



17-20
Dicembre
2025
Napoli

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Studi di Napoli
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E GERIATRIA

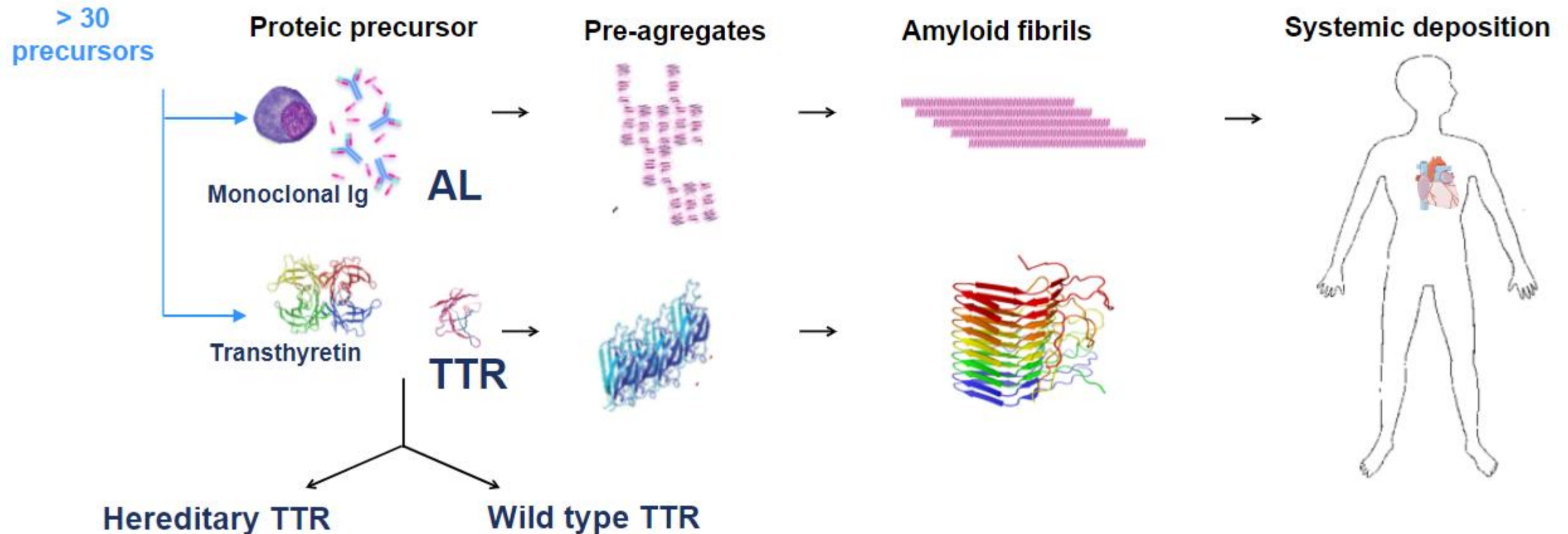
Eplontersen nel Trattamento della Polineuropatia Amiloidotica

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Amyloidosis or amyloidoses ?

Various precursors = various types of amyloidosis

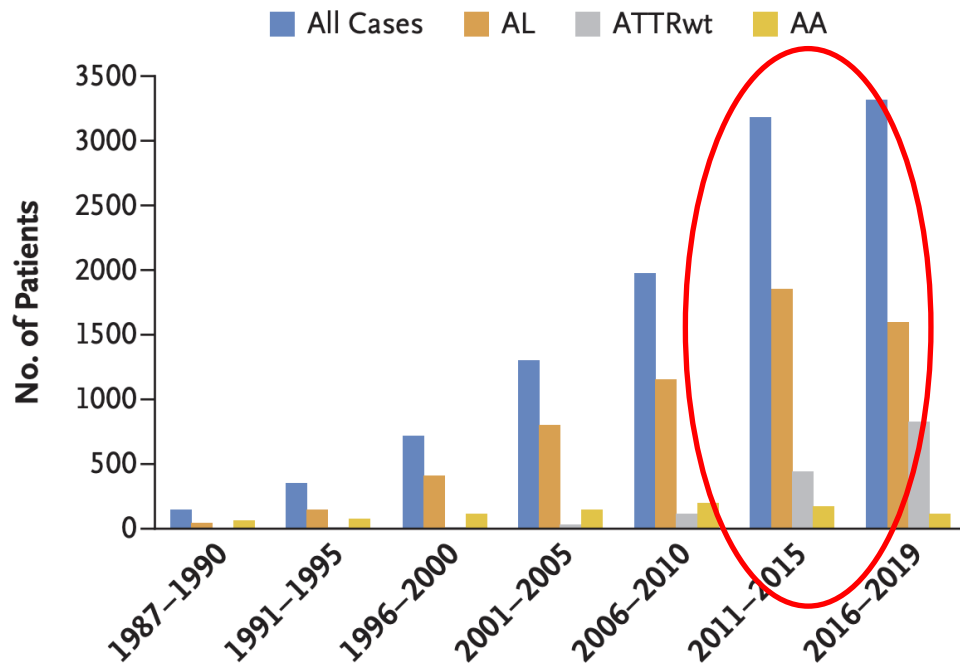


Trends in Diagnoses

National Amyloidosis Centre, London, United Kingdom

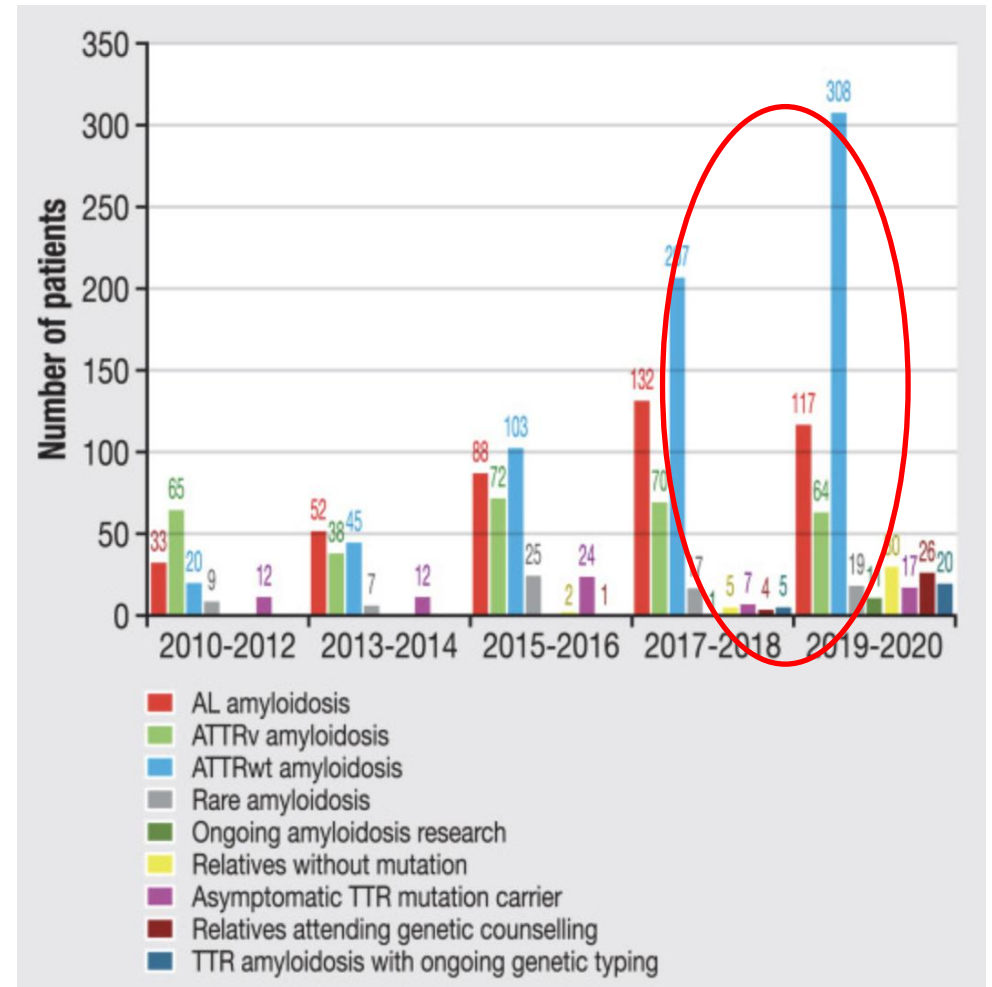
Mondor Cardiology Cardiac Amyloidosis Referral Centre, France

A Diagnoses of Amyloidosis According to Time Period and Type



The incidence of ATTRwt amyloidosis increased from less than 3% of all cases in the period 1987–2009 to 14% in the period 2010–2015 and to 25% in the past 4 years.

Ravichandran S. et al. *N Engl J Med* 2020



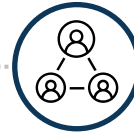
Damy T. et al. *Arch Cardiovasc Dis* 2023

There are two types of ATTR, each with distinct clinical features

Hereditary (ATTRv)

Autosomal dominant **inheritance** with variable penetrance^{1,2}

- Mutations in TTR gene lead to destabilization of the TTR tetramer and formation of amyloid



Age of onset typically in **3rd to 5th decade of life**²



Characterized by **peripheral sensorimotor neuropathy, autonomic neuropathy, cardiomyopathy**, carpal tunnel syndrome, and other symptoms and manifestations³



Median survival from diagnosis with **predominantly neuropathic symptoms is 5-15 years** and **2.5-4 years with predominant cardiomyopathy symptoms**^{1,4}



Wild-type (ATTRwt)

Develops with age (acquired)^{2,5}

- TTR tetramers destabilize with age, in the absence of a TTR gene mutation

Patients are typically **aged >60 years, white, and male**^{5,6}

Characterized mainly by **cardiomyopathy**, but can also include other manifestations such as polyneuropathy, carpal tunnel syndrome, or lumbar spinal stenosis^{6,7}

Median survival from diagnosis is **3-5 years**, with heart failure as the primary cause of death^{4,5,7}

ATTR = transthyretin-mediated [amyloidosis]; ATTRv = hereditary transthyretin-mediated [amyloidosis]; ATTRwt = wild-type transthyretin-mediated [amyloidosis]; TTR = transthyretin.

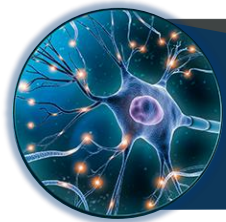
1. Hawkins P et al. *Ann Med*. 2015;47(8):625-638; 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31; 3. Conceição I et al. *J Peripher Nerv Syst*. 2016;21(1):5-9; 4. Kittleson MM et al. *Circulation*. 2020;142(1):e7-e22; 5. Connors LH et al. *Circulation*. 2016;133(3):282-290; 6. Brunjes DL et al. *J Card Fail*. 2016;22(12):996-1003;

7. Witteles RM et al. *JACC Heart Fail*. 2019;7(8):709-716.

ATTRv often presents as a mixed phenotype with symptoms of both polyneuropathy and cardiomyopathy¹⁻⁶

ATTRv amyloidosis is a systemic disease^{1,a}

V30M Early Onset	V28M	S77Y	F64L	P24S	E89Q	I107V	T60A	A45T	I84A	I68L
G54G	I107P	E89L	G47A	V30M Late Onset	T49A	L111M	V20I	G65L	V122I	



Neurologic Features

Mixed Phenotype

Cardiac Features



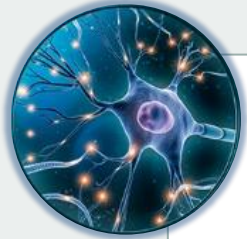
Evaluation of symptoms across the spectrum of ATTRv are critical steps in the diagnostic and treatment pathways

^aThe numbering of TTR genetic variants based on the mature protein (i.e., without leader sequence or propeptides) as recommended by the ISA Nomenclature Committee.⁷

ATTRv = hereditary transthyretin-mediated [amyloidosis]; ATTRwt = wild-type transthyretin-mediated [amyloidosis]; ISA = International Society of Amyloidosis; TTR = transthyretin.

1. Adams D et al. *J Neurol*. 2021;268(6):2109-2122; 2. Maurer MS et al. *Circ Heart Fail*. 2019;12(9):e006075; 3. Conceição I et al. *Amyloid*. 2019;26(1):3-9; 4. Coelho T et al. A guide to transthyretin amyloidosis. 2018. Amyloidosis Foundation website; 5. Sekijima Y. *J Neurol Neurosurg Psychiatry*. 2015;86(9):1036-1043; 6. Wixner J et al. *Orphanet J Rare Dis*. 2014;9:61; 7. Buxbaum JN et al. *Amyloid*. 2024;31(4):249-256.

The exact global prevalence of ATTR is unknown and presumably underestimated



Hereditary ATTR-PN¹⁻⁴

~10K to 40K patients

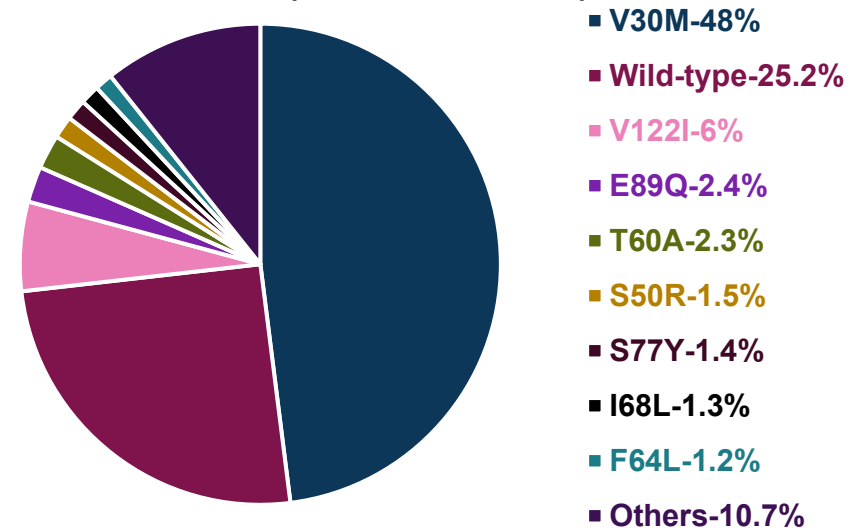


ATTR-CM³

Hereditary Wild-type

~300K to 500K patients

Genotype Prevalence in ATTR Population (THAOS; n=6368)^{5,a}

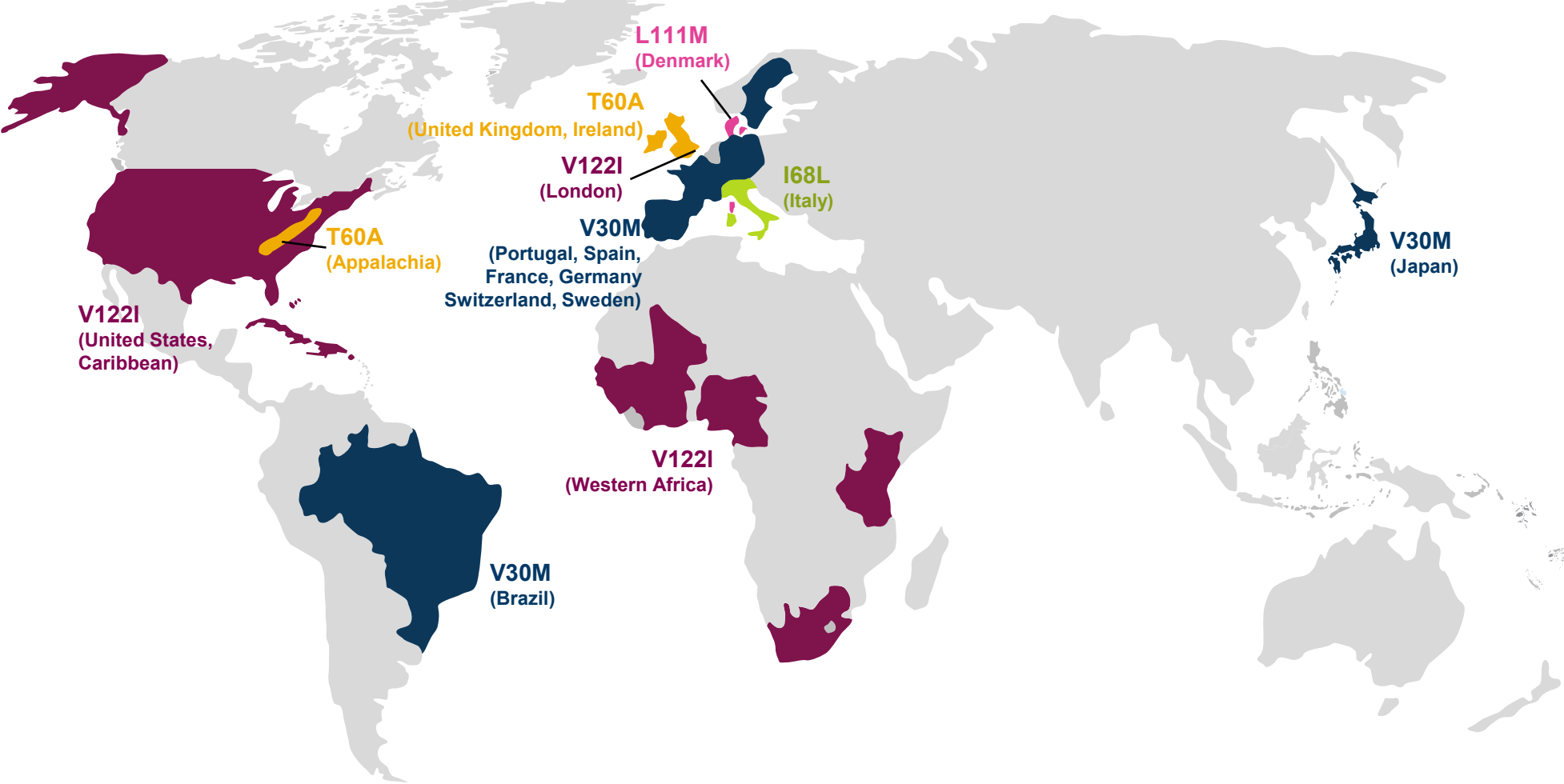


Note: The exact prevalence of ATTR-PN and ATTR-CM is difficult to establish due to variable geographic distribution of TTR gene variants and differing clinical presentations.^{1,6}

^aData from 4428 symptomatic patients, 1707 asymptomatic gene carriers, and 233 wild-type patients (who did not meet the definition for symptomatic) enrolled in THAOS from 23 countries. ATTR = transthyretin-mediated [amyloidosis]; ATTR-CM = transthyretin-mediated amyloidosis with cardiomyopathy; ATTR-PN = polyneuropathy of transthyretin-mediated [amyloidosis]; ATTRv = hereditary transthyretin-mediated [amyloidosis]; THAOS = Transthyretin Amyloidosis Outcomes Survey; TTR = transthyretin.

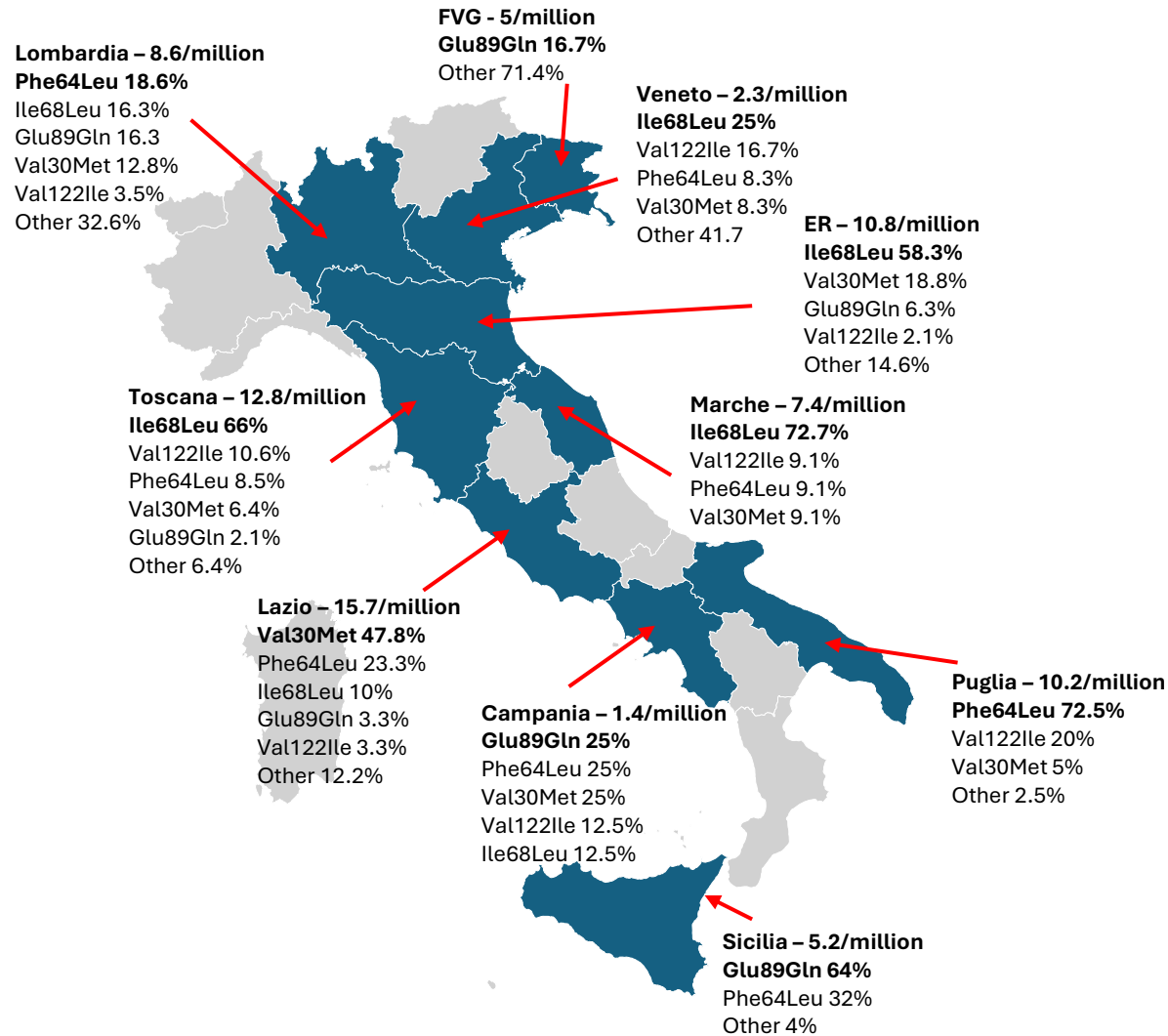
1. Hawkins PN et al. *Ann Med*. 2015;47(8):625-638; 2. Adams D et al. *J Neurol*. 2021;268:2109-2122; 3. Ionis. SEC Filing Details. 2022;
4. Rintell D et al. *Orphanet J Rare Dis*. 2021;16(1):70; 5. Gentile L et al. Article and supplemental content. *Orphanet J Rare Dis*. 2023;18:350;
6. Witteles RM et al. *JACC Heart Fail*. 2019;7(8):709-716.

The prevalence of ATTRv genotypes varies by region



ATTRv = hereditary transthyretin-mediated [amyloidosis].
Obi CA et al. *Methodist Debaquey Cardiovasc J.* 2022;18(2):17-26.

Change in prevalence of ATTR variants in Italy – Results from a National Survey

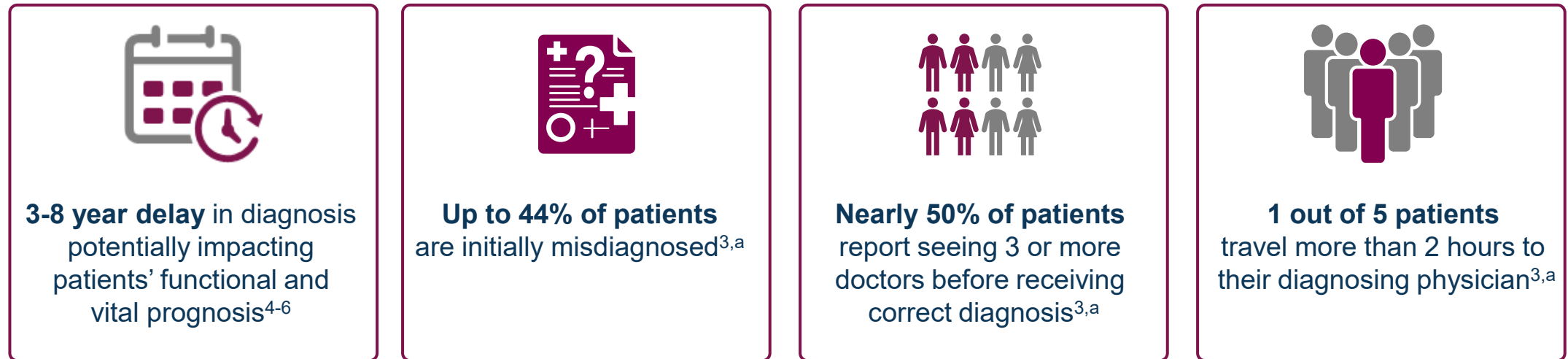


- Includere diagnosi di ATTRv dal 2004 al 2024 da 16 centri italiani di riferimento.
- A marzo 2024, **373 pazienti con ATTRv** erano sotto osservazione, con un **aumento della prevalenza nazionale** a 6.33/milione. (**↑ del 50% in 4 anni**), con una tendenza verso fasi più lievi e fenotipi misti, riflettendo una maggiore consapevolezza della malattia e screening genetico potenziato.
- La distribuzione geografica delle mutazioni varia tra Nord, Centro e Sud Italia. Le **mutazioni più comuni: Ile68Leu (25.1%), Phe64Leu (21.9%) e Val30Met (19.3%)**.
- **Fenotipi:**
 - **ATTRv-CM** n=133 (**35.6%**)
 - **ATTRv-PN** n=124 (**33.2%**)
 - **ATTRv mixed** n=116 (**31.3%**)

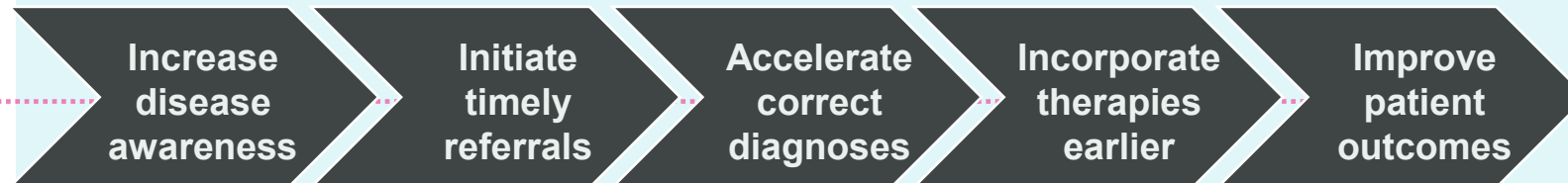
Mutazione	Età Diagnosi	% Uomini	Fenotipo Misto	Fenotipo Cardiaco	Fenotipo Neuropatico
Ile 68 Leu n=94 (25.1%)	65 [50-75]	71.3	26.6	70.2	3.2
Glu 89 Gln n=40 (10.7%)	49 [37-55]	60.0	27.5	37.5	35.0
Val 122 Ile n=24 (6.4%)	65 [47-74]	79.2	29.2	66.7	4.1
Phe 64 Leu n=82 (21.9%)	62 [49-74]	69.5	15.9	7.3	76.8
Val 30 Met n=72 (19.3%)	61 [44-70]	76.4	52.7	9.7	37.5
Altro n=61 (16.4%)	48 [38-64]	54.1	36.7	38.3	25.0

ATTR is under-recognized and often misdiagnosed, contributing to delayed diagnosis and poor patient outcomes

Due to the **heterogeneity and non-specificity of symptoms**, many patients experience **multiple misdiagnoses**¹⁻⁴



Cross-specialty collaboration is required to:



^aSurvey of patients and/or caregivers of those with ATTRv (n=114) and ATTRwt (n=70) conducted by the Amyloidosis Research Consortium.

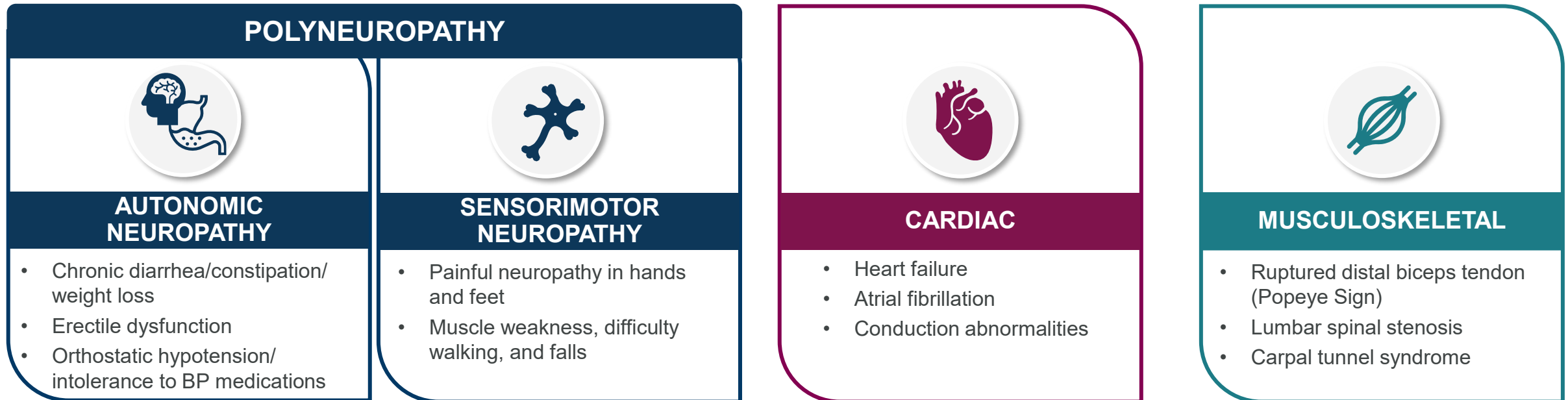
ATTR = transthyretin-mediated [amyloidosis]; ATTRv = hereditary transthyretin-mediated [amyloidosis]; ATTRwt = wild-type transthyretin-mediated [amyloidosis].

1. Witteles RM et al. *JACC Heart Fail.* 2019;7(8):709-716; 2. Nativi-Nicolau JN et al. *Heart Fail Rev.* 2022;27(3):785-793; 3. Lousada I et al. Poster presented at: XVI ISA; March 26-29, 2018; Kumamoto, Japan; 4. Adams D et al. *J Neurol.* 2021;268(6):2109-2122; 5. Hawkins PN et al. *Ann Med.* 2015;47(8):625-638;

6. Rozenbaum MH et al. *Cardiol Ther.* 2021;10(1):141-159.

ATTR is a systemic disease that manifests with non-specific and heterogeneous symptoms

Although clinical presentation can be **polyneuropathy** or **cardiomyopathy** dominant, **mixed phenotypes** are common^{1,2}



Globally, **up to 80%** of patients with hereditary ATTR amyloidosis have **mixed phenotype**^{3,4}

Note: Additional manifestations also include central nervous system, ocular, and renal effects.²

ATTR = transthyretin-mediated [amyloidosis]; BP = blood pressure.

1. Nativi-Nicolau JN et al. *Heart Fail Rev.* 2022;27(3):785-793; 2. Gertz MA. *Am J Manag Care.* 2017;23(suppl 7):S107-S112; 3. Adams D et al. *J Neurol.* 2021;268(6):2109-2122;

4. Planté-Bordeneuve V et al. *Lancet Neurol.* 2011;10(12):1086-1097.

ATTR is a debilitating disease that profoundly impairs quality of life¹

Patient-reported burden of ATTRv on function and well-being^{2,a}



80%

Difficulty gripping or holding objects



43%

Had loss of balance/dizziness



60%

Difficulty dressing or bathing



85%

Had fatigue/lethargy



71%

Expressed fear/anxiety



80%

Unable to participate in social activities

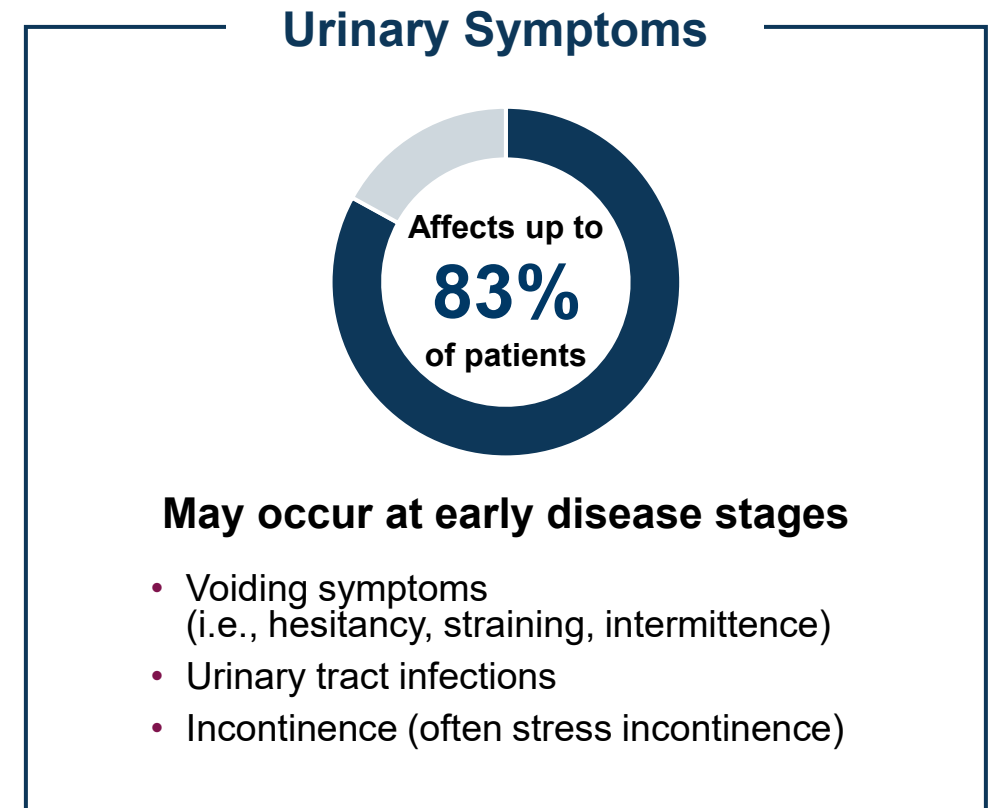
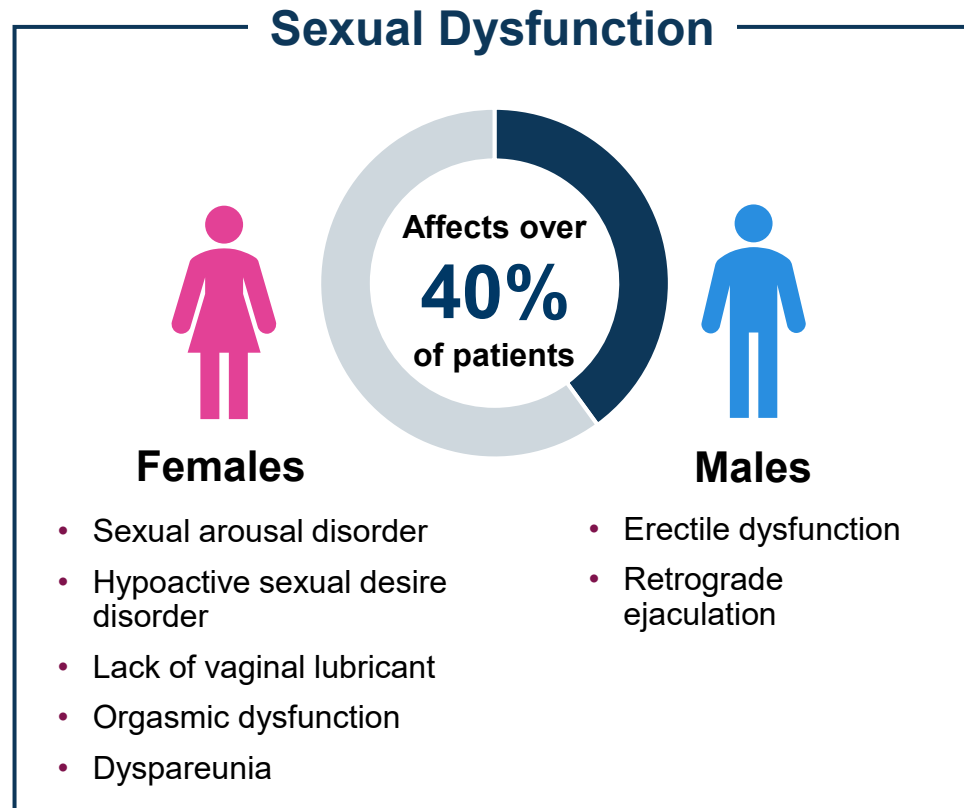
^aData from semistructured interviews in a qualitative, non-interventional study of 14 adults with ATTRv. Mean age of patients was 61.5 years; and mean time since diagnosis of ATTRv was 5 years.²

ATTR = transthyretin-mediated [amyloidosis]; ATTRv = hereditary transthyretin-mediated [amyloidosis].

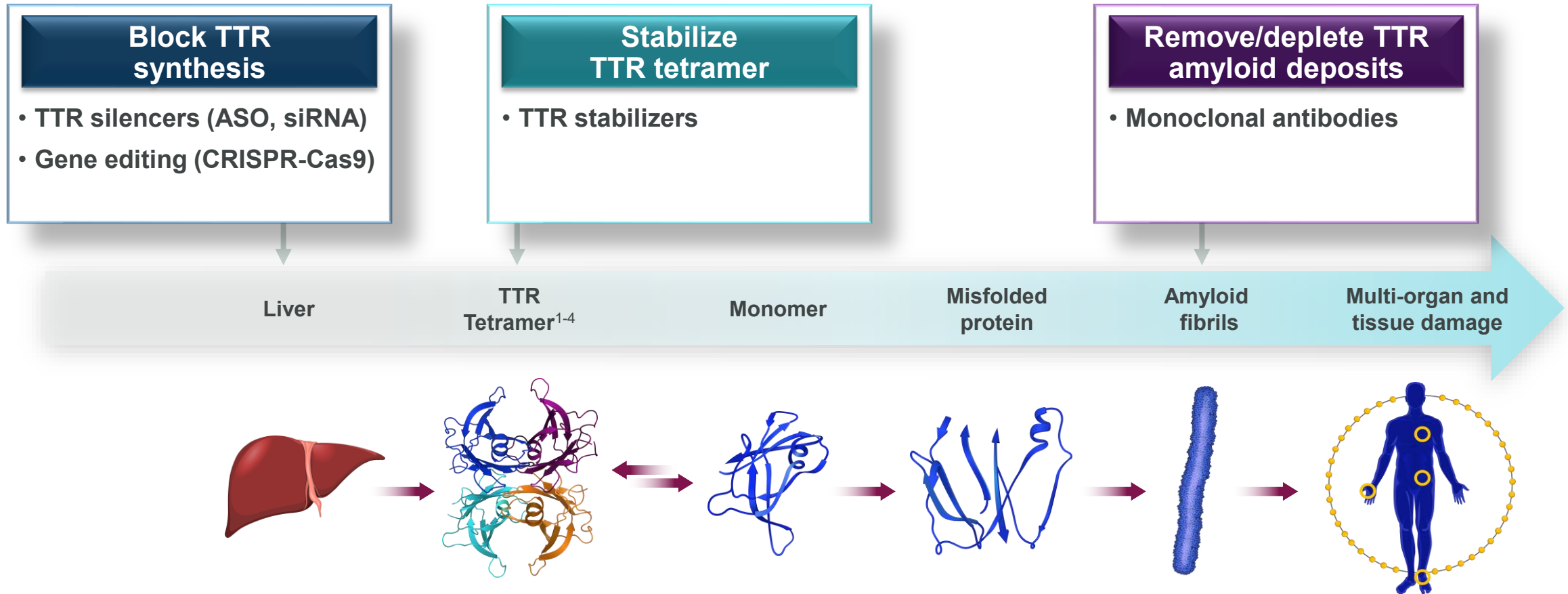
1. Rintell D et al. *Orphanet J Rare Dis.* 2021;16(1):70; 2. Lovley A et al. *J Patient Rep Outcomes.* 2021;5(1):3.

Urinary and sexual dysfunction are highly prevalent in ATTR patients

Lower urinary tract and sexual dysfunction in ATTR can result from **neurogenic, vasculogenic, and myogenic** mechanisms



ATTRv Amyloidosis Therapeutic Approach

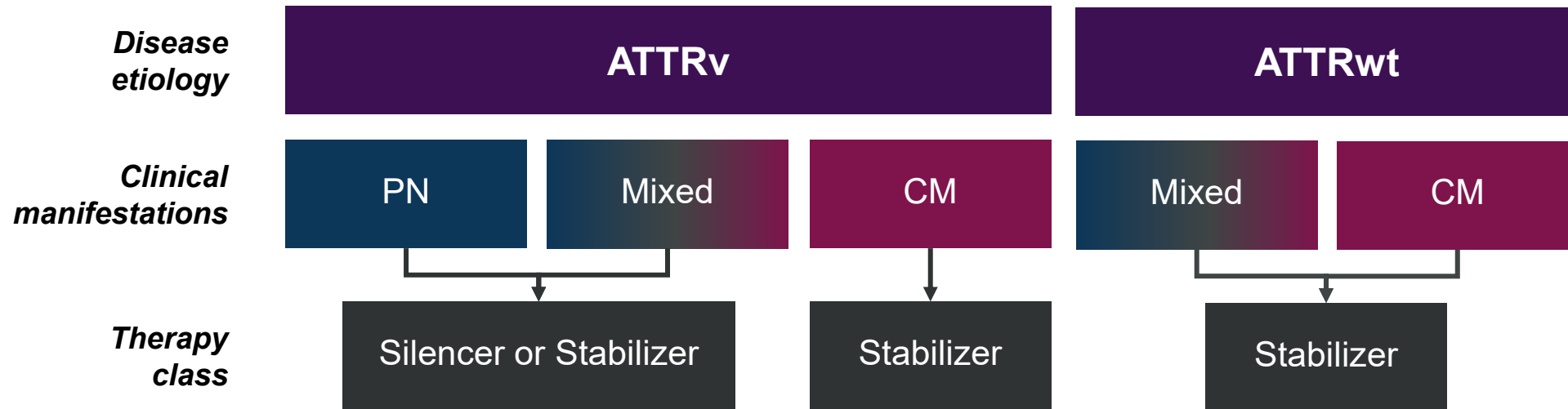


ASO = antisense oligonucleotide; Cas9 = CRISPR associated protein 9; CRISPR = clustered regularly interspaced short palindromic repeats; siRNA = small interfering ribonucleic acid; TTR = transthyretin.

1. Ruberg FL et al. *J Am Coll Cardiol.* 2019;73(22):2872-2891; 2. Ando Y et al. *Amyloid.* 2022; 3. Carroll A et al. *J Neurol Neurosurg Psychiatry.* 2022;93:668-678; 4. Muller ML et al. *Eur J Heart Fail.* 2020;22(1):39-53.

Slowing disease progression, improving survival, and maximizing QoL are the main goals of therapy for ATTR¹⁻³

ATTR treatments are currently segmented based on disease etiology and clinical manifestations¹⁻⁵

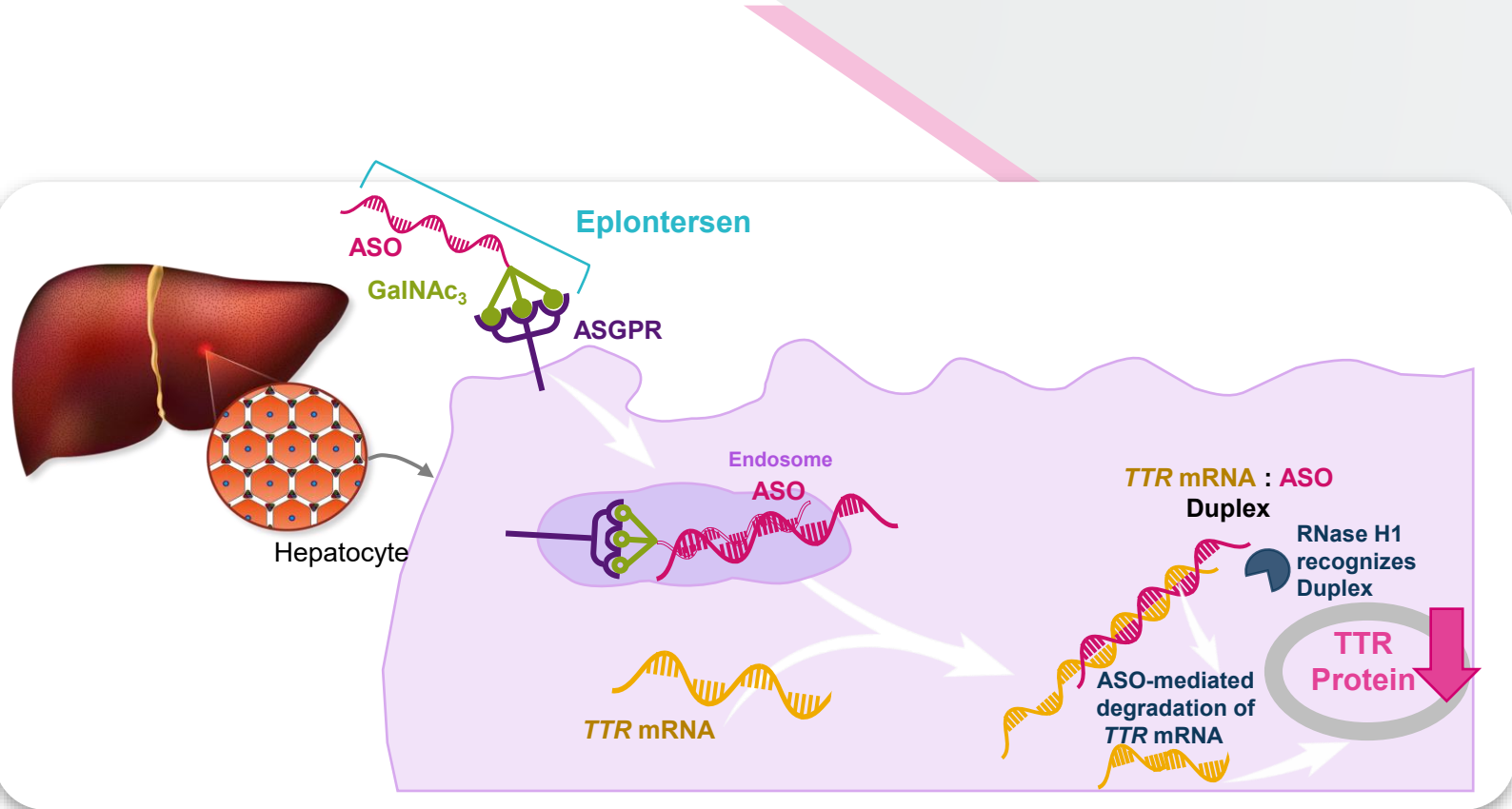


Continued evidence generation from clinical trials of ATTR therapies will inform guidelines for optimal management strategies

Note: This diagram is for illustrative purposes only based on current ATTR guidelines and expert consensus statements.

ATTR = transthyretin-mediated [amyloidosis]; ATTRv = hereditary transthyretin-mediated [amyloidosis]; ATTRwt = wild-type transthyretin-mediated [amyloidosis]; CM = cardiomyopathy; PN = polyneuropathy; QoL = quality of life.

1. Ando Y et al. *Amyloid*. 2022;29(3):143-155; 2. Brito D et al. *Global Heart*. 2023;18(1):59; 3. Garcia-Pavia P, et al. *Eur J Heart Fail*. 2021;23(4):512-526; 4. Kittleson MM, et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126; 5. Heidenreich PA et al. *J Am Coll Cardiol*. 2022;79(17):e263-e421.



GalNAc₃-conjugated ASO mechanism



Degrades TTR mRNA to reduce serum TTR protein



Targeted delivery reduces systemic exposure



Monthly SC autoinjector



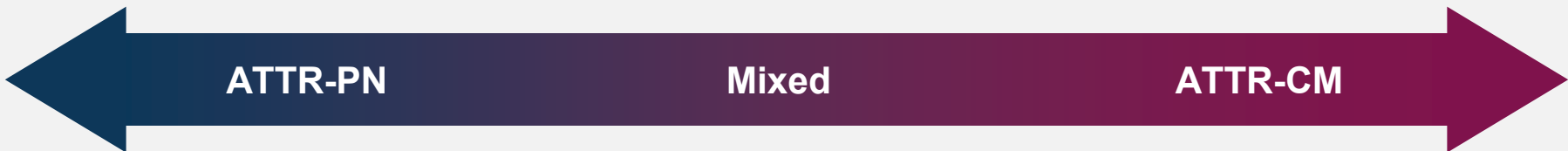
Figure adapted from Coelho T et al. *Neurol Ther.* 2021;10(1):375-389 and Crooke ST et al. *Nucleic Acid Ther.* 2019;29(1):16-32.^{1,5}

ASGPR = asialoglycoprotein receptor; ASO = antisense oligonucleotide; GalNAc₃ = triantennary N-acetyl galactosamine; LICA = ligand conjugated antisense; mRNA = messenger ribonucleic acid; RNase H1 = ribonuclease H1; SC = subcutaneous; TTR = transthyretin.

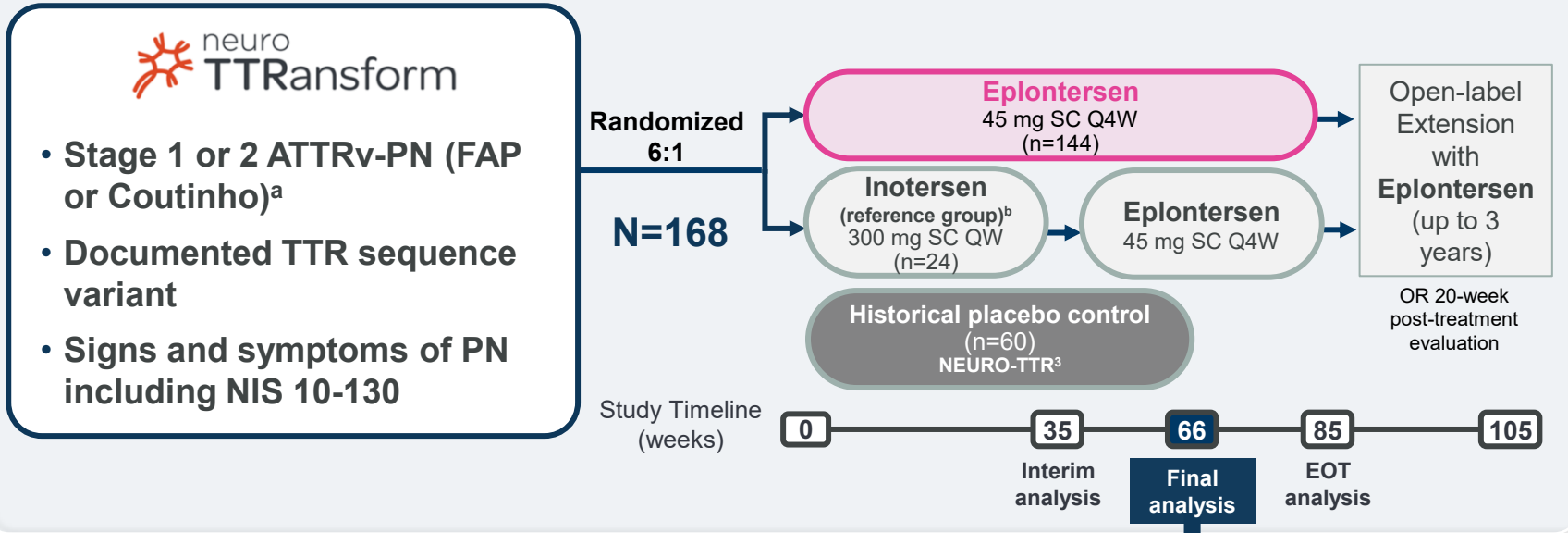
1. Coelho T et al. *Neurol Ther.* 2021;10(1):375-389; 2. Viney NJ et al. *ESC Heart Fail.* 2021;8(1):652-661; 3. WAINUA Prescribing Information. September 2024. 4. WAINZUA. Summary of product characteristics. March 2025; 5. Crooke ST et al. *Nucleic Acid Ther.* 2019;29(1):16-32.


Global, multicenter,
randomized, crossover,
open-label study in
patients with
ATTRv-PN¹


Global, multicenter,
randomized double-blind,
placebo-controlled study
in patients with
ATTR-CM²



Phase III, open-label, multicenter study^{1,2}



Secondary Endpoints Include:¹

Change from baseline vs. placebo in:

- NSC score at Weeks 35 and 66
- SF-36 PCS score at Week 65
- PND score at Week 65
- mBMI at Week 65

Exploratory and Post Hoc Endpoints Include:^{1,2}

Patients with cardiac involvement (Week 66):

- Frequency of all-cause hospitalizations
- Change from baseline in ECHO parameters and NT-proBNP

Change from baseline at Week 85 in:

- Serum TTR
- mNIS+7
- Norfolk QoL-DN

Co-primary endpoints^{1,2,c}

Serum TTR	mNIS+7	Norfolk QoL-DN
% change from baseline at Week 65	change from baseline at Week 66	change from baseline at Week 66

^aStage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance);^{1,2} ^bThe inotersen reference group was included to confirm sufficiently comparable disease progression and treatment response patterns between NEURO-TTR³ and NEURO-TTRansform;² ^cAll endpoints were compared with the placebo group of the earlier NEURO-TTR trial. The final analysis endpoints were distributed over two visits (Week 65 and Week 66), as prespecified in the protocol.²

Baseline characteristics²



Age

Eplontersen: 53 years
Placebo: 60 years



Coutinho
Stage 1^a

Eplontersen: 80%
Placebo: 70%



Duration of disease from
onset of ATTRv-PN symptoms

Eplontersen: 54 months
Placebo: 48 months



V30M TTR
variant

Eplontersen: 59%
Placebo: 55%



Previous use of
a stabilizer^b

Eplontersen: 69%
Placebo: 60%



CM baseline diagnosis
+ ECHO subgroup^c

Eplontersen: 34%
Placebo: 50%



The eplontersen and placebo groups were generally well balanced across baseline characteristics

Compared to the placebo group, patients in the eplontersen group:

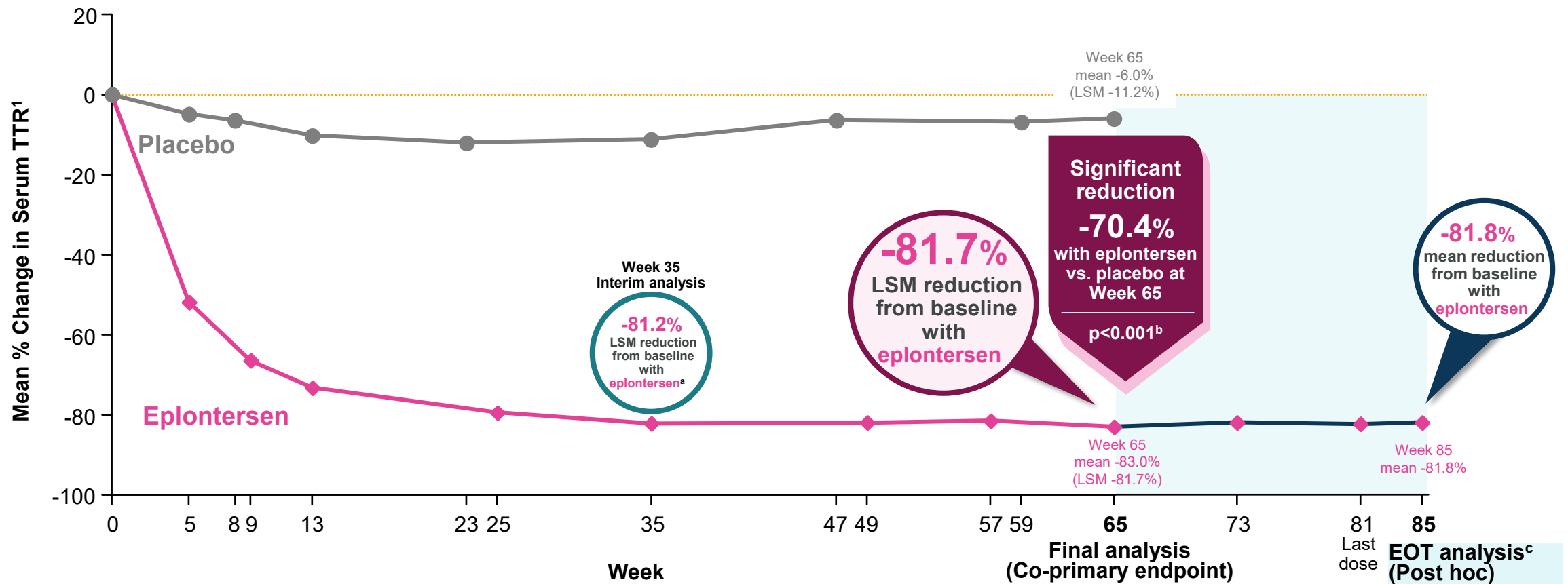
- were slightly younger
- had less severe disease
- had ATTRv-PN for longer duration
- were more likely to have the V30M variant
- were more likely to have received previous treatment with stabilizers
- were less likely to have cardiomyopathy

Note: The placebo group refers to the placebo arm from the previous NEURO-TTR trial.

^aAmbulatory without assistance; ^bRefers to tafamidis or diflunisal. Concomitant use of tafamidis or diflunisal were not permitted during the trial; ^cPatients with 1) a clinical diagnosis of ATTRv-CM on their case report form (ie, the CM baseline diagnosis-only subgroup), or 2) interventricular septum thickness ≥ 13 mm on baseline ECHO plus no hypertension (in past medical history or diagnosed during the trial) plus no two consecutive systolic blood pressure readings of ≥ 150 mm Hg at any time during the trial (including screening and baseline visits).

Additional Baseline Characteristics

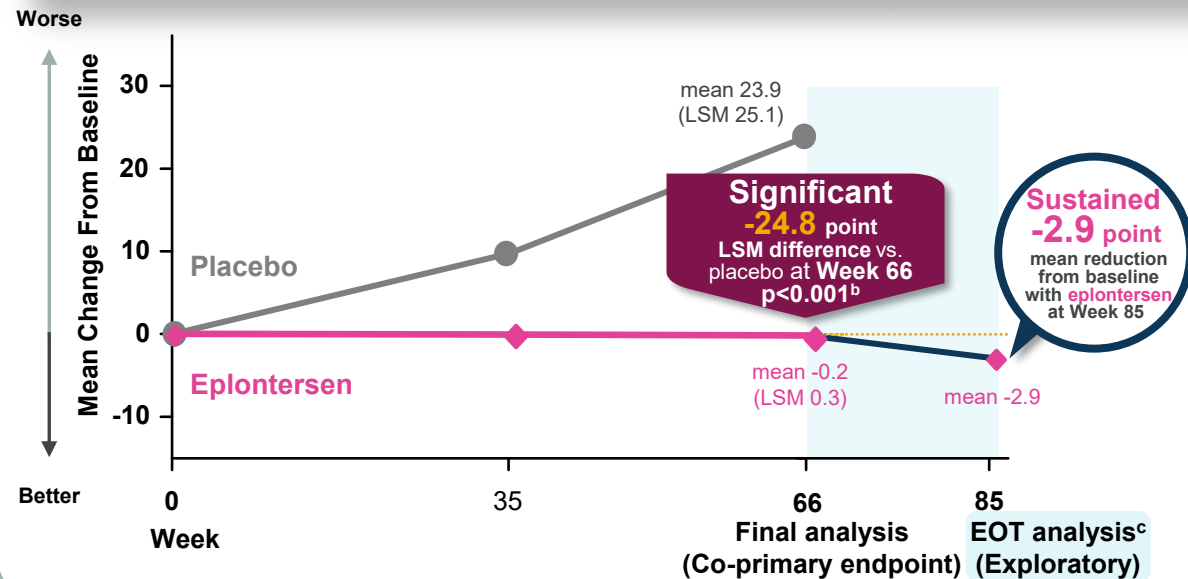




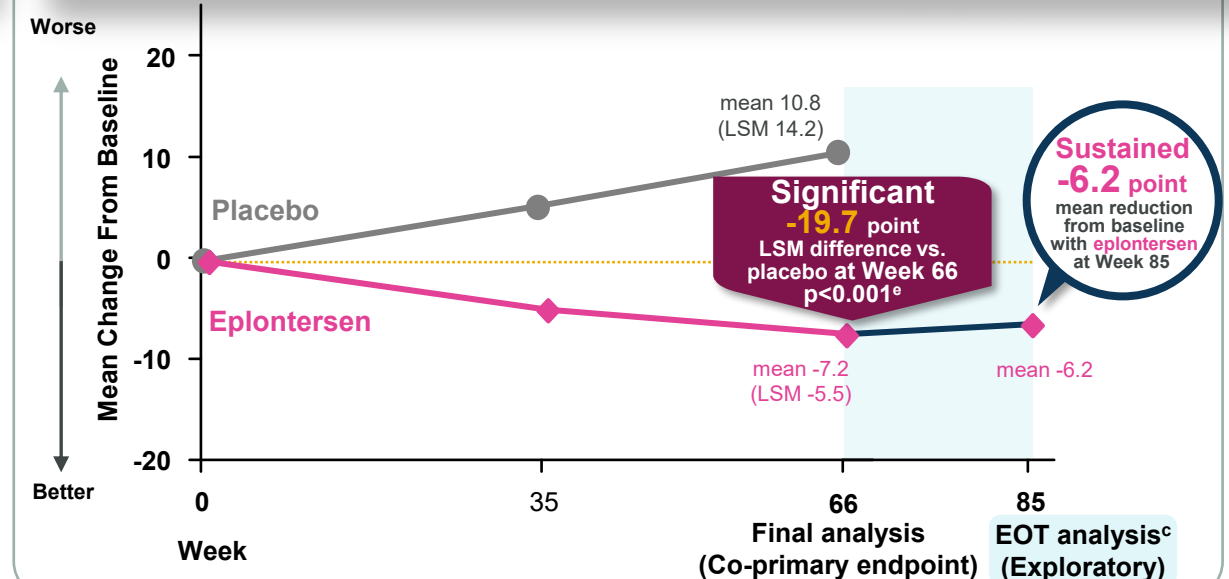
Note: The placebo group refers to the placebo arm from the previous NEURO-TTR trial.

^aStatistically significant difference of -66.4% vs. placebo (LSM -14.8%); 95% CI, -71.4% to 61.5%; p < 0.001; ^bp-value not formally tested due to statistically significant results at Week 35 interim analysis; 95% CI, -75.2% to -65.7%; ^{1,2}From Week 66 to Week 85, there was no historical placebo group because NEURO-TTR concluded at Week 66. No statistical comparisons relative to baseline were made at Week 85.

mNIS+7 Composite Score^{1,a}



Norfolk QoL-DN Total Score^{1,d}



Statistically significant differences in mNIS+7 and Norfolk QoL-DN were also observed at Week 35 interim analysis ($p < 0.001$)^{1,f}

Consistent treatment effects across prespecified subgroups and individual mNIS+7 components and Norfolk QoL-DN domains at Week 66 were observed¹

Subgroups 🔍

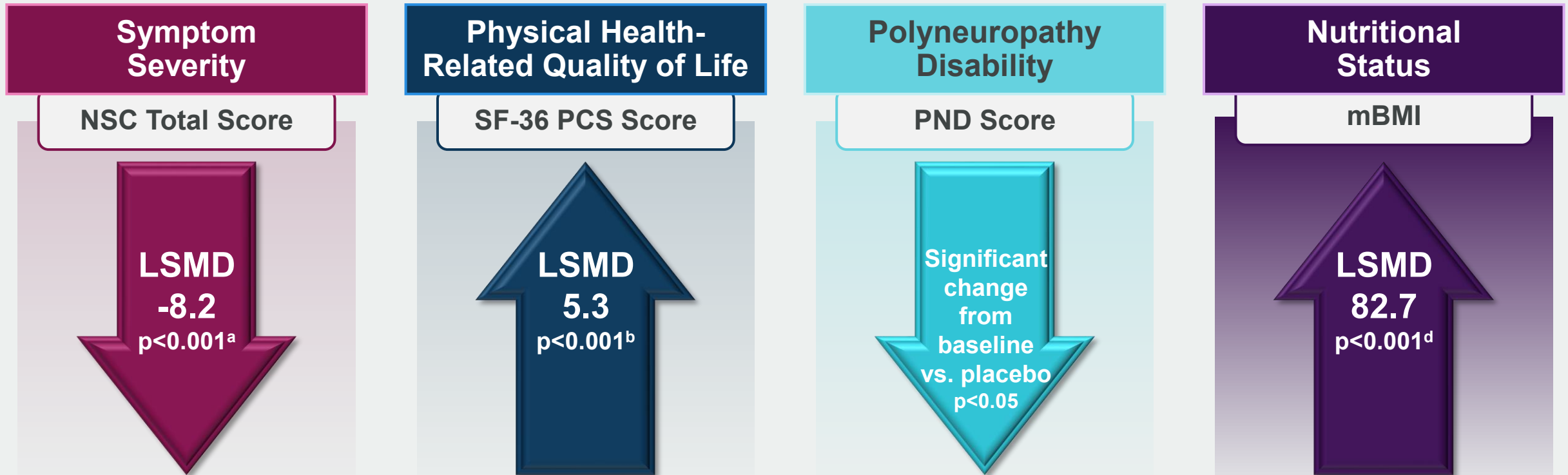
Mixed Phenotype 🔍

Components/ Domains 🔍

Responder analysis 🔍

Note: The placebo group refers to the placebo arm from the previous NEURO-TTR trial.

^amNIS+7 scores can range from -22.3 to 346.3, with higher scores indicative of greater neuropathic impairment; a decrease in score indicates improvement;^{1,b} p -value not formally tested due to statistically significant results at Week 35 interim analysis; 95% CI, -31.0 to -18.6;^{1,2} ^cFrom Week 66 to Week 85, there was no historical placebo group because NEURO-TTR concluded at Week 66. No statistical comparisons relative to baseline were made at Week 85; ^dNorfolk QoL-DN scores can range from -4 to 136, with higher scores indicative of worse quality of life; a decrease in score indicates improvement;¹ p -value not formally tested due to statistically significant results at Week 35 interim analysis; 95% CI, -25.6 to -13.8;^{1,2} ^eResults at Week 35 interim analysis for mNIS+7 ($n=140$ eplontersen; $n=59$ placebo) were LSM change from baseline 0.2 eplontersen vs. 9.2 placebo, LSM difference -9.0 (95% CI, -13.5 to -4.5); and for Norfolk QoL-DN ($n=133$ eplontersen; $n=58$ placebo) were LSM change from baseline -3.1 eplontersen vs. 8.7 placebo, LSM difference -11.8 (95% CI, -16.8 to -6.8).¹



Note: All secondary endpoints were prespecified per protocol. The placebo group refers to the placebo arm from the previous NEURO-TTR trial. The final analysis endpoints were distributed over two visits (Week 65 and Week 66), as prespecified in the protocol.

Decreases in NSC total score, and increases in SF-36 PCS score and mBMI indicate improvement. Lower PND scores indicate less disability. PND Score: I = unassisted walking; II = impaired unassisted walking, IIIa = assisted walking (1 cane or 1 crutch); IIIb = assisted walking (2 canes or 2 crutches); IV = confined to wheelchair or bedridden.

^aNSC total score final analysis: Week 35: 95% CI, -6.1 to -1.8, Week 66: 95% CI, -10.7 to -5.8; ¹ SF-36 PCS score final analysis: Week 35: 95% CI, 0.5 to 3.9, Week 65: 95% CI, 3.2 to 7.4; ¹ p-value not reported at Week 13; ¹ mBMI final analysis: Week 35: 95% CI, 10.4 to 57.2, Week 65: 95% CI, 54.6 to 110.8. ¹

1. Coelho T et al. Article and supplement 2. *JAMA*. 2023;330(15):1448-1458; 2. Cruz MW et al. Presented at: 4th International ATTR Amyloidosis Meeting; November 2-3, 2023; Madrid, Spain.

AEs were comparable between eplontersen and placebo

- At 85 weeks, incidence of TEAEs with eplontersen remained consistent with Week 66
- Majority of the TEAEs occurring with eplontersen were mild
- No AEs of special interest led to drug discontinuation
- No patients receiving eplontersen experienced ocular events assessed by ophthalmic examination to be consistent with vitamin A deficiency
- Three non-drug related deaths occurred in the eplontersen group; all related to known sequelae of ATTR amyloidosis^j

Incidence, n (%)	Week 66		Week 85+ ^a
	Placebo (N=60)	Eplontersen (N=144)	Eplontersen (N=144)
Any TEAE	60 (100)	140 (97)	141 (98)
Leading to study drug discontinuation	2 (3) ^b	6 (4) ^c	8 (6) ^d
Maximum severity of TEAEs			
Mild	7 (12)	74 (51)	64 (44)
Moderate	40 (67)	53 (37)	57 (40)
Severe	13 (22)	13 (9)	20 (14)
AE of special interest	12 (20)	41 (29)	43 (30)
Vitamin A deficiency/decrease/abnormal ^e	NR ^f	23 (16)	23 (16)
Ocular events potentially related to vitamin A deficiency (excluding events related to vitamin A deficiency/decreased/abnormal)	9 (15)	24 (17)	26 (18)
Thrombocytopenia ^g	1 (2)	3 (2)	3 (2)
Glomerulonephritis	2 (3) ^h	0	0
Leading to study drug discontinuation	0	0	0
Injection site reactions	7 (12)	12 (8)	13 (9)
Flu-like symptoms	2 (3)	0	1 (1)
Abnormal liver functionⁱ	4 (7)	9 (6)	11 (8)
Any serious TEAE	12 (20)	21 (15)	27 (19)
Related to study drug	1 (2)	0	0
Death^j	0	2 (1)	3 (2)
Death due to study drug	0	0	0

Note: Data shown are treatment-emergent AEs, defined as AEs that first occurred, or worsened, after the first dose of study drug.¹ Week 66 data includes safety data at the Week 66 analysis and Week 85+ data includes all safety data collected through April 7, 2023, including data after Week 85. The placebo group refers to the placebo arm from the previous NEURO-TTR trial which concluded at Week 66.

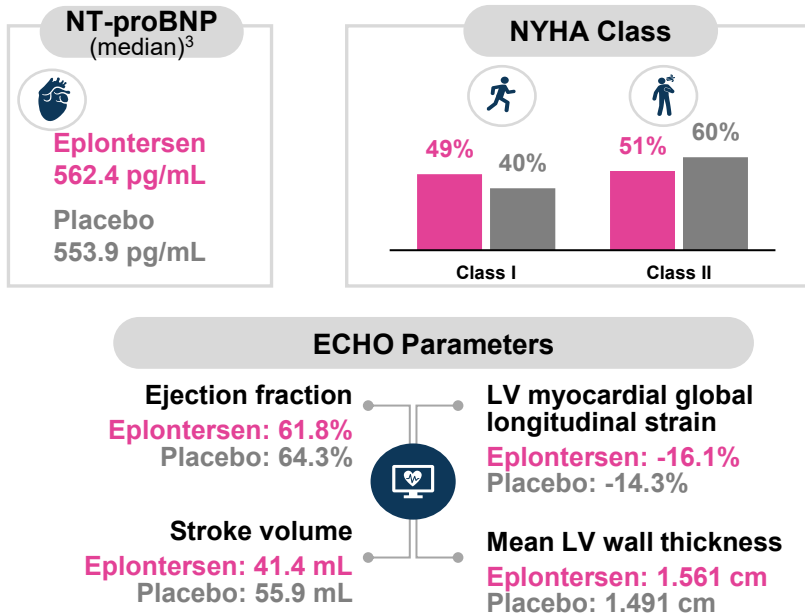
^aPart of the Week 85 exploratory analysis; ^bPlacebo group: 1 pain at the administration site, weight increase, arthralgia; 1 proteinuria (stopping rule met); ^cEplontersen group: 1 fatal cardiac arrhythmia, 1 fatal intracerebral hemorrhage, 1 urosepsis, 1 proteinuria, 1 renal impairment, 1 transaminases abnormal (the AE started before Week 66 and the patient's last dose was before Week 66, but the patient discontinued study drug after Week 66); ^dAdditional 2 patients from Week 66: 1 acute myocardial infarction; 1 malignant lung neoplasm; ^eSerum vitamin A levels were available to NEURO-TTR transform investigators (eplontersen group) but were blinded per protocol in NEURO-TTR (placebo group) to avoid unmasking the double-blind treatment groups; ^fIn NEURO-TTR, vitamin A levels were blinded from investigators during the study, so this event was not reportable as an AE; ^gReported in 3 patients (4 events) in the eplontersen group. All events were mild, did not lead to bleeding events, and were recovered from with no dosing change or interruption and without sequelae. Nadir platelet counts in the 3 patients on eplontersen with thrombocytopenia were between 102 x 10⁹/L and 136 x 10⁹/L. Thrombocytopenia was reported in 1 patient in the placebo group (2 events); ^hTwo cases of potential glomerulonephritis were identified in placebo group (1 glomerulonephritis chronic, 1 nephrotic syndrome); ⁱThere were no Hy law (severe drug-induced liver injury) cases; ^jDeaths consistent with known sequelae of ATTRv. One patient with known ATTRv-CM had a fatal cardiac arrhythmia after 4 doses of eplontersen by Week 66, one patient had intracerebral hemorrhage in the setting of normal platelet counts and coagulation parameters after 10 doses of eplontersen by Week 66, and one patient with known ATTRv-CM had a fatal myocardial infarction after receiving 19 doses of eplontersen between Weeks 66 and 85. After the Week 85 analysis was completed, an additional patient was confirmed to have died before the Week 85 analysis cutoff. This patient died 103 weeks after enrollment in the study (Study Day 726). The patient discontinued treatment 64 weeks (Study Day 272) prior to their death, having received 5 doses of eplontersen, and elected for survival follow-up before their death from pneumonia sepsis.



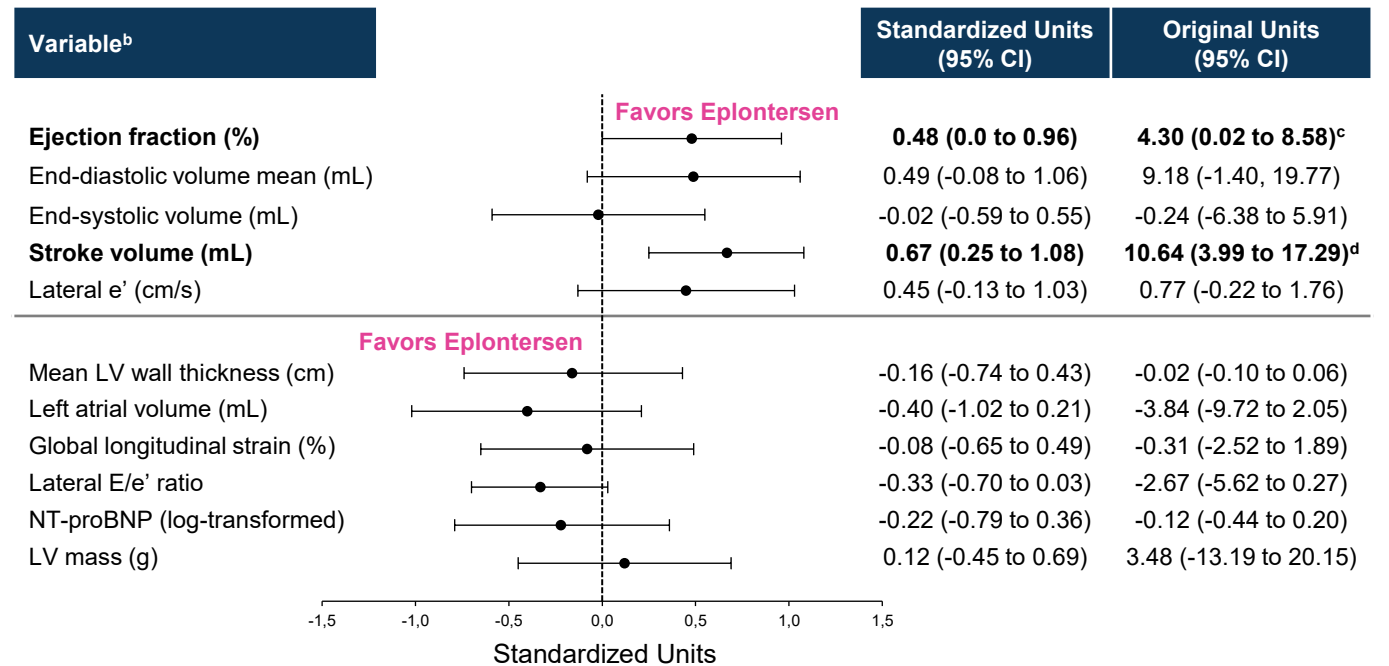
~1/3 of patients treated with **eplontersen** had **ATTRv mixed phenotype (PN + CM^a)**¹ (n=49)

Eplontersen demonstrated **consistent benefits in halting progression of neuropathy impairment and improving QoL** in patients with mixed phenotype²

Key Cardiac Baseline Characteristics in the Mixed Phenotype Subgroup¹



In an exploratory analysis of patients with mixed phenotype, **eplontersen was associated with stable or improved measures of cardiac structure and function vs. placebo at Week 65¹**



Further investigation into the effect of eplontersen on ATTR-CM is being conducted in **CARDIO-TTRansform**, the largest ATTR-CM study to date

^aCardiomyopathy subgroup includes patients with 1) a clinical diagnosis of hereditary ATTR-CM on their CRF or 2) interventricular septum thickness ≥ 13 mm on baseline ECHO plus no hypertension (in past medical history or diagnosed during the trial) plus no 2 consecutive systolic blood pressure readings of ≥ 150 mm Hg at any time during the trial (including screening and baseline visits); ^bFor each variable, the changes from baseline were standardized using a mean of 0 and a standard deviation of 1; ^cnominal p<0.05; ^dnominal p<0.01.

1. Masri A et al. In press-corrected proof; posted online December 7, 2023. *J Card Fail.* 2023. doi:10.1016/j.cardfail.2023.11.016; 2. Coelho T et al. Article and supplement 2. *JAMA.* 2023;330(15):1448-1458; 3. Masri A et al. Presented at: HFSA Annual Scientific Meeting 2023; October 6-9, 2023; Cleveland, Ohio.



Eplontersen treatment resulted in clinically and statistically significant benefits with a well-tolerated safety profile

Co-primary Endpoints

- ▶ Compared to placebo through Week 66, eplontersen treatment resulted in:¹
 - **sustained reductions in serum TTR levels**
 - **halted progression of neuropathy impairment**
 - **improved quality of life**
- ▶ Eplontersen sustained effects in all three endpoints through Week 85^{1,2,a}

Secondary Endpoints

- ▶ Statistically significant **improvements in all secondary endpoints** at Week 66 with eplontersen vs. placebo¹

Safety

- ▶ Eplontersen was **well-tolerated** through Week 85^{1,2}

^aFrom Week 66 to Week 85, there was no historical placebo group because NEURO-TTR concluded at Week 66. At Week 85, exploratory endpoints included change from baseline in mNIS+7 and Norfolk QoL-DN, and change from baseline in serum TTR levels concentration was assessed as a post hoc outcome. No statistical comparisons relative to baseline were made at Week 85.

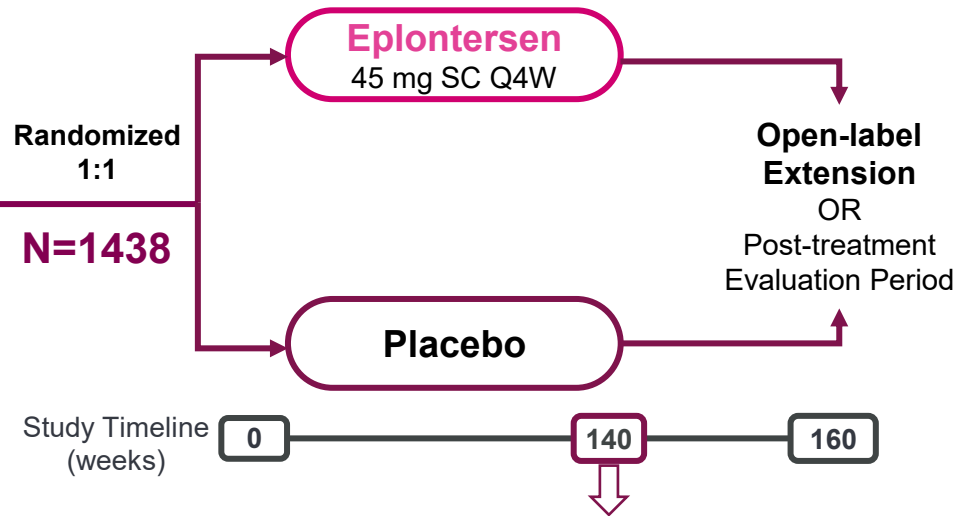
mNIS+7 = modified Neuropathy Impairment Score+7; Norfolk QoL-DN = Norfolk Quality of Life Questionnaire-Diabetic Neuropathy; TTR = transthyretin.

1. Coelho T et al. Article and supplement 2. *JAMA*. 2023;330(15):1448-1458; 2. Ionis Pharmaceuticals, Inc. press release. Published July 10, 2023.

Ongoing, Phase III, double-blind, placebo-controlled, multicenter study²⁻⁴



- History of heart failure due to ATTRv-CM or ATTRwt-CM^a
- Confirmed amyloid deposits in cardiac or non-cardiac tissue^b
- NYHA Class I-III
- NT-proBNP ≥ 600 pg/mL^c
- End-diastolic interventricular septum thickness of >12 mm
- 6MWT ≥ 100 m
- With or without concomitant stabilizer use^d



Primary endpoint⁴



Composite of CV mortality and recurrent CV clinical events up to Week 140

Secondary endpoints⁴

- Change from baseline in 6MWT and KCCQ scores at Week 121
- Rate of CV clinical events, CV mortality, and all-cause mortality up to Week 140

Exploratory endpoints⁵

Change from baseline in:

- cardiac imaging parameters
- renal function
- biomarkers
- patient-reported outcomes questionnaires and disease scores

Imaging sub-studies measuring amyloid burden

Change from baseline to Week 140 in:

- percent of ECV assessed by MRI⁶
- Perugini Grading Score from scintigraphy scan images⁷

^aWith at least one prior hospitalization for HF (may include hospitalization for arrhythmia or pacemaker/implantable cardioverter defibrillator placement) OR signs/symptoms of volume overload or elevated intracardiac pressure requiring treatment with diuretics (other than MRAs);² ^bConfirmed by Congo Red staining or PYP-Tc/DPD-Tc/HMDP-Tc scan with Grade 2 or 3 cardiac uptake in the absence of abnormal light chains ratio;² ^c ≥ 1200 pg/mL if atrial fibrillation;² ^dConcomitant tafamidis/tafamidis meglumine was allowed according to standard of care at any time during the study.²

1. Ionis Pharmaceuticals, Inc InBrief. Published April 29, 2022; 2. Maurer M et al. Poster presented at: CCC (Virtual); October 20-23, 2021; 3. In House Data, Ionis Pharmaceuticals, Inc. CSP ION-682884-CS2. September 15, 2022; 4. Study NCT04136171. ClinicalTrials.gov website; 5. Falk RH et al. *Blood*. 2019;134(suppl 1):5764; 6. Study NCT06073574. ClinicalTrials.gov website; 7. Study NCT06073587. ClinicalTrials.gov website.