A Phase 1, Single Ascending Dose Study to Evaluate ALN-TTRsc04, a Next-Generation RNA Interference Therapeutic, in Healthy Participants for Potential Treatment of Transthyretin Amyloidosis

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Disclosures

- Ali Murad is an employee of Alnylam Pharmaceuticals Inc, and owns equity in Alnylam Pharmaceuticals Inc
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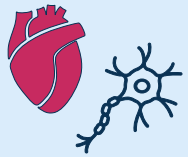
Introduction



ATTR (transthyretin amyloidosis) is a progressive, fatal disease, caused by toxic TTR amyloid deposition in multiple tissues and organs, including the heart, resulting in progressive organ damage[1–3]

RNAi therapeutics have the potential to “silence” the genes that cause or contribute to disease, without changing them[4]

The first approved RNAi therapeutic, patisiran, and the second-generation vutrisiran are currently approved for the treatment of hATTR-PN[5–8]

The randomized, placebo-controlled, double-blind, HELIOS-B study, evaluated 25 mg vutrisiran SC q3M in patients with ATTR-CM and reported the following:[9]

- Achieved 28% reduction in the composite of all-cause mortality and recurrent CV events in the overall population
- Acceptable safety and tolerability profiles

Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; CV, cardiovascular; hATTR-PN, hereditary ATTR with polyneuropathy; q3M, every 3 months; RNAi, RNA interference; SC, subcutaneous; siRNA, small interfering RNA; TTR, transthyretin.

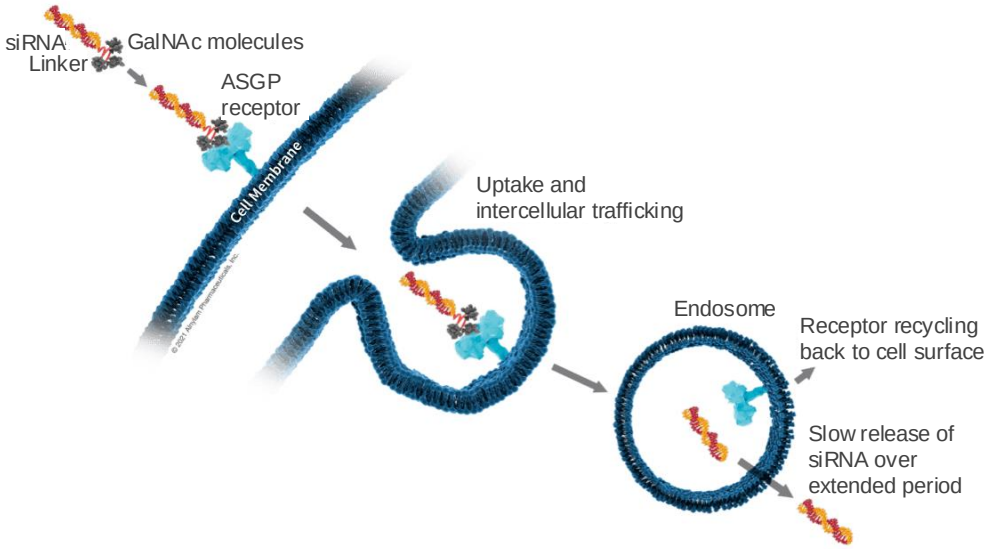
References: 1. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 2. Ghosh et al. *Amyloid* 2023;30:379–93; 3. Adams et al. *J Neurol* 2021:268:2109–22; 4. Kim. *Exp Mol Med* 2022;54:455–65; 5. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use (2020); 6. Alnylam Pharmaceuticals Inc. US prescribing information: AMVUTTRA (vutrisiran) injection, for subcutaneous use (2022); 7. European Medicines Agency. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf; 8. European Medicines Agency. 2022. Available from: https://www.ema.europa.eu/documents/product-information/amvuttra-epar-product-information_en.pdf; 9. Fontana et al. *N Engl J Med* 2024. DOI:10.1056/NEJMoa2409134. Epub ahead of print.

Next-Generation RNAi Therapeutic ALN-TTRsc04 (nucresiran)

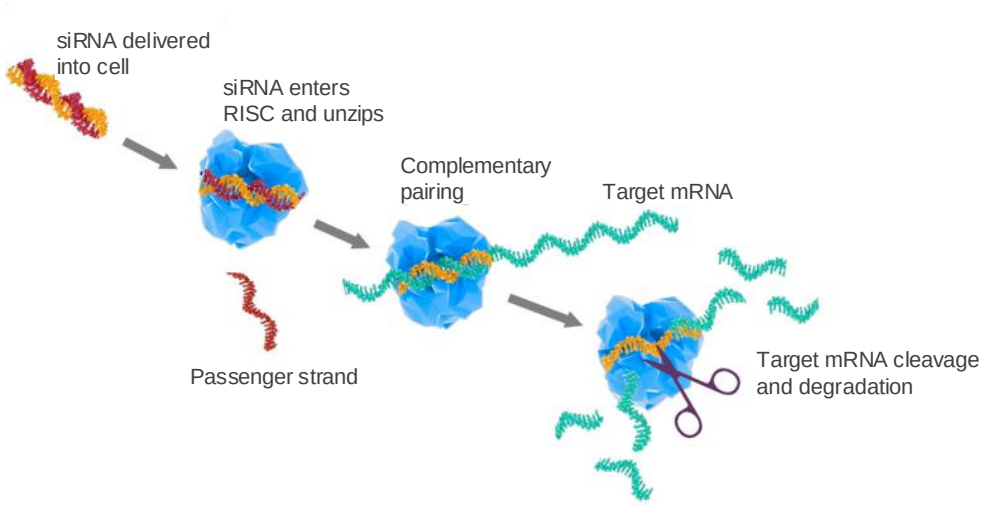
- ALN-TTRsc04, is a subcutaneously administered, third-generation RNAi therapeutic that inhibits hepatic synthesis of both wild-type and variant TTR messenger RNA and is being developed to potentially offer less frequent dosing with deep and sustained TTR reduction with lower interpatient variability

Mode of Action of ALN-TTRsc04[1]

Cell Entry



RNAi Mechanism

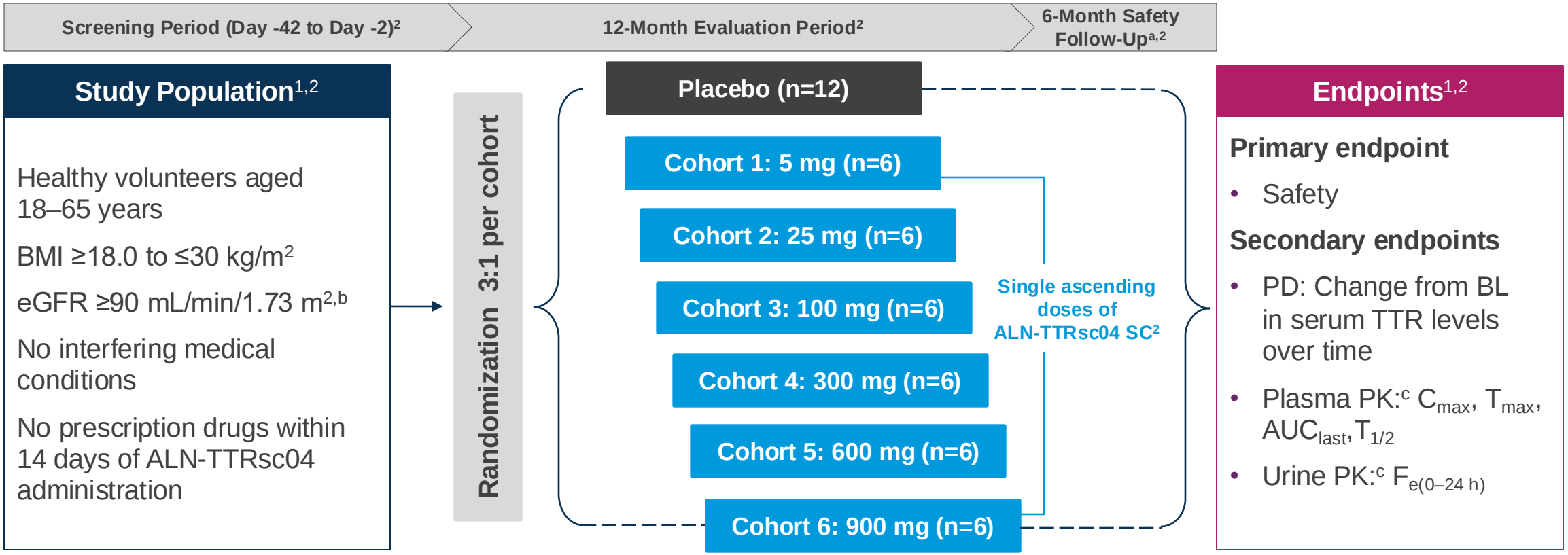


We present Phase 1 data of ALN-TTRsc04 from healthy volunteers

Abbreviations: ASGP, asialoglycoprotein; GalNAc, N-acetylgalactosamine; mRNA, messenger ribonucleic acid; RISC, RNA-induced silencing complex; RNAi, RNA interference; SC, subcutaneous; siRNA, small interfering RNA; TTR, transthyretin.
Reference: 1. Copyright Alnylam 2024.

Study Design

Ongoing, Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study of ALN-TTRsc04 SC (NCT05661916)[1,2]



- At the time of data cut for this presentation, each cohort had a minimum of 6 months' follow-up data available with some cohorts having 12 months

[a]Follow-up for subjects who received ALN-TTRsc04 and have serum TTR levels that have not returned to ≥80% of pre-dose Day 1 level by the last post-dose follow-up visit (Day 360). [b]Calculation based on CKD-EPI formula.
[c]Urine and plasma concentrations measured on Days 12 and 14, respectively.
Abbreviations: AUC_{last}, area under the curve between time 0 and last observable concentration; BL, baseline; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; C_{max}, maximum plasma concentration; eGFR, estimated glomerular filtration rate; $F_{e(0-24\ h)}$, fractional excretion between time 0 and 24 h; h, hours; PD, pharmacodynamics; PK, pharmacokinetics; R, randomization; SC, subcutaneous; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, time to reach maximum concentration; TTR, transthyretin.
References: 1. NCT05661916 Available from: https://clinicaltrials.gov/study/NCT05661916. Accessed 11 September, 2024; 2. Study protocol, data on file.

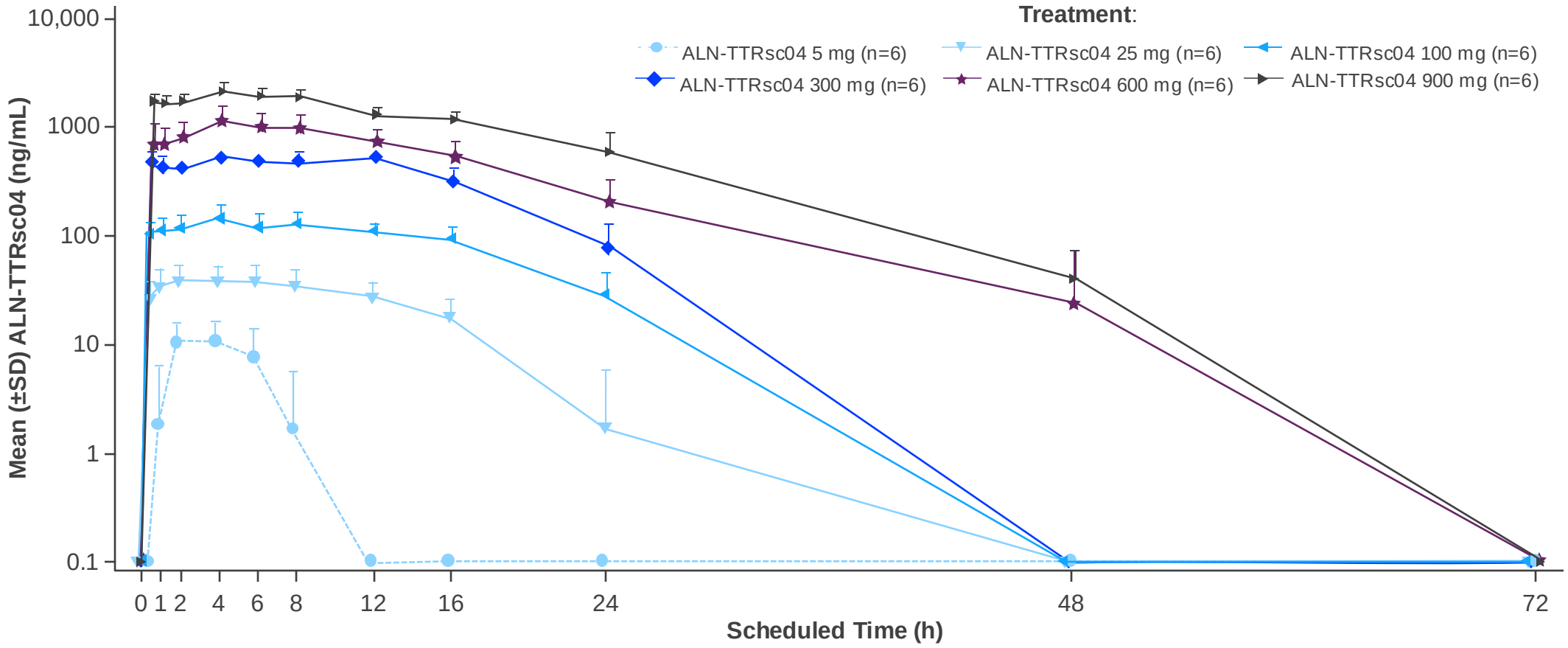
Study Population

Baseline demographics

		ALN-TTRsc04					
	Placebo (n=12)	5 mg (n=6)	25 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)	900 mg (n=6)
Age, years, median (range)	26.0 (21–40)	22.5 (20–28)	24.0 (20–29)	24.5 (22–36)	27.5 (25–30)	25.0 (18–33)	28.0 (20–37)
Male, n (%)	7 (58.3)	4 (66.7)	3 (50.0)	1 (16.7)	1 (16.7)	4 (66.7)	4 (66.7)
Race, n (%)							
Asian	3 (25.0)	1 (16.7)	3 (50.0)	1 (16.7)	0 (0)	0 (0)	2 (33.3)
Black / African American	2 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0)	1 (16.7)	2 (33.3)
White	7 (58.3)	4 (66.7)	2 (33.3)	3 (50.0)	4 (66.7)	4 (66.7)	2 (33.3)
Other	0 (0)	0 (0)	0 (0)	1 (16.7)	2 (33.3)	1 (16.7)	0 (0)
>1 race	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Weight, kg, median (range)	67.40 (53.5–84.0)	72.90 (57.8–88.8)	65.45 (48.4–84.0)	63.10 (54.6–75.4)	60.30 (55.4–70.6)	69.20 (53.6–88.0)	65.10 (58.0–75.6)
Height, cm, median (range)	170.5 (159–186)	176.5 (164–195)	173.0 (155–185)	171.0 (155–187)	168.5 (155–175)	170.0 (161–190)	172.0 (157–185)
BMI, kg/m^2, median (range)	22.95 (19.4–24.9)	23.55 (18.8–25.0)	22.20 (20.1–24.5)	22.85 (18.2–24.5)	23.30 (18.2–24.6)	23.60 (20.6–24.8)	21.75 (20.4–23.8)

Abbreviation: BMI, body mass index.

Plasma Pharmacokinetic Profile of ALN-TTRsc04 Following a Single SC Dose

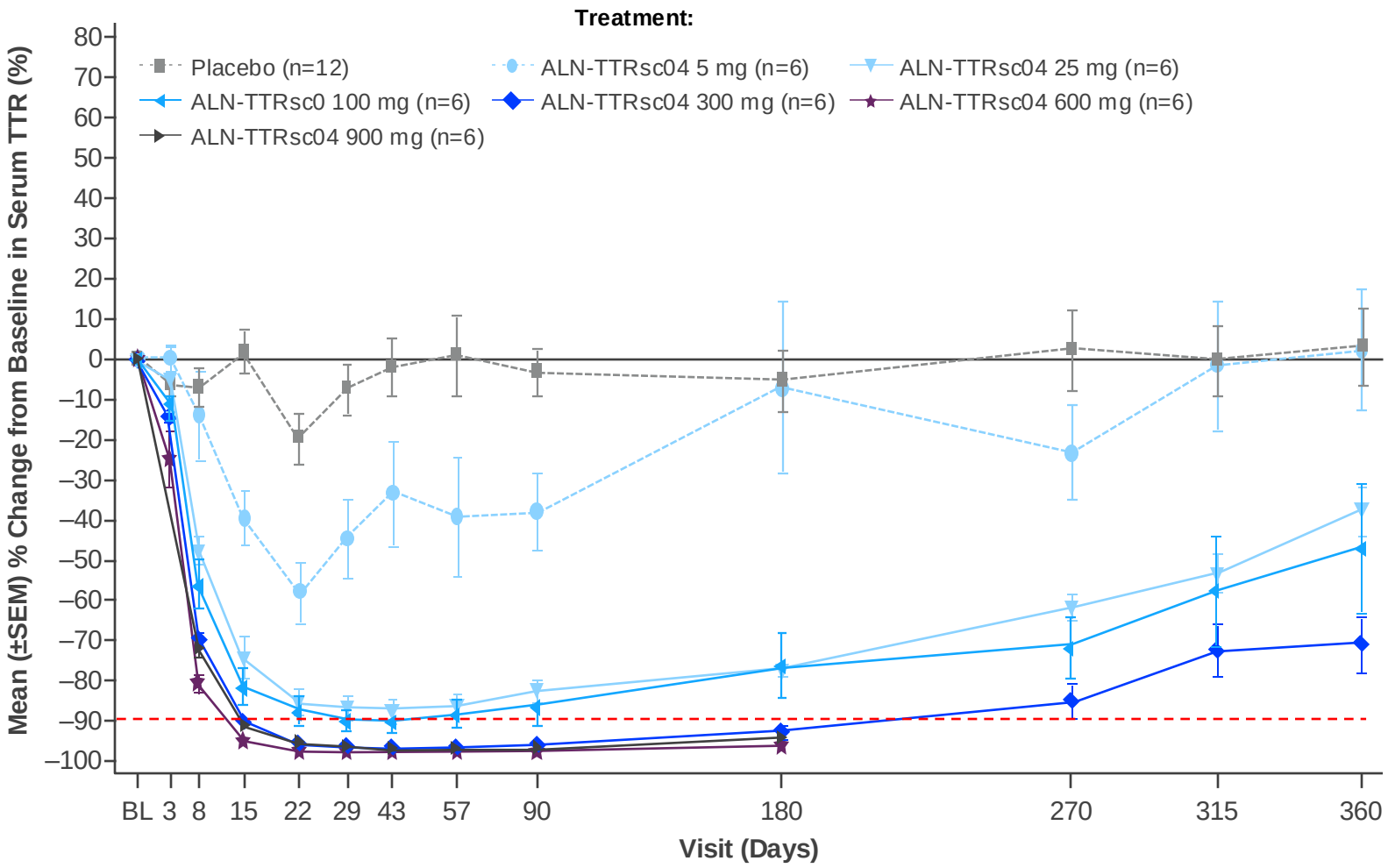


- ALN-TTRsc04 plasma levels declined below lower limit of quantification within 72 hours
- Mean (CV%) plasma half-life ranged from 4.5 (32.3) to 7.6 (41.3) hours across doses ranging from 25 mg to 900 mg
- ALN-TTRsc04 was minimally excreted by renal route (<21%) after 24 hours

Concentration values below the limit of quantification (10 ng/mL) are set to 0 for summary statistics calculation. For semi-logarithmic plot, only upper bar is shown and where mean value is zero, it is displayed as 0.1 ng/mL for visualization purposes.
Abbreviations: SC, subcutaneous; SD, standard deviation.

Mean Percent Change from Baseline in Serum TTR Levels over Time

Deep and sustained TTR knockdown was observed for participants receiving ≥300 mg of ALN-TTRsc04



- **Rapid** knockdown in serum TTR at Day 15; mean reductions of 90.3% (300 mg), 95.0% (600 mg)
- **Deep** knockdown of TTR by Day 29; mean reductions of 96.5% (300 mg), 97.8% (600 mg)
- **Sustained** knockdown of TTR through Day 180; mean reductions of 92.6% (300 mg), 96.0% (600 mg)
- **Low variability** of TTR knockdown on Day 29 (% TTR reduction range): 96.0–96.7% (300 mg), 96.6–98.6% (600 mg)

Abbreviations: BL, baseline; SEM, standard error of the mean; TTR, transthyretin

Safety Summary within 360 Days of Dosing

Acceptable safety and tolerability profile at all doses tested

Event, n (%)		ALN-TTRsc04					
	Placebo (n=12)	5 mg (n=6)	25 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)	900 mg (n=6)
At least 1 AE	11 (91.7)	5 (83.3)	5 (83.3)	6 (100.0)	6 (100.0)	4 (66.7)	5 (83.3)
At least 1 SAE	0 (0)	1 (16.7)[a]	1 (16.7)[a]	0 (0)	1 (16.7)[b]	0 (0)	0 (0)
At least 1 severe AE	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)[b]	0 (0)	0 (0)
AE related to study drug	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AEs occurring in ≥2 patients in any cohort							
Upper respiratory tract infection	8 (66.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	1 (16.7)	3 (50.0)
Viral upper respiratory tract infection	3 (25.0)	4 (66.7)	3 (50.0)	1 (16.7)	3 (50.0)	0 (0)	0 (0)
Headaches	3 (25.0)	0 (0)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	0 (0)
Gastroenteritis	0 (0)	0 (0)	1 (16.7)	0 (0)	1 (16.7)	2 (33.3)	1 (16.7)

- Majority of AEs across doses were mild; none were considered related to treatment
- No injection-site reactions or safety signals, including liver-related signals, were identified
- No deaths were reported

[a]Abortion spontaneous. [b]Sigmoid collection (secondary to Crohn's disease).
Abbreviations: AE, adverse event; SAE, serious AE.

Conclusions

For US HCPs Only

- The plasma pharmacokinetic profile of ALN-TTRsc04 (nucresiran) is comparable to other GalNAc-conjugated siRNAs
- Single ALN-TTRsc04 doses led to a rapid and sustained knockdown in serum TTR; a mean reduction of ≥90% from baseline was achieved at Day 15 and sustained at least until Day 180 with ALN-TTRsc04 doses ≥300 mg
- In addition to the deep and sustained reduction of circulating TTR, ALN-TTRsc04 has potential to reduce interpatient variability in TTR lowering and reduce patient burden with decreased dosing frequency compared with vutrisiran
- All ALN-TTRsc04 doses have been well tolerated to date
- A Phase 3 study of nucresiran in ATTR with cardiomyopathy is expected to initiate in the near future

If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.

Abbreviations: ATTR, transthyretin amyloidosis; GalNAc, N-acetylgalactosamine; siRNA, small-interfering ribonucleic acid; TTR, transthyretin.

Thank you