# Vutrisiran: Pharmacokinetic and Pharmacodynamic Properties

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## SUMMARY


- Vutrisiran is a chemically stabilized, double-stranded siRNA specifically designed for delivery to the liver through conjugation of a trivalent carbohydrate ligand, known as GalNAc. The duration of action of vutrisiran observed in clinical studies may be attributable to metabolic stability, long liver residence time within hepatocytes, and the slow turnover of human hepatocytes.[1]
- In nonclinical studies, targeted delivery of vutrisiran to the liver via ASGPR was confirmed by consistently higher concentrations in the liver compared with the plasma and kidney in mice, rats, and monkeys. Vutrisiran concentrations declined at a significantly slower rate in the liver compared with plasma.[2]
- In a phase 1 study, vutrisiran reduced serum TTR in a dose-dependent manner, with onset of effect observed within days. The $t_{max}$ for vutrisiran ranged between 3–5 hours post-dose, the mean $t_{1/2}$ ranged between 4.2–7.5 hours, and the total plasma clearance ranged between 18–31 L/hour (mean, 22 L/hour).[1]
- In the phase 3 HELIOS-A study, the mean (SD) steady-state peak and trough serum TTR reductions from baseline in the vutrisiran arm were 87.6% (15.7%) and 81.0% (21.0%) following 18 months of treatment.[3]
- In the phase 3 HELIOS-B study, the mean (95% CI) trough serum TTR reduction with vutrisiran was 81.0% (79% to 83.0%) at 30 months in the overall population and the median (95% CI) percent change in TTR level was -86.8 (-88.2, -83.7) in the vutrisiran arm compared to -7.9 (-12.2, -3.2) in the placebo arm.[4,5]


## INDEX



## NONCLINICAL DATA

### Pharmacokinetics

After a single SC dose, vutrisiran was rapidly absorbed and reached peak plasma concentrations between 0.5 and 1 hour in rats and 1.9 and 2.8 hour in monkeys. Estimated plasma half-lives ranged

from 2 to 3.3 hours in rats and 3.3 to 4.7 hours in monkeys. In both species, there was a dose-proportional increase in vutrisiran plasma exposure up to 3 mg/kg, but the increase was greater than dose-proportional at higher dosage, attributed to saturation of ASGPR-mediated uptake of vutrisiran in the liver.[2] Repeat-dose plasma PK parameter estimates following 4 monthly SC doses of 1 mg/kg in rats and 0.3 or 1 mg/kg in monkeys were consistent with single-dose PK parameters indicating linear PK.[6]

Targeted delivery of vutrisiran to the liver via ASGPR was confirmed by consistently higher concentrations in liver compared with plasma and kidney in studies across mice, rats, and monkeys. Vutrisiran concentrations peaked in rat and monkey liver by 8 and 24 hours, respectively, and declined at a significantly slower rate in the liver compared with plasma, with liver $t_{1/2}$ values of about 4 to 6 days in rats and 20 to 30 days in monkeys.[2]

Similar targeted delivery to the liver in human is expected. To evaluate the potential for accumulation of vutrisiran in human liver, the PK data in monkey liver was used and allometric scaling with exponents of 1.0 for Vd and 0.75 for clearance was applied. Using this approach, the $t_{1/2}$ of vutrisiran in human liver was estimated to be about 53 days for a 70-kg patient. Considering this $t_{1/2}$ and the once quarterly dosing regimen, no significant accumulation of vutrisiran in human liver at steady state is expected.[6]

Once delivered into the hepatocytes, vutrisiran is loaded onto the cytoplasmic RISC. Data in mice using other GalNAc–siRNA conjugates similar to vutrisiran showed that peak siRNA concentrations in the liver were observed 4 to 24 hours after an SC dose, yet the maximal RISC-loaded siRNA concentrations were observed 3 to 7 days post dose. Liver residence times were observed to last up to 42 days.[1,7,8]

## CLINICAL DATA

The gradual loading of RISC is hypothesized to be a result of slow endosomal trafficking and release of the siRNA into the cytosol, where RISC is present. Furthermore, hepatocytes are long lived, with a life span reported to range from 180–400 days in healthy adults. Therefore, the long duration of action of vutrisiran observed in clinical studies may be attributable to metabolic stability, long liver residence time within hepatocytes, and the slow turnover of human hepatocytes.[1]

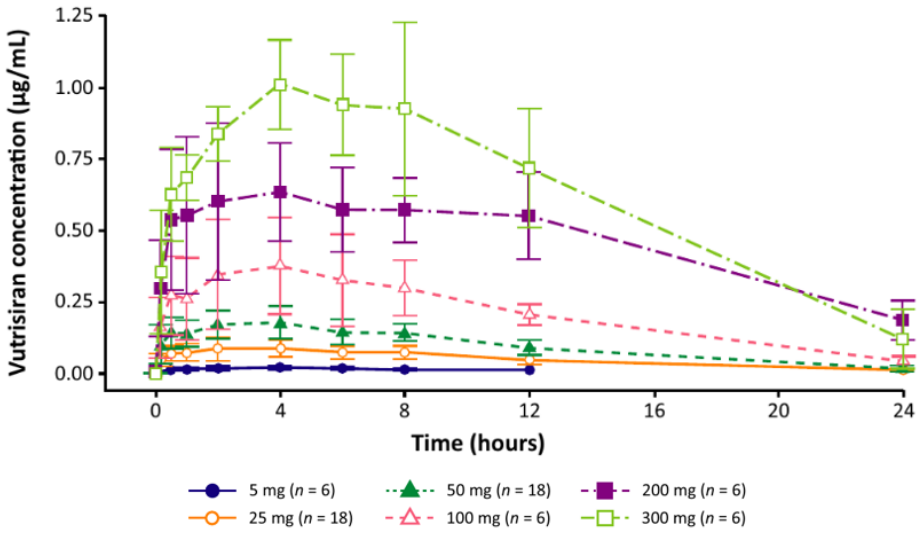
### Phase 1 Study

A phase 1, randomized, single-blind, placebo-controlled, single ascending dose study was conducted to evaluate the PK, PD, and safety profile of SC vutrisiran in healthy subjects (N=80). The subjects were scheduled to receive a single dose of either vutrisiran (n=60) or placebo (n=20). Study subjects were enrolled in cohorts to receive 25 mg (n=6), 50 mg (n=6), 100 mg (n=6), 200 mg (n=6), or 300 mg (n=6) of vutrisiran. Following the enrollment of these cohorts, five additional cohorts were enrolled: a 5 mg cohort (n=6); two additional cohorts of 25 mg (n=6) and 50 mg (n=6) to better characterize these doses; and two cohorts of Japanese subjects, for whom dosing was initiated at a level shown to be tolerable in a prior cohort (25 mg [n=6] and 50 mg [n=6]).[1]

Plasma Pharmacokinetics

For PK assessments, blood samples were collected at the following intervals: 1 hour prior to dosing and at 10 minutes, 30 minutes, and 1, 2, 4, 6, 8, 12, 24, and 48 hours after dose administration. The plasma concentration profiles of vutrisiran across doses are shown in **Figure 1**.[1]

**Figure 1. Vutrisiran Plasma Concentration Over Time.**[1]




From Habtemariam et al.[1]

Across all doses of vutrisiran, the $t_{max}$ ranged between 3–5 hours post-dose. The mean $t_{1/2}$ ranged between 4.2–7.5 hours. CL/F ranged between 18–31 L/hour (mean, 22 L/hour). For the 5 mg dose, there were insufficient data in the terminal elimination phase to calculate $t_{1/2}$. The systemic exposures of vutrisiran were characterized by low to moderate inter-individual variability (percent coefficient of variation was <30% of the AUC; <48% for $C_{max}$).[1]

Urine Pharmacokinetics

Urine samples were collected from each subject after vutrisiran administration on Day 1, with pooled collections obtained over the intervals of 0–6, 6–12, and 12–24 hours. The percentage of vutrisiran dose excreted unchanged in urine through 24 hours ranged between 15-25%. The percentages increased slightly with increasing dose, with a majority excreted within the first 12 hours. Across the doses tested, mean $CL_R$ of vutrisiran ranged between 4.45–5.74 L/hour (mean, 5 L/hour). The $CL_R$/[CL/F] ranged between 15.5-27.5%.[1]

Pharmacodynamics

For PD assessments, blood samples were collected at the following time periods: Day -1, 1, 3, 8, 15, 22, 29, 43, 57, 90 and every 28 days thereafter until serum TTR levels returned to 80% of baseline. Serum TTR reduction from baseline across the doses studied is shown in **Table 1**. Vutrisiran reduced serum TTR in a dose-dependent manner, with onset of effect observed within days of dosing. The nadir (lowest point) of serum TTR reduction from baseline ranged between 57–97%. Across all vutrisiran dose groups, nadir TTR levels were achieved by 50–90 days. On Day 314 post-dose, the mean percentage of TTR reduction relative to baseline ranged from 43% with 5 mg to 83% with 300 mg.[1]

**Table 1. Phase 1 Study: Summary of TTR Reduction Profiles by Dose.[1]**

| Vutrisiran Dose | TTR Change from Baseline, % | | | Time to Nadir, days |
|---|---|---|---|---|
| | Day 15 | Nadir | Day 314 | |
| 5 mg | | | | |
| Mean (%RSD) | -32.7 (48.1%) | -57.1 (24.4%) | -43.3 (61.9%)[a] | |
| Median (min, max) | -32.7 (-9.6, -54.9) | -54.5 (-39.4, -74.7) | -43.3 (-24.4, -62.3)[a] | 66.5 (22, 90) |
| 25 mg | | | | |
| Mean (%RSD) | -46.6 (53.3%) | -80.2 (14.6%) | -55.3 (42.9%)[b] | |
| Median (min, max) | -51.7 (20.2, -78.9) | -82.9 (-52.9, -93.7) | -63.1 (-13.0, -78.2)[b] | 73.5 (22, 174) |
| 50 mg | | | | |
| Mean (%RSD) | -55.3 (27.6%)[c] | -87.3 (9.4%)[d] | -63.6 (36.6%)[e] | |
| Median (min, max) | -55.7 (-19.3, -75.7)[c] | -90.2 (-70.0, -94.9)[d] | -66.5 (-14.1, -94.2)[e] | 90 (43, 286)[d] |
| 100 mg | | | | |
| Mean (%RSD) | -73.1 (16.1%) | -90.7 (9.5%) | -66.7 (35.8%) | |
| Median (min, max) | -74.3 (-57.0, -86.2) | -95.3 (-78.8, -97.6) | -67.5 (-40.8, -95.5) | 57 (43, 118) |
| 200 mg | | | | |
| Mean (%RSD) | -86.9 (3.7%) | -96.6 (3.0%) | -77.6 (27.6%)[a] | |
| Median (min, max) | -85.7 (-83.1, -91.4) | -97.8 (-90.8, -98.3) | -77.6 (-62.4, -92.8)[a] | 50 (29, 146) |
| 300 mg | | | | |
| Mean (%RSD) | -79.4 (10.5%) | -97.1 (1.3%) | -83.4 (9.7%) | |
| Median (min, max) | -79.5 (-66.8, -91.3) | -97.6 (-95.0, -98.4) | -85.9 (-67.2, -88.5) | 57 (43, 90) |

Abbreviations: min = minimum; max = maximum; RSD = relative standard deviation; TTR = transthyretin.
[a]n=2. [b]n=10. cn=16. [d]n=17. [e]n=11.

**HELIOS-A**

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

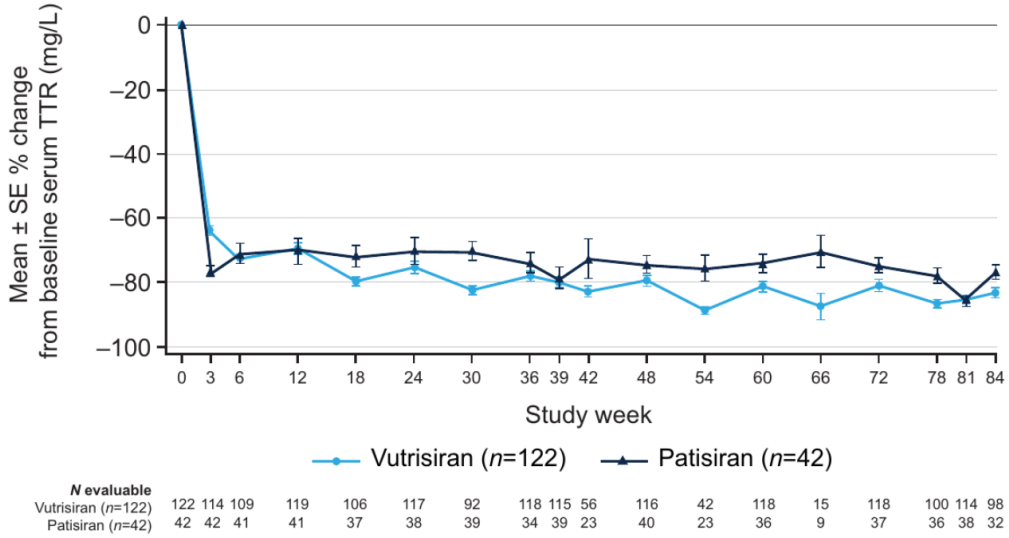
Pharmacokinetics

In the HELIOS-A study, individual $t_{max}$ values ranged from 2–6.6 hours. Vutrisiran plasma concentrations reached the lower limit of quantitation by 24 hours in a majority of patients. At steady state (Day 253), there was no accumulation of vutrisiran in plasma after the recommended dose regimen of 25 mg q3M.[2]

Pharmacodynamics

The percent change from baseline in serum TTR levels through 18 months in the vutrisiran and within-study patisiran arms was evaluated as a secondary endpoint. Following 18 months of vutrisiran treatment, mean (SD) steady-state peak and trough serum TTR reductions from baseline were 87.6% (15.7%) and 81.0% (21.0%), respectively. Assessed by mean trough serum TTR levels over 18 months, TTR reduction with vutrisiran was statistically non-inferior to within-study patisiran in the TTR per-protocol population. 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%) (**Figure 2**).[3]

**Figure 2. Mean Percent Change from Baseline in Serum TTR Levels through Month 18 for Vutrisiran and Patisiran.[3]**




Abbreviations: SE = standard error; TTR = transthyretin.
From Adams et al.[3]

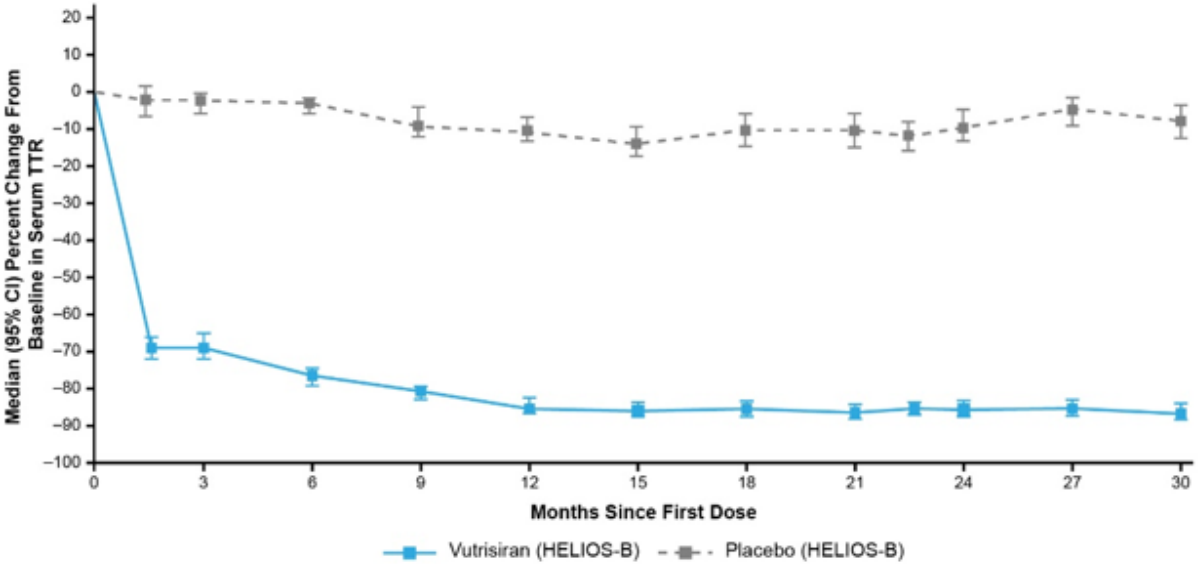
**HELIOS-B**

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an OLE.[4]

Pharmacodynamics

A pharmacodynamic endpoint of the study was the change in serum TTR levels with vutrisiran in the overall population and in the monotherapy population. Following 30 months of vutrisiran treatment, the mean (95% CI) trough serum TTR reduction was 81.0% (79% to 83.0%) in the overall population.[4] The median (95% CI) percent change in serum TTR level was -86.8 (-88.2, -83.7) in the vutrisiran arm compared to -7.9 (-12.2, -3.2) in the placebo arm, as seen in **Figure 3**.[5]

**Figure 3. Median Percent Change from Baseline in Serum TTR Levels through Month 30.**[5]




Abbreviations: CI = confidence interval; TTR = transthyretin.
Data on File.[5]

## AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The **CLINICAL PHARMACOLOGY** section provides the following information[9]:

***Pharmacodynamics***

*The pharmacodynamic effects of AMVUTTRA were evaluated in patients with hATTR-PN and ATTR-CM, treated with 25 mg AMVUTTRA administered by subcutaneous injection once every 3 months.*

*Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis*

*In HELIOS-A, vutrisiran reduced mean serum TTR at steady state by 83%. Similar TTR reductions were observed regardless of Val30Met genotype status, weight, sex, age, or race.*

*Vutrisiran also reduced the mean steady state serum vitamin A by 62% over 9 months.*

*Cardiomyopathy of Wild-type (wt) or Hereditary Transthyretin-mediated Amyloidosis (hATTR)*

*In HELIOS-B, the mean serum TTR reduction profile was similar with that observed in HELIOS-A, and consistent across all the subgroups studied (age, sex, race, body weight, anti-drug antibody [ADA] status, ATTR disease type (wtATTR versus hATTR), NYHA class, and baseline tafamidis use).*

*Vutrisiran reduced the mean steady state serum vitamin A by 65% over 36 months.*

*Cardiac Biomarkers*

*Biomarkers associated with heart failure (NT-proBNP and Troponin I) favored AMVUTTRA over placebo.*

*Cardiac Electrophysiology*

*At a dose 12 times the recommended dosage of 25 mg once every three months, AMVUTTRA does not prolong the QT interval to any clinically relevant extent.*

***Pharmacokinetics***

*The pharmacokinetic (PK) properties of AMVUTTRA were evaluated following a single dose in healthy subjects and multiple doses in patients with hATTR amyloidosis, as summarized in Table 2.*

***Table 2: Pharmacokinetic Parameters of Vutrisiran***

| | ***Vutrisiran*** |
|---|---|
| ***General Information*** | |
| ***Dose Proportionality*** | *Vutrisiran $C_{max}$ showed dose proportional increase while $AUC_{last}$ and $AUC_{inf}$ were slightly more than dose proportional following single subcutaneous doses ranging from 5 to 300 mg (i.e., 0.2 to 12 times the recommended dose)* |
| ***Accumulation*** | *No accumulation of vutrisiran was observed in plasma after repeated every 3 months dosage[a]* |
| ***Absorption*** | |
| ***$T_{max}$ [Median (Range)]*** | *4 (0.17, 12.0) hours[b]* |
| ***Distribution*** | |
| ***Estimated Vd/F (%RSE)*** | *10.1 (5.8) L[c]* |
| ***Protein Binding*** | *80%[d]* |
| ***Organ Distribution*** | *Vutrisiran distributes primarily to the liver after subcutaneous dosing* |
| ***Elimination*** | |
| ***Half-Life [Median (Range)]*** | *5.2 (2.2, 6.4) hours[b]* |
| ***Apparent Clearance [Median (Range)]*** | *21.4 (19.8, 30) L/hour[b]* |
| ***Metabolism*** | |
| ***Primary Pathway*** | *Vutrisiran is metabolized by endo- and exonucleases to short nucleotide fragments of varying sizes within the liver* |
| ***Excretion*** | |
| ***Primary Pathway*** | *The mean fraction of unchanged vutrisiran eliminated in urine was approximately 19.4% at the recommended dose of 25 mg. The mean renal clearance of vutrisiran ranged from 4.5 to 5.7 L/hour[e]* |

*$AUC_{inf}$ = area under the concentration-time curve from the time of dosing extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve from the time of dosing to the last measurable concentration; $C_{max}$ = maximum plasma concentration; CV = coefficient of variation;*
*RSE = relative standard error; $T_{max}$ = time to maximum concentration; Vd/F = apparent volume of distribution*
*[a]After 25 mg every 3 months dosage in hATTR amyloidosis patients*
*[b]After 25 mg single dose in healthy subjects*
*[c]Based on population PK model estimation*
*[d]Vutrisiran plasma protein binding was concentration-dependent and decreased with increasing vutrisiran concentrations (from 78% at 0.5 mcg/mL to 19% at 50 mcg/mL)*
*[e]After single subcutaneous vutrisiran dose from 5 to 300 mg (i.e., 0.2 to 12 times the recommended dose) in healthy subjects*

*Specific Populations*

*No clinically significant differences in the pharmacokinetics of vutrisiran were observed based on age, sex, race, mild and moderate renal impairment (eGFR≥30 to <90 mL/min/1.73 m2), or mild (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) and moderate (total bilirubin >1.5 to 3 × ULN and any AST) hepatic impairment. Vutrisiran has not been studied in patients with severe renal impairment, end-stage renal disease, severe hepatic impairment, or in patients with prior liver transplant*

*Drug Interaction Studies*

*No clinical drug-drug interaction studies have been performed with vutrisiran. In vitro studies suggest that vutrisiran is not a substrate or inhibitor of cytochrome P450 enzymes. Vutrisiran is not expected to cause drug-drug interactions by inducing CYP enzymes or modulating the activities of drug transporters.*

## ABBREVIATIONS

ASGPR = asialoglycoprotein receptor; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; AUC = area under the curve; CI = confidence interval; CL/F = total plasma clearance; CLR = renal clearance; Cmax = maximum serum concentration; CV = cardiovascular; GalNAc = N-acetylgalactosamine; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; max = maximum; min = minimum; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; q3M = every 3 months; RISC = ribonucleic acid–induced silencing complex; RSD = relative standard deviation; SC = subcutaneous; SD = standard deviation; SE = standard error; siRNA = small interfering ribonucleic acid; $t_{1/2}$ = half-life; $t_{max}$ = time to maximum concentration; TTR = transthyretin; Vd = volume of distribution; wtATTR = wild-type transthyretin amyloidosis.

*Updated 26 March 2025*

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