4TH INTERNATIONAL ATTR Amyloidosis meeting for patients and doctors

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AMYLOIDOSIS ALLIANCE
THE VOICE OF PATIENTS

Hospital Universitario Puerta de Hierro Majadahonda

Enabling the development of serum [TTR] as a biomarker for treatment of ATTR amyloidosis

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on behalf of:

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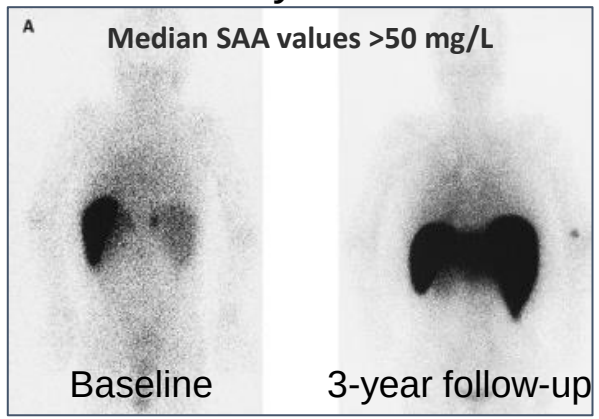
Disclosures

- Adviser for Alnylam, AstraZeneca, Attralus, BridgeBio, Ionis, Pfizer, and Intellia

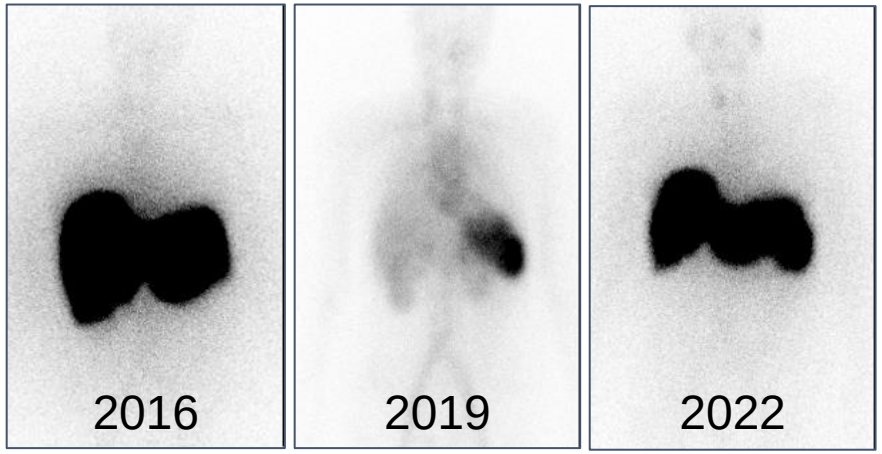
Treatment outcomes in systemic amyloidosis associate with the residual concentration of the amyloid precursor protein[1,2]

AA Amyloidosis[1]



Unresponsive to methotrexate and steroids

AL Amyloidosis[a]



Hematologic response **Hematologic relapse**

- More amyloid = worse outcomes
  Less amyloid = better outcomes
- "Natural" clearance of *in vivo* amyloid deposits occurs slowly
- Clearance of amyloid occurs at different rates in different organs
  Liver vs heart
- The rate of amyloid clearance varies between individuals
  A 75% reduction in fibril precursor protein concentrations may be sufficient to permit amyloid regression in one patient but may result in amyloid accumulation in another

AA, amyloid A; AL, amyloid light chain; SAA, serum amyloid A.

1. Gillmore JD, et al. *Lancet.* 2001;358(9275):24-29.
2. Lachmann HJ, et al. *Br J Haematol.* 2003;122(1):78-84.

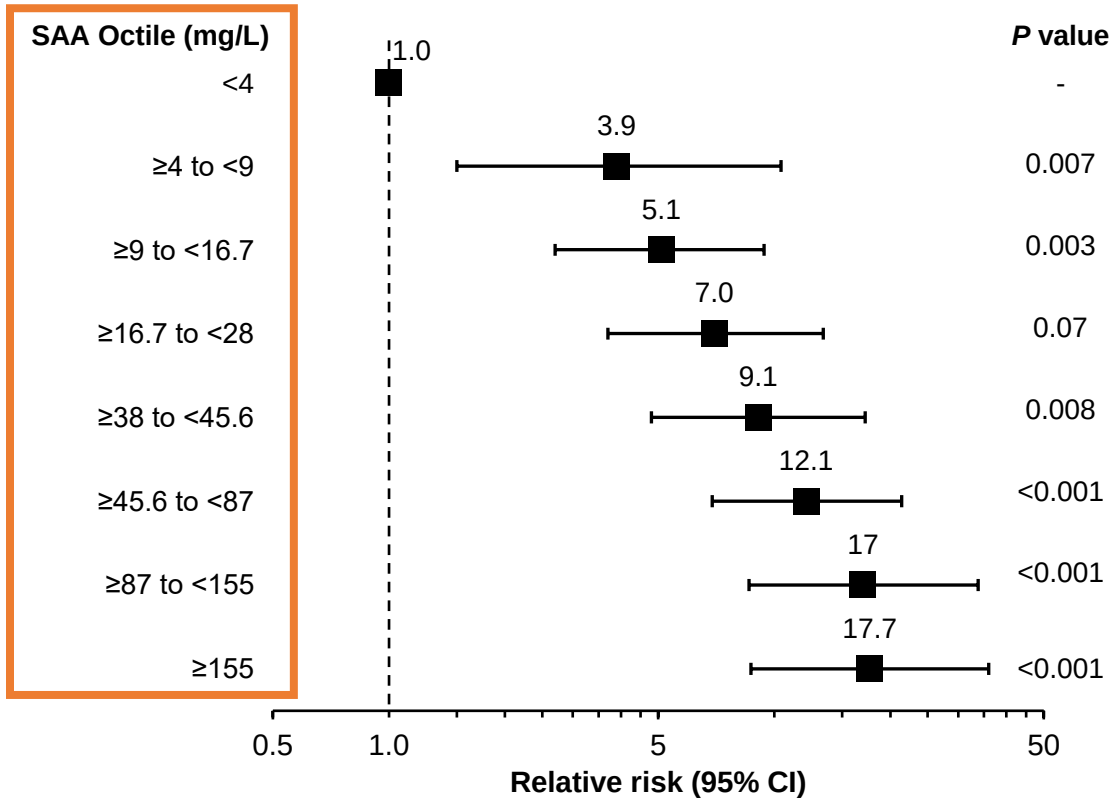
[a]Unpublished.

Our community has incorporated this information to advance therapy in AA and AL amyloidosis

Specific concentration thresholds inform outcomes

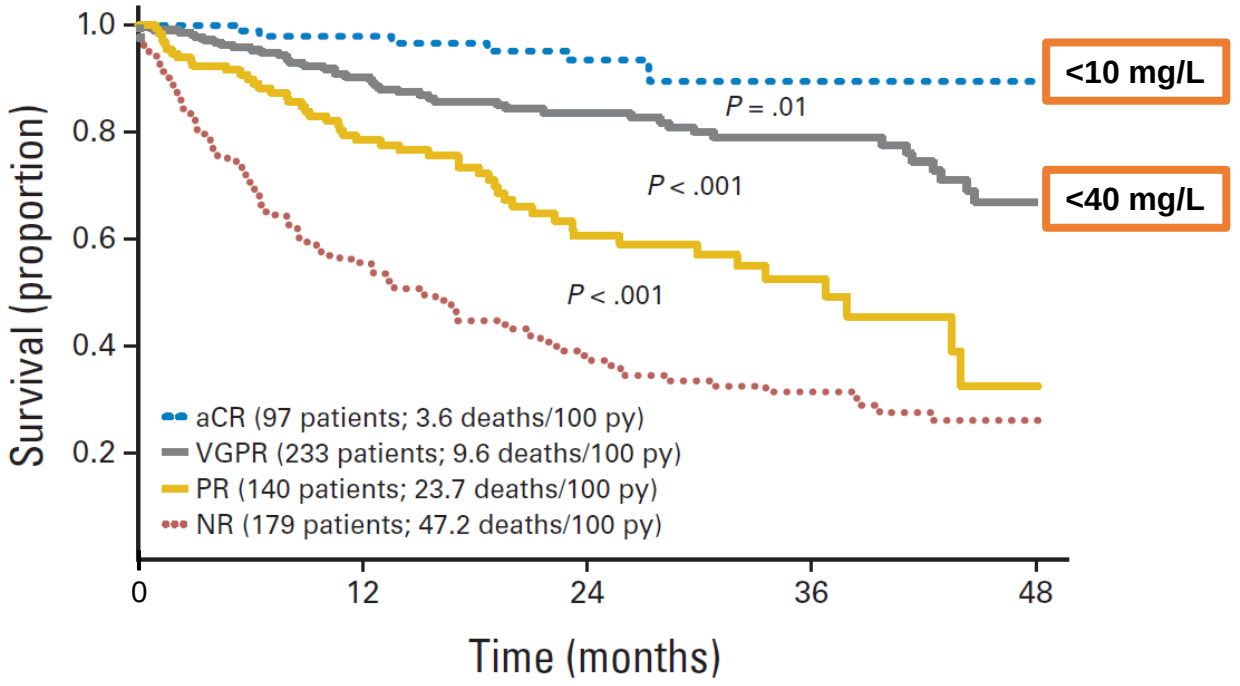
AA amyloidosis[1]

Unadjusted relative risk of death associated with the most recent median annual SAA concentration during follow-up[a]



[a]The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.

AL amyloidosis[2]



1. Lachmann HJ, et al. *N Engl J Med.* 2007;356(23):2361-2371.
2. Palladini G, et al. *J Clin Oncol.* 2012;30(36):4541-4549.

AA, amyloid A; aCR, amyloidosis complete response; AL, amyloid light chain; CI, confidence interval; NR, no response; PR, partial response; py, person years;SAA, serum amyloid A; VGPR, very good partial response.

There is an equilibrium between circulating amyloid fibril precursor protein concentration and change in amyloid burden

Precursor protein

Amyloid

Amyloid clearance

Amyloid formation

Reduce supply of amyloid precursor protein

- **Chemotherapy in AL**
- **Anti-inflammatory therapy in AA**
- **Gene "silencers" and gene editing in ATTR**

Stabilise amyloid-forming proteins

- β sheet breakers

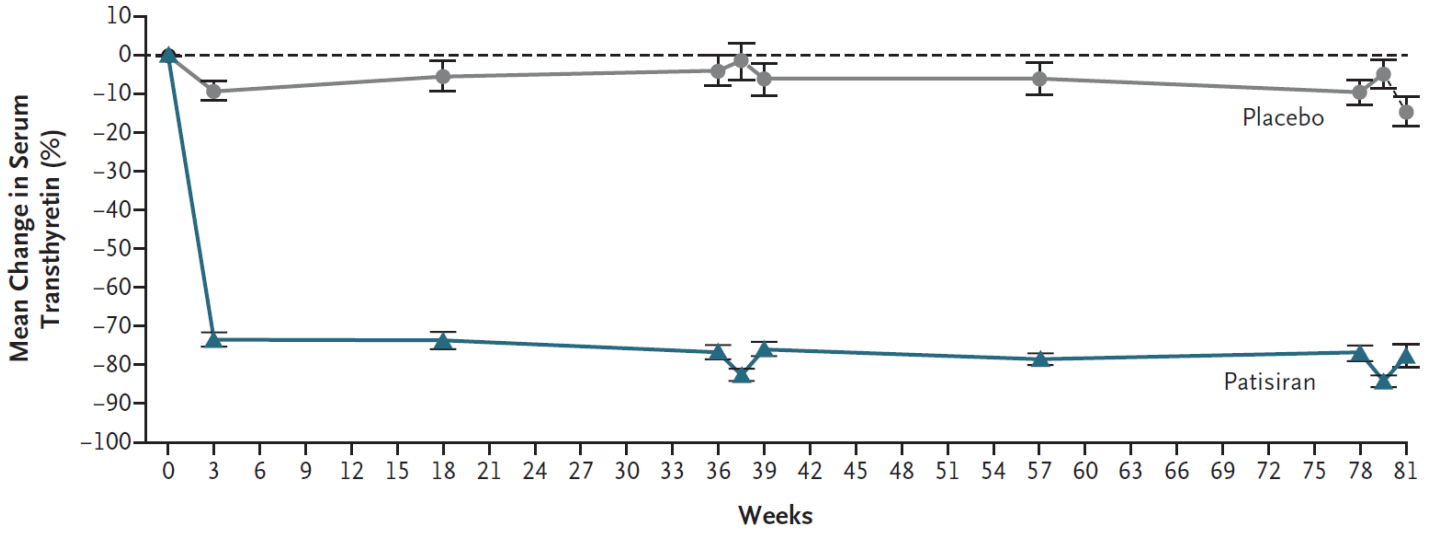
Reduce supply of amyloid precursor protein

- Immunotherapy
- SAP depletion

AA, amyloid A; AL, amyloid light chain; ATTR, transthyretin amyloidosis; SAP, serum amyloid P component.

Percent reduction in serum [TTR] is associated with clinical benefit in ATTR amyloidosis

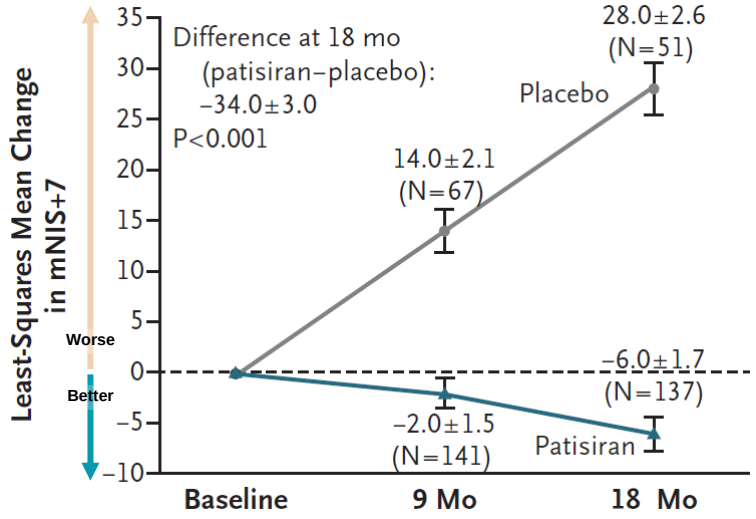
Pharmacodynamics: % change in serum TTR over 18 months[1]



Median reduction in serum TTR in the patisiran group was 81% (range, -38% to 95%) and was similar across age, sex, or genotype[1]

In a post hoc analysis of the cardiac subpopulation (n=126), there was **an approximate 45% reduction** in the **composite rate of cardiac hospitalization and all-cause mortality**[2]

Primary endpoint: mNIS+7 neuropathy score[1]



56% vs 4%

of patisiran- and placebo-treated patients, respectively, experienced a **halting or reversal of disease progression** (change <0 point mNIS+7)[1]

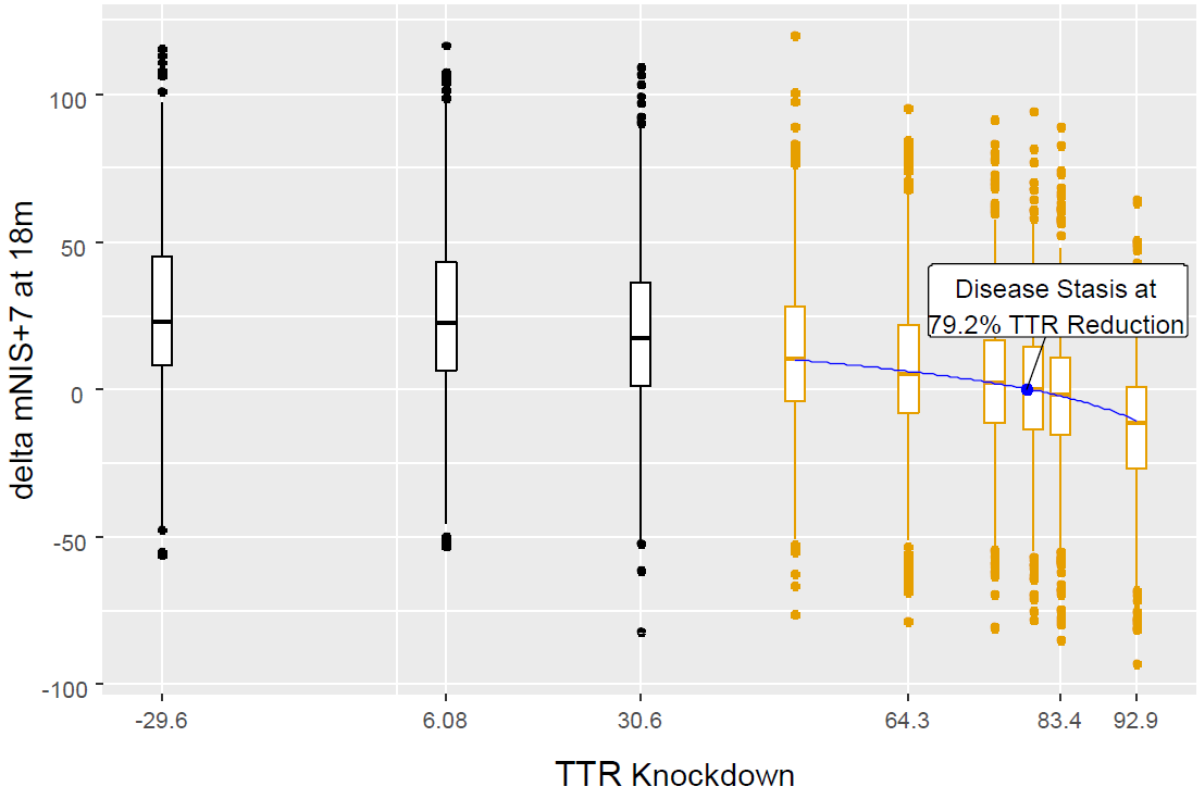
1. Adams D, et al. *N Engl J Med.* 2018;379(1):11-21.
2. Solomon SD, et al. *Circulation*. 2019;139(4):431-443.

ATTR, transthyretin amyloidosis; mNIS+7, modified neuropathy impairment score +7; TTR, transthyretin.

Serum [TTR] is typically expressed as % reduction from baseline – should we be using residual absolute serum [TTR] instead?

% serum TTR reduction vs ΔmNIS+7 by nonile in APOLLO A

At the population level, ≈80% TTR lowering is associated with improved score



Same % serum TTR reduction can mean different risk for ongoing fibril formation

	80% knockdown	
	Patient 1	Patient 2
Predose [TTR] (µg/mL)	350	150
Postdose [TTR] (µg/mL)	70	30

Both represent 80% knockdown,
but >2× available substrate for ongoing amyloid formation in Patient 1 post-treatment

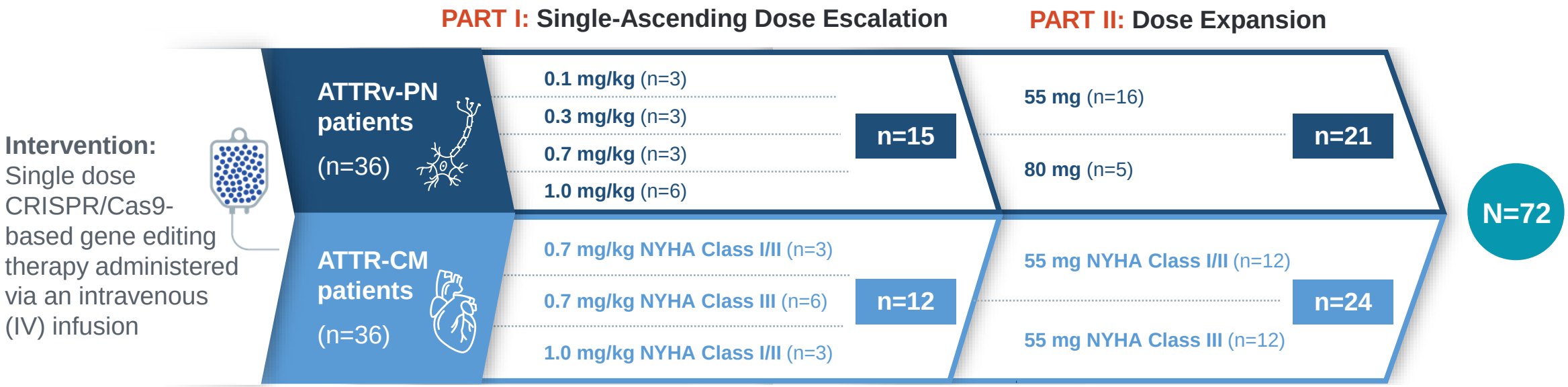
Should we be using residual absolute serum [TTR] instead?

Polydefkis M, et al. Presented at ISA. Mar 26-29, 2018; Kumamoto, Japan. Graph used with permissions from first author.

ΔmNIS+7, change in modified neuropathy impairment score +7; TTR, transthyretin.

The NTLA-2001 phase 1 study in ATTR amyloidosis has completed enrollment (N=72)

Two-part, open-label, multicenter study in adults with hereditary ATTR amyloidosis with polyneuropathy (ATTRv-PN) or ATTR amyloidosis with cardiomyopathy (ATTR-CM)



PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK, and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

- *Neurologic function in patients with ATTRv-PN*
- *Cardiac disease in patients with ATTR-CM*

Clinicaltrials.gov ID: NCT0460105.

ATTR, transthyretin amyloidosis; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; NYHA, New York Heart Association; PD, pharmacodynamics; PK, pharmacokinetics.

Patient demographics and characteristics

Characteristic		PN Patients (N=36)	CM Patients (N=29)	All Patients (N=65)
Age, years	Median (min, max)	61 (19, 75)	78 (46, 86)	68 (19, 86)
Sex, n (%)	Male	26 (72)	28 (97)	54 (83)
Weight, kg	Median (min, max)	77 (55, 117)	82 (63, 115)	81 (55, 117)
***TTR* genotype, n (%)**	p.V50M	11 (31)	0	11 (17)
	p.V142I	1 (3)	6 (21)	7 (11)
	p.T80A	7 (19)	1 (3)	8 (12)
	p.S97Y	7 (19)	0	7 (11)
	p.E62D	4 (11)	0	4 (6)
	Other	6 (17)	2 (7)	8 (12)
	WT	0	20 (69)	20 (31)
NYHA Class, n (%)	No diagnosis of heart failure	12 (33)	0	12 (18)
	I	19 (53)	3 (10)	22 (34)
	II	5 (14)	14 (48)	19 (29)
	III	0	12 (41)	12 (18)
NT-proBNP, ng/L	Median (min, max)	127 (<50, 1878)	1845 (851, 19,624)	757 (<50, 19,624)

Data cutoff May 11, 2023.
Interim data presented are for the first 65 (dosed and reached at least 28 days post-infusion by the data cutoff) of 72 patients dosed. Results from the final 7 patients will be reported at a future date. CM, cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PN, polyneuropathy; TTR, transthyretin.

Most frequent treatment emergent adverse events

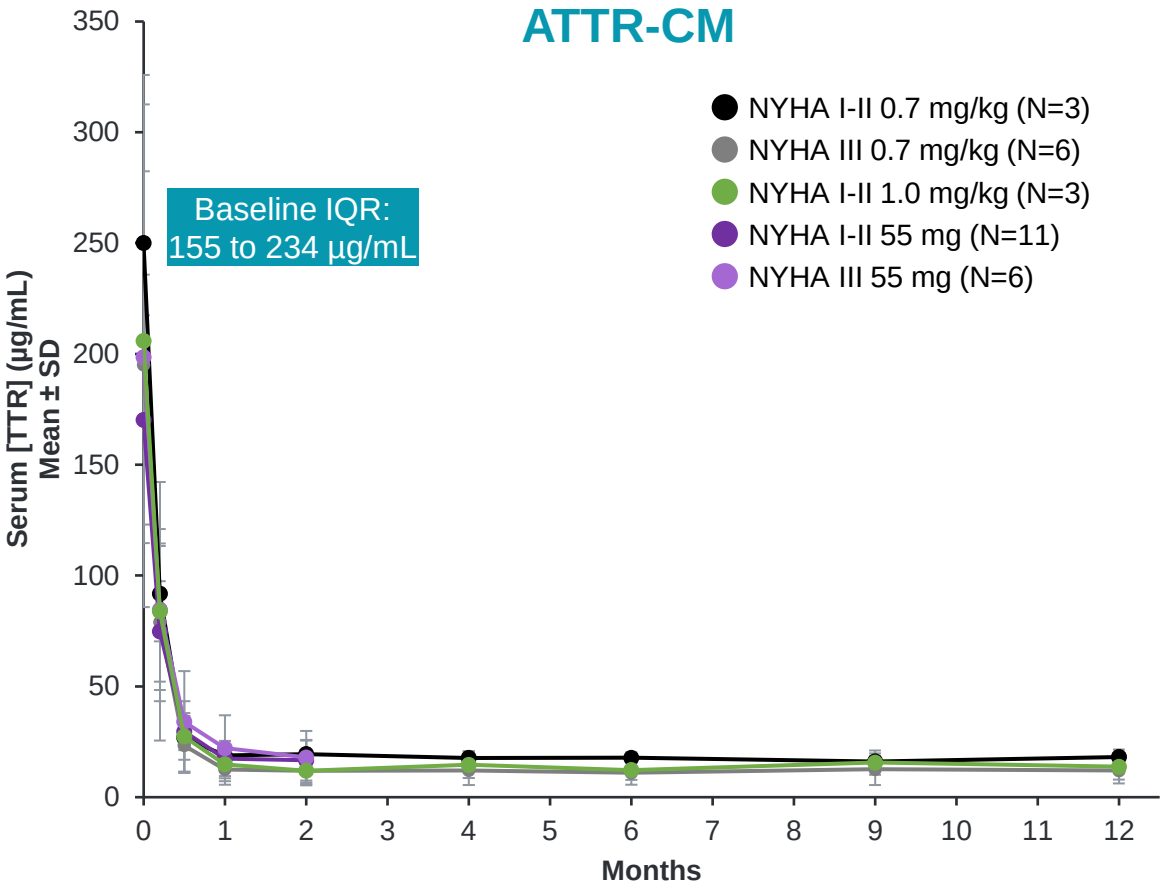
TEAEs by Maximum Toxicity Grade and Preferred Term Reported in >5% of All ATTRv-PN and ATTR-CM Patients (N=65)

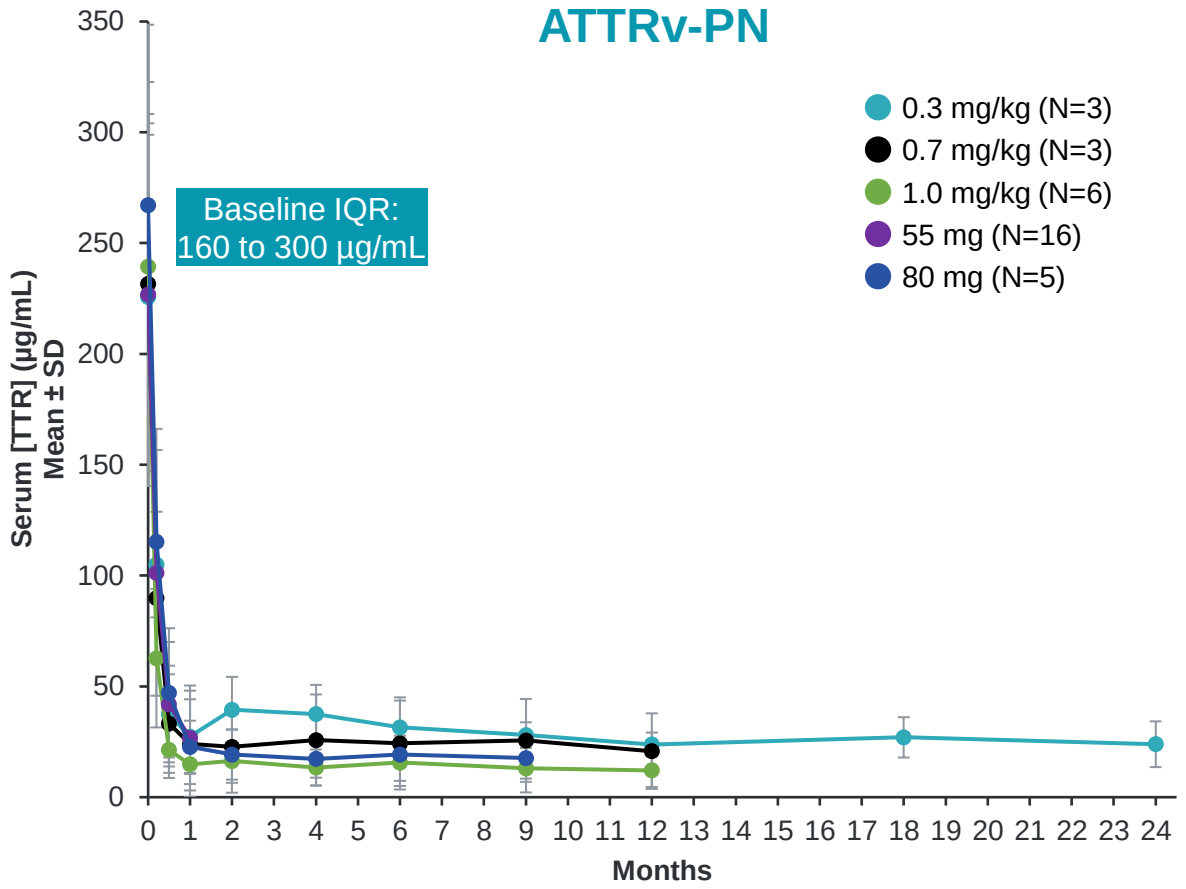
AE, Preferred Term, n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3
Infusion-related reaction	25 (38)	10 (15)	14 (22)	1 (2)
Headache	12 (18)	12 (18)		
Diarrhea	11 (17)	10 (15)	1 (2)	
Back pain	7 (11)	7 (11)		
COVID-19 infection	6 (9)	5 (8)	1 (2)	
Cardiac failure	6 (9)	2 (3)	2 (3)	2 (3)
Upper respiratory tract infection	6 (9)	6 (9)		
AST increased	5 (8)	3 (5)	1 (2)	1 (2)
Dizziness	5 (8)	5 (8)		
Fatigue	5 (8)	5 (8)		
Muscle spasms	5 (8)	4 (6)	1 (2)	
Vision blurred	5 (8)	5 (8)		
Atrial flutter	4 (6)		1 (2)	3 (5)
Constipation	4 (6)	2 (3)	2 (3)	
Rash	4 (6)	4 (6)		

- This includes all reported events, including those unrelated to NTLA-2001 (e.g., atrial flutter and cardiac failure hospitalizations)
- Infusion-related reactions were most common; nearly all were considered mild and resolved without sequelae, and all patients received the complete, planned dose
- Any liver enzyme elevations resolved spontaneously, were asymptomatic, and required no intervention (e.g., steroids) or hospitalization

Data cutoff May 11, 2023.
Patients reporting more than one AE related to NTLA-2001 are counted only once using the maximum toxicity grade. AEs coded to preferred term using Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 for PN and version 24.0 for CM. Interim data presented are from the initial 65 of 72 patients dosed. Results from the final 7 patients enrolled after the data cutoff will be reported at a future date. AE, adverse event; AST, aspartate transaminase; CM, cardiomyopathy; PN, polyneuropathy; TEAE, treatment-emergent adverse event.

Regardless of baseline TTR levels, NTLA-2001 led to consistently low and sustained absolute serum [TTR] in all patients





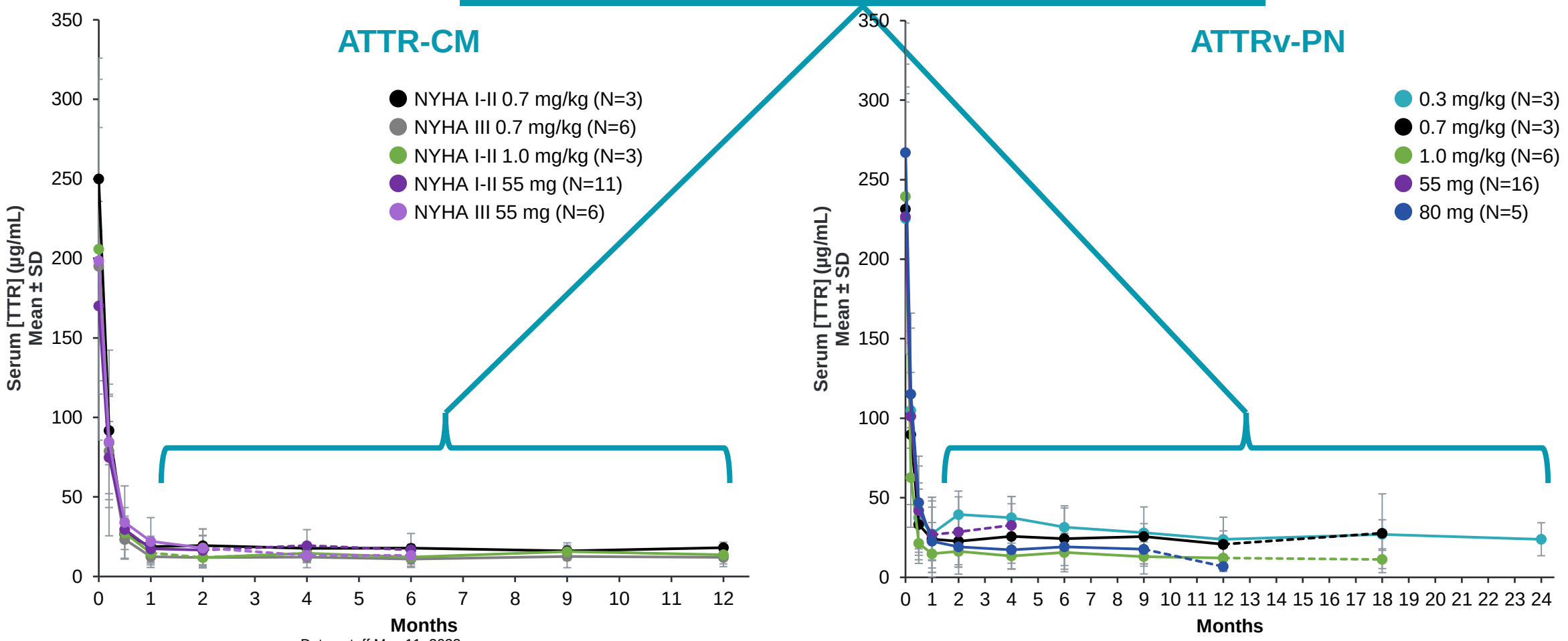
Median (IQR) Serum [TTR] at Day 28 (n=62)	Residual absolute TTR concentration at day 28	17 µg/mL (11 to 24)
	% Change from baseline in serum TTR at day 28	-91% (-88 to -94)

Data cutoff May 11, 2023.

Figure notes: Results for each dose level are shown out to the last time point with complete follow-up for the entire cohort. Interim data presented excludes the 0.1 mg/kg cohort from the dose-escalation of the polyneuropathy arm. The three patients in the 0.1 mg/kg cohort have been re-dosed at 55 mg and results will be shared in a future presentation. The 55 mg and 80 mg doses are the fixed doses corresponding to 0.7 mg/kg and 1.0 mg/kg, respectively. ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin.

Regardless of baseline TTR levels, NTLA-2001 led to consistently low and sustained absolute serum [TTR] in all patients

The median (IQR) maximum change from day 28 onward (measure of fluctuations) = -1.4 µg/mL (-4.7 to 1.7)



Data cutoff May 11, 2023.

Figure notes: Mean depicted only when there are two or more data points. Subsequent points connected by a dashed line denotes less than full group follow-up. Interim data presented excludes the 0.1 mg/kg cohort from the dose-escalation of the polyneuropathy arm. The three patients in the 0.1 mg/kg cohort have been re-dosed at 55 mg and results will be shared in a future presentation. The 55 mg and 80 mg doses are the fixed doses corresponding to 0.7 mg/kg and 1.0 mg/kg, respectively. ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin.

Summary

- In other systemic amyloidoses, the residual, absolute concentration of the amyloid precursor protein is closely associated with clinical outcomes
- Interim data from 62 patients with ATTR amyloidosis treated with NTLA-2001 continue to show a favorable safety and tolerability profile, with rapid, consistent, and durable reductions of serum [TTR] to low levels in all patients
- For treatments that reduce total serum [TTR], with nonfluctuating steady state measures, the residual absolute serum [TTR] could be a robust biomarker of ATTR amyloidosis therapy outcomes
- With collaboration, this approach to biomarker development has facilitated progress in care and better outcomes in AA and AL amyloidosis

AA, amyloid A; AL, amyloid light chain; ATTR, transthyretin amyloidosis; TTR, transthyretin.

Acknowledgments

We extend our gratitude to the patients who participated in the NTLA-2001 Phase 1 study and their family and caregiver networks

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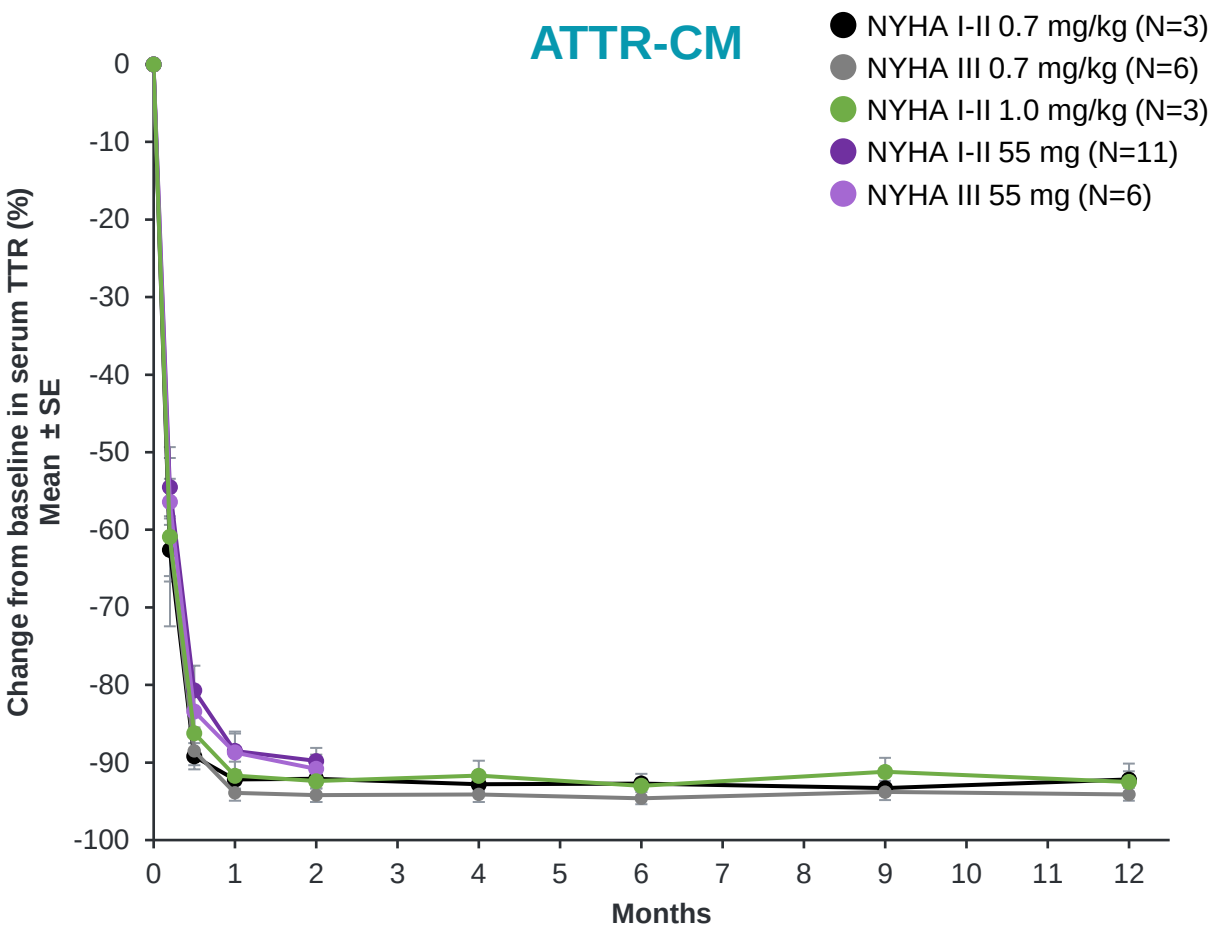
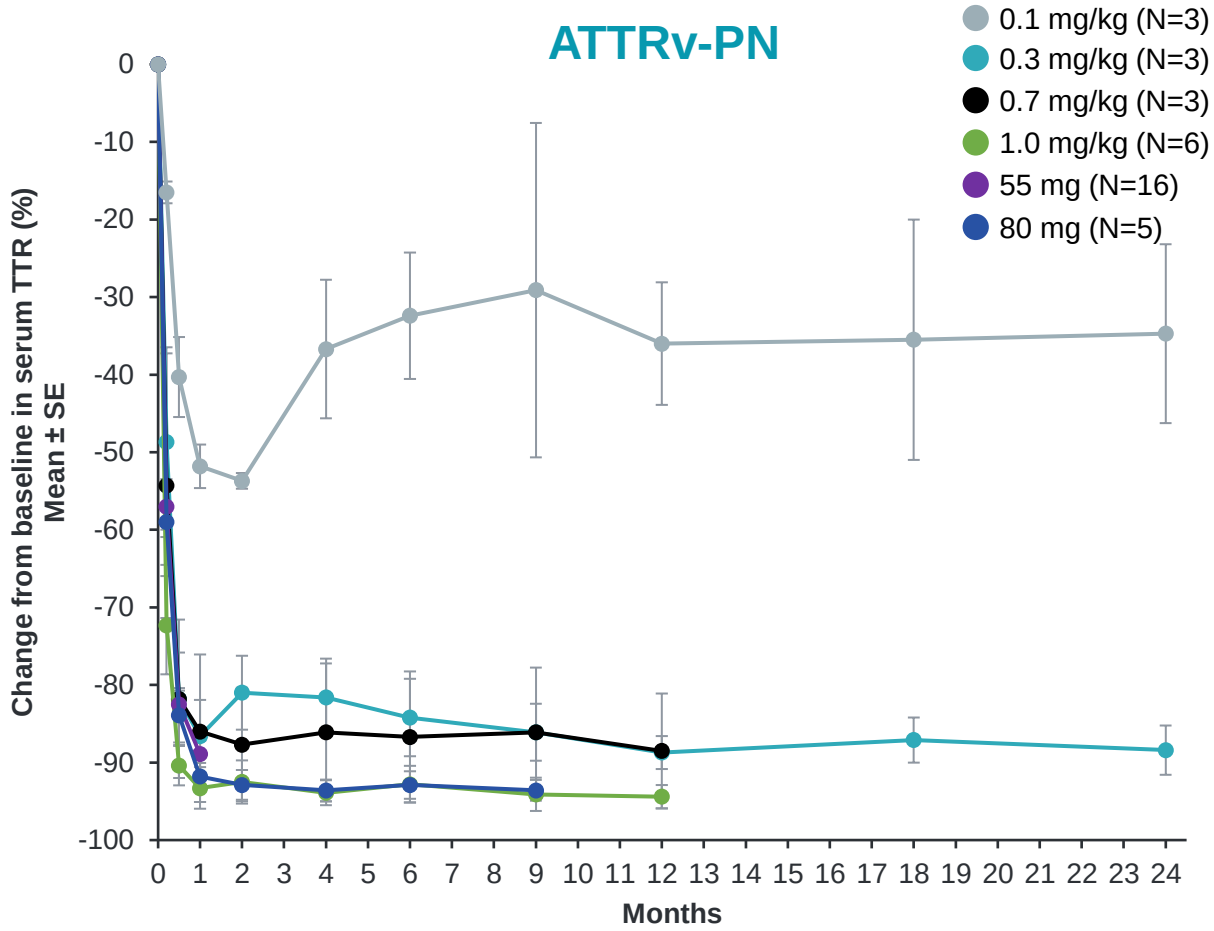
Appendix

Dose-responsive rapid and deep serum TTR reduction sustained across all patients





% Change from baseline in serum TTR at Day 28 (n=62, excludes the 0.1 mg/kg cohort)	
Mean (SE) serum [TTR]	-90% (0.86)
Median (IQR) serum [TTR]	-91% (-88 to -94)

Data cutoff May 11, 2023.
Figure notes: Results for each dose level are shown out to the last time point with complete follow-up for the entire cohort.
ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; NYHA, New York Heart Association; SE, standard error; TTR, transthyretin.