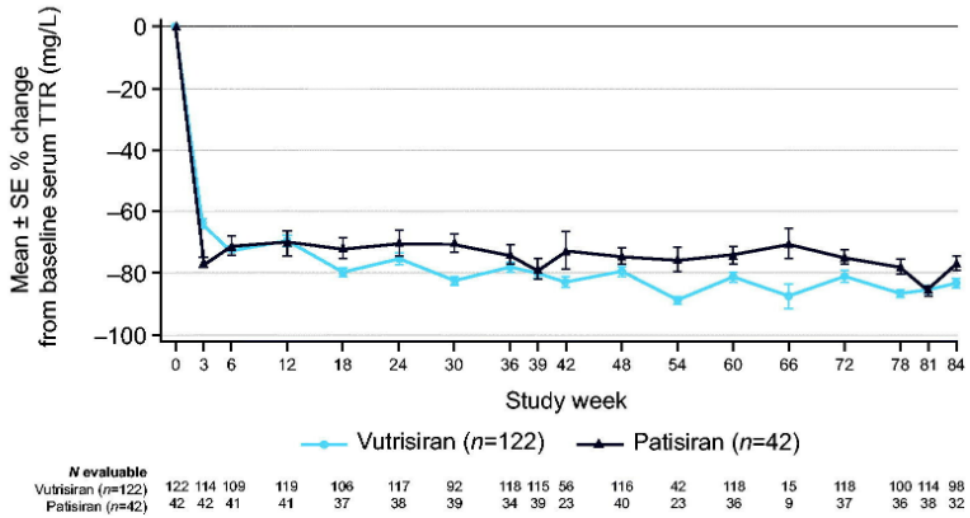
MED-US-TTRSC02-220059 | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Pharmacodynamics

Percent Change from Baseline in Serum TTR Levels with Vutrisiran and Patisiran through 18 Months of the HELIOS-A study



- Vutrisiran treatment resulted in rapid (≤3 weeks) and sustained reduction in serum TTR levels over 18 months, similar to what was observed in the within-study patisiran group.
- TTR reduction with vutrisiran was statistically non-inferior to within-study patisiran in the TTR per-protocol population (secondary endpoint), assessed by mean trough serum TTR levels over 18 months.
- Serum TTR reduction with vutrisiran was also similar across all patient subgroups. As expected from previous studies, serum vitamin A levels were reduced in parallel with reductions in serum TTR levels in both treatment groups.[1]

1. Zhang et al. *J Clin Pharmacol* 2020;60:37-49.

Summary of Trough and Peak Serum TTR Reduction from Baseline (mITT population)

	HELIOS-A	
	Vutrisiran (n=122)	Patisiran (n=42)
Steady-state trough TTR % reduction[a]	n=118	n=37
Mean (SD)	81.0 (21.0)	74.7 (14.7)
Median (IQR)	86.2 (19.0)	78.2 (14.7)
Steady-state peak TTR % reduction[b]	n=15	n=38
Mean (SD)	87.6 (15.7)	86.0 (10.0)
Median (IQR)	91.6 (10.0)	88.3 (11.6)

[a]Steady-state trough samples taken at Week 72 (Day 505) for vutrisiran and patisiran.
[b]Steady-state peak samples taken at Week 66 (Day 463) for vutrisiran and Month 18 (non-trough) sample for patisiran.

- Following 18 months of vutrisiran treatment, steady-state mean (SD) peak and trough serum TTR reductions from baseline were 87.6% (15.7%) and 81.0% (21.0%), respectively.
- The fluctuation between median steady-state peak and trough values was lower with vutrisiran (peak-trough=Δ; 91.6–86.2%=5.4%) compared with patisiran (88.3–78.2%=10.1%), which was reflected in the reduced variability in TTR reduction (smaller standard error) observed at most time points with vutrisiran.

Abbreviations

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

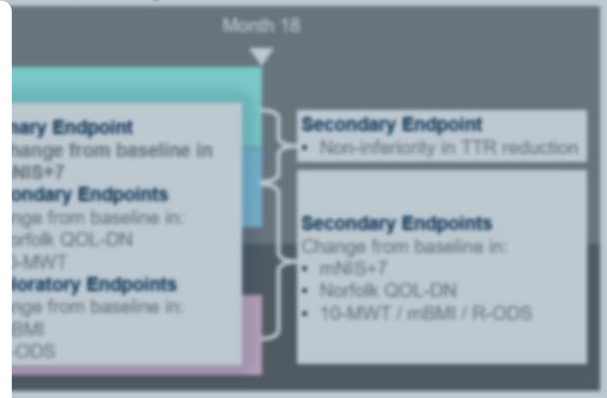
hATTR amyloidosis, also known as ATTRv amyloi
progressive, debilitating, and fatal disease caused
gene variants, that has a heterogeneous clinical p
sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces seru
synthesis of variant and wild-type TTR and is giver

Patisiran is an RNAi therapeutic encapsulated in a
directs it to the liver following Q3W IV administrati
RNAi approach as vutrisiran to target variant and

The HELIOS-A study aimed to assess the effect o
with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)



Conclusions

- In HELIOS-A, vutrisiran met the primary and all secondary efficacy endpoints at 9 and 18 months
  - Vutrisiran demonstrated significant improvements in neuropathy impairment, QOL, gait speed, nutritional status, and disability compared with the external placebo group
  - Improvement in neuropathy and QOL relative to baseline was observed in approximately half of vutrisiran-treated patients, demonstrating reversal of disease manifestations
- Vutrisiran was generally well tolerated and demonstrated an acceptable safety profile, with most AEs being mild or moderate in severity and generally consistent with those expected as a consequence of hATTR amyloidosis[1,2]
  - In vutrisiran-treated patients, there was a low mortality rate and a low rate of treatment discontinuation due to AEs, and none of these events were considered to be related to vutrisiran treatment
- Improvements in efficacy outcomes with vutrisiran were generally similar to those observed with patisiran
  - No statistical testing of efficacy outcomes was conducted as HELIOS-A was not designed to compare the efficacy of the two treatments
- TTR reduction with vutrisiran Q3M SC injection was statistically non-inferior to patisiran Q3W IV infusion
- Vutrisiran is given by SC administration without the need for premedication,and 4% ISR AEs were reported

1. Adams et al. *Neurology* 2015;85:675-82; 2. Adams et al. *Curr Opin Neurol* 2016;29(Suppl. 1):S14-S26.

Abbreviations

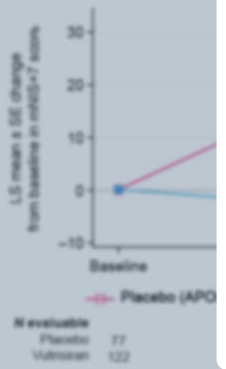
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neurop



Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

dpoints

r secondary efficacy endpoints
T)
nBMI)
also reported

c Endpoints

trisiran Q3M was rapid, sustained, and statistically
tudy patisiran Q3W
rum TTR reduction
on

Safety Assessments

Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths

- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

MED-US-TTRSC02-2200059 | July 2022 |

Abbreviations

Efficacy and Safety of Vutrisiran for Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: A Randomized Clinical Trial

Adams D et al. *Amyloid* 2022. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

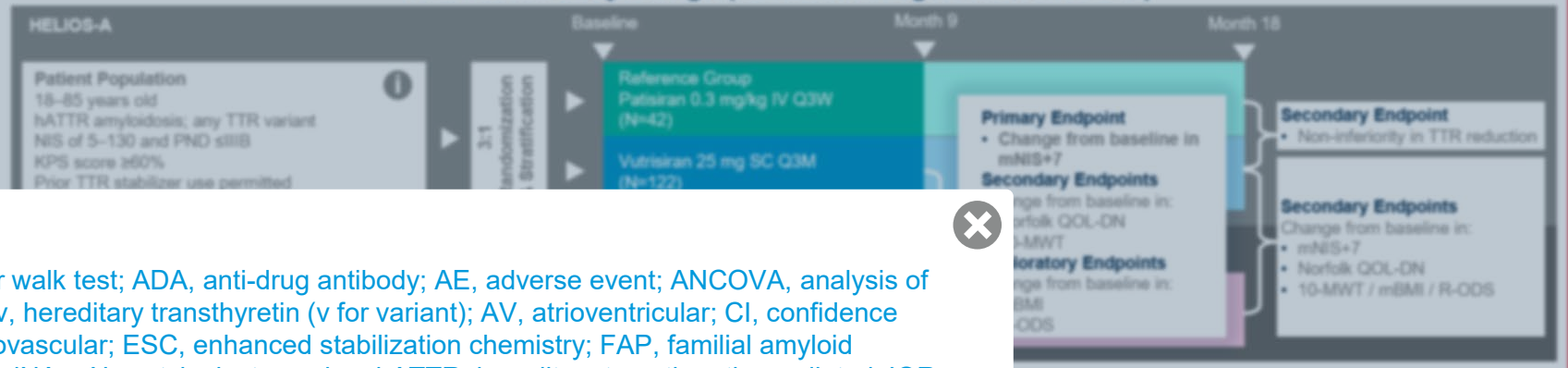
hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, rapidly progressive, debilitating, and fatal disease caused by transthyretin (*TTR*) gene variants, that has a heterogeneous clinical presentation including sensory, motor and autonomic polyneuropathy

Vutrisiran is an RNAi therapeutic that reduces serum TTR levels by reducing synthesis of variant and wild-type TTR and is given by Q3M SC injection

Patisiran is an RNAi therapeutic encapsulated in a [illegible] directs it to the liver following Q3W IV administration [illegible] RNAi approach as vutrisiran to target variant and

The HELIOS-A study aimed to assess the effect o[illegible] with hATTR amyloidosis with polyneuropathy

HELIOS-A Study Design (ClinicalTrials.gov NCT03759379)



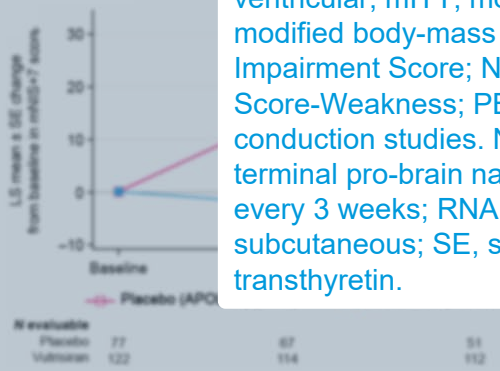
Results

Patients

HELIOS-A enrolled 164 patients and had a high rate of completion

The HELIOS-A population and external placebo group had widely overlapping baseline characteristics and were clinically comparable

Neurop[illegible]



Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 (**primary endpoint**) and Month 18 versus the external placebo group

Consistent improvement in mNIS+7 seen across all prespecified subgroups and across mNIS+7 components

Vutrisiran treatment also significantly improved total Norfolk QOL-DN score compared with the external placebo group at Month 9 and Month 18

Consistent improvement in Norfolk QOL-DN score seen across all prespecified subgroups and across Norfolk QOL-DN score domains

[illegible]dpoints
[illegible] secondary efficacy endpoints
[illegible]T)
[illegible]BMI)
[illegible] also reported

[illegible]c Endpoints
[illegible]trisiran Q3M was rapid, sustained, and statistically
[illegible]study patisiran Q3W
[illegible]rum TTR reduction
[illegible]on

Safety Assessments
Two (1.6%) patients experienced serious AEs considered related to vutrisiran (one dyslipidemia and one urinary tract infection). . There were no drug-related discontinuations or deaths
- Summary of AEs
- Summary of deaths
- Impact on doses due to COVID-19

Conclusions: In HELIOS-A, vutrisiran significantly improved multiple disease-relevant outcomes for hATTR amyloidosis vs external placebo, with an acceptable safety profile

Abbreviations

10-MWT, 10-meter walk test; ADA, anti-drug antibody; AE, adverse event; ANCOVA, analysis of covariance; ATTRv, hereditary transthyretin (v for variant); AV, atrioventricular; CI, confidence interval; CV, cardiovascular; ESC, enhanced stabilization chemistry; FAP, familial amyloid polyneuropathy; GalNAc, *N*-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; IQR, interquartile range; IRR, infusion-related reaction; ISR, injection site reaction; IV, intravenous; KPS, Karnofsky Performance Status; LS, least squares; LSMD, least-squares mean difference; LV, left ventricular; mITT; modified intent-to-treat; MMRM, mixed-effects model for repeated measures; mBMI, modified body-mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; NIS-R: Neuropathy Impairment Score-Reflexes; NIS-W: Neuropathy Impairment Score-Weakness; PBP: postural blood pressure; QST: quantitative sensory testing; Σ5 NCS: Σ5 nerve conduction studies. Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; RNAi, RNA interference; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; SE, standard error; SD, standard deviation; siRNA, small interfering RNA; TTR, transthyretin.

MED-US-TTRSC02-2200059 | July 2022 |