Nucresiran: Phase 1 Study

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The safety and efficacy of nucresiran are currently being investigated in clinical studies and have not been evaluated by US Food and Drug Administration or any health authority.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Nucresiran is a subcutaneously administered, third-generation RNAi therapeutic that inhibits hepatic synthesis of both wild-type and variant TTR mRNA and is being investigated for the treatment of transthyretin amyloidosis.[1]
- The safety, tolerability, PK, and PD of nucresiran in healthy patients are being evaluated in a randomized, double-blind, placebo-controlled, single ascending dose, phase 1 study (NCT05661916). At the time of data cutoff for the Phase 1 study, a minimum of 6 months' follow-up data was available for each cohort (with some cohorts having 12 months).[1,2]
  - The plasma levels of nucresiran declined below LLOQ within 72 hours.[1]
  - A mean reduction in serum TTR levels of ≥90% from baseline was achieved at Day 15 and sustained at least until Day 180 with doses ≥300 mg of nucresiran.[1]
  - The majority of AEs were mild in severity, and none were considered related to treatment.[1]

INDEX

STUDY DESIGN

The Phase 1 study of nucresiran (ALN-TTRsc04) is a randomized, double-blind, placebo-controlled, single ascending dose study designed to evaluate the safety, tolerability, PK, and PD of nucresiran in healthy patients.[1,2] Enrolled patients are randomized 3:1 per cohort to receive subcutaneous injections of 5, 25, 100, 300, 600, or 900 mg nucresiran (n=6 per cohort) or placebo (n=12) during the 12-month double-blind evaluation period, followed by a minimum 6-month safety period for patients who have serum TTR levels that have not returned to ≥80% of pre-dose Day 1 level by the last post-dose follow-up visit on Day 360.[1]

The primary endpoint is to assess the safety of nucresiran by the frequency of AEs. Secondary endpoints assess the change from baseline in serum TTR levels over time, urine PK through the fraction excreted in the urine until 24 hours, and plasma PK through the C_{max}, T_{max}, AUC_{last}, and $T_{1/2}$.[1,2]

Key study inclusion criteria are[1]:

- Healthy volunteers aged 18-65 years
- BMI ≥18.0 to ≤30 kg/m^2
- eGFR ≥90 mL/min/1.73 m^2

Key study exclusion criteria are[1]:

- Interfering medical conditions
- Prescription drugs within 14 days of nucresiran administration

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Patient demographics and baseline characteristics for 48 patients randomized to placebo or nucresiran by cohort are presented in **Table 1**.[1]

Table 1. Patient Demographics and Baseline Characteristics.[1]

Characteristic	Placebo (n=12)	Nucresiran					
		5 mg (n=6)	25 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)	900 mg (n=6)
Median age, years (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)
Median weight, kg (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)
Median height, cm (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)
Median BMI, kg/m^2 (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)

Abbreviations: BMI = body mass index.

SAFETY RESULTS

The majority of AEs occurring among the nucresiran cohorts within 360 days of dosing were mild in severity, and none were considered related to treatment. There were no injection-site reactions or safety signals reported, including liver-related signals. No deaths were reported.[1]

Table 2. Adverse Events Within 360 Days of Dosing.[1]

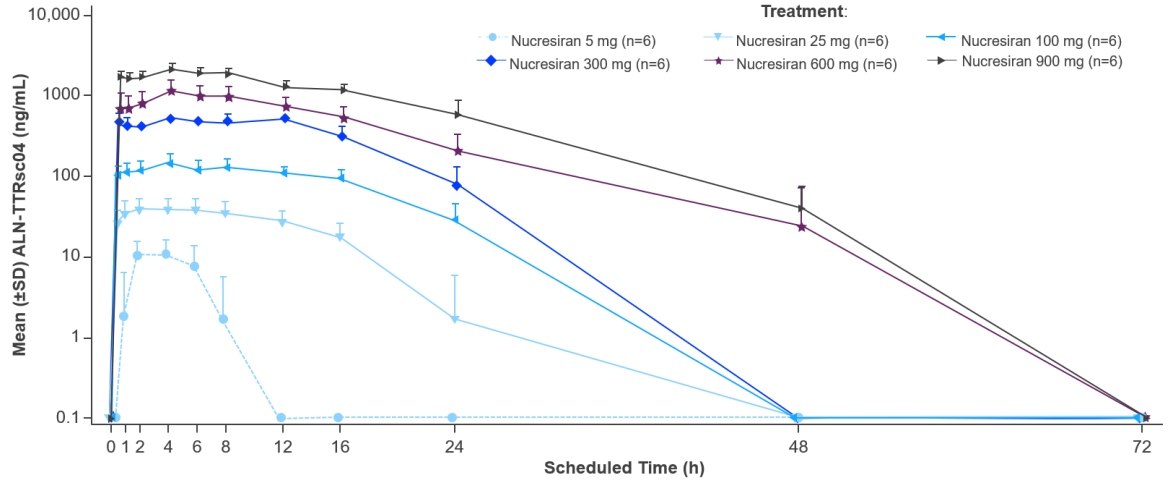
Characteristic, n (%)	Placebo (n=12)	Nucresiran					
		5 mg (n=6)	25 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)	900 mg (n=6)
At least 1 AE	11 (91.7)	5 (83.3)	5 (83.3)	6 (100.0)	6 (100.0)	4 (66.7)	5 (83.3)
At least 1 SAE	0 (0)	1 (16.7)[a]	1 (16.7)[a]	0 (0)	1 (16.7)[b]	0 (0)	0 (0)
At least 1 severe 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							
URTI	8 (66.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	1 (16.7)	3 (50.0)
Viral URTI	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)

Abbreviations: AE = adverse event; SAE = serious adverse event; URTI = upper respiratory tract infection.
[a]Abortion spontaneous. [b]Sigmoid collection (secondary to Crohn's disease).

PHARMACOKINETIC RESULTS

The mean concentration of nucresiran following a single subcutaneous dose was evaluated over time for the six dose cohorts; plasma levels of nucresiran declined below LLOQ within 72 hours (**Figure 1**). Mean (CV%) plasma half-life ranged from 4.5 (32.3) to 7.6 (41.3) hours across doses ranging from 25 to 900 mg. Nucresiran was minimally excreted by renal route (<21%) after 24 hours.[1]

Figure 1. Mean Concentration of Nucresiran Following a Single Subcutaneous Dose.[1]



Abbreviations: SD = standard deviation.
From Murad et al.[1]

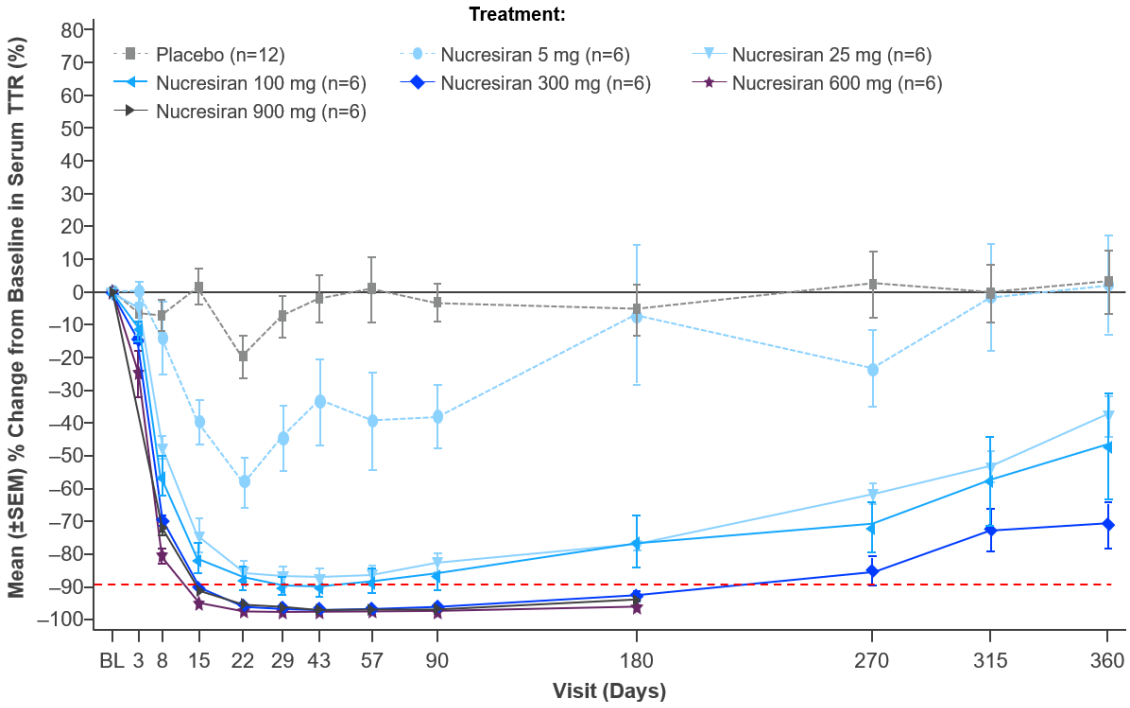
PHARMACODYNAMIC RESULTS

Serum TTR Levels

The mean percent change from baseline in serum TTR levels was evaluated over 360 days (**Figure 2**). In the 300 mg cohort, a 90.3% mean reduction in serum TTR levels was observed on Day 15, 96.5% on

Day 29, and 92.6% on Day 180. In the 600 mg cohort, a 95.0% mean reduction in serum TTR levels was observed on Day 15, 97.8% on Day 29, and 96.0% on Day 180. On Day 29, there was low variability in the range for percent TTR reduction in both the 300 mg cohort (96.0-96.7%) and 600 mg cohort (96.6-98.6%).[1]

Figure 2. Mean Percent Change from Baseline in Serum TTR Levels Over Time.[1]



Abbreviations: BL = baseline; SEM = standard error of the mean; TTR = transthyretin.
From Murad et al.[1]

ABBREVIATIONS

AE = adverse event; AUC_{last} = area under the curve between time 0 and last observable concentration; BL = baseline; BMI = body mass index; C_{max} = maximum observed plasma concentration; CV% = coefficient of variation; eGFR = estimated glomerular filtration rate; LLOQ = lower limit of quantitation; mRNA = messenger RNA; PD = pharmacodynamics; PK = pharmacokinetics; RNA = ribonucleic acid; RNAi = ribonucleic acid interference; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; $T_{1/2}$ = half-life; T_{max} = time to maximum observed plasma concentration; TTR = transthyretin; URTI = upper respiratory tract infection.

Updated 07 October 2025

REFERENCES

1. Murad A, Lasko MJ, Badri P, et al. 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. Presented at: American Heart Association (AHA) Scientific Sessions; November 16-18, 2024; Chicago, IL, USA.
2. Alnylam Pharmaceuticals: A study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of ALN-TTRSC04 in healthy subjects. Available from: https://clinicaltrials.gov/study/NCT05661916. Accessed October 07, 2025.