Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis

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Background and Rationale

Transthyretin-Mediated (ATTR) Amyloidosis

- Multi-system disease caused by an inherited mutation in transthyretin (hATTR) resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract[1-5], or deposition of wild-type TTR in patients without a pathogenic mutation (wtATTR)
- Amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, central nervous system, gastrointestinal tract, and kidneys[1]
  - Accumulation of fibrils in nerves can lead to manifestations of polyneuropathy, including peripheral neuropathy, autonomic dysfunction, and motor weakness causing fine and gross motor impairments
  - Accumulation of fibrils in the heart leads to myocardial dysfunction, arrhythmias and clinical heart failure
- Disease penetrance and rate of progression may be influenced by TTR genotype which can vary by geographical region[7]
- hATTR and wtATTR are both fatal diseases:
  - hATTR, with a median survival of 4.7 years following diagnosis with a reduced survival (3.4 years) for patients presenting with cardiomyopathy[8-10]
  - wtATTR can result in heart failure and mortality within 2 to 6 years[11-13]
- Limited treatment options are available
- Continued high unmet medical need for novel therapeutic options
  - Patisiran, an investigational RNAi therapeutic for hATTR amyloidosis with Phase 3 completed, is currently under EMA/FDA review[14]

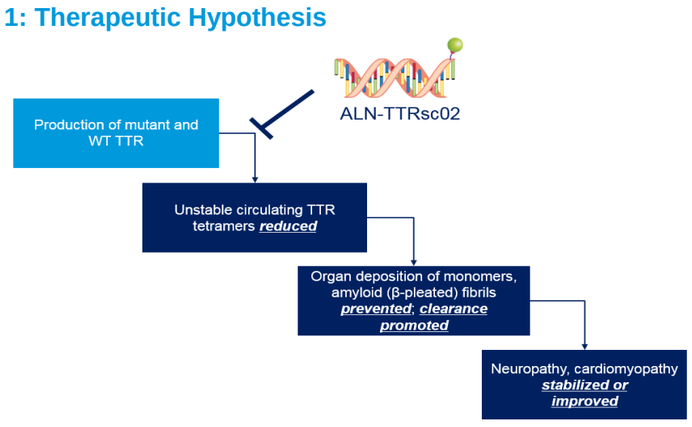
ALN-TTRsc02

- Subcutaneously (SC) administered small interfering RNA (siRNA) with enhanced stability chemistry (ESC) conjugated to GalNAc to target hepatic production of WT and mutant TTR (Figure 1)

Objective

- Evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of ALN-TTRsc02 in healthy adult volunteers

Figure 1: Therapeutic Hypothesis

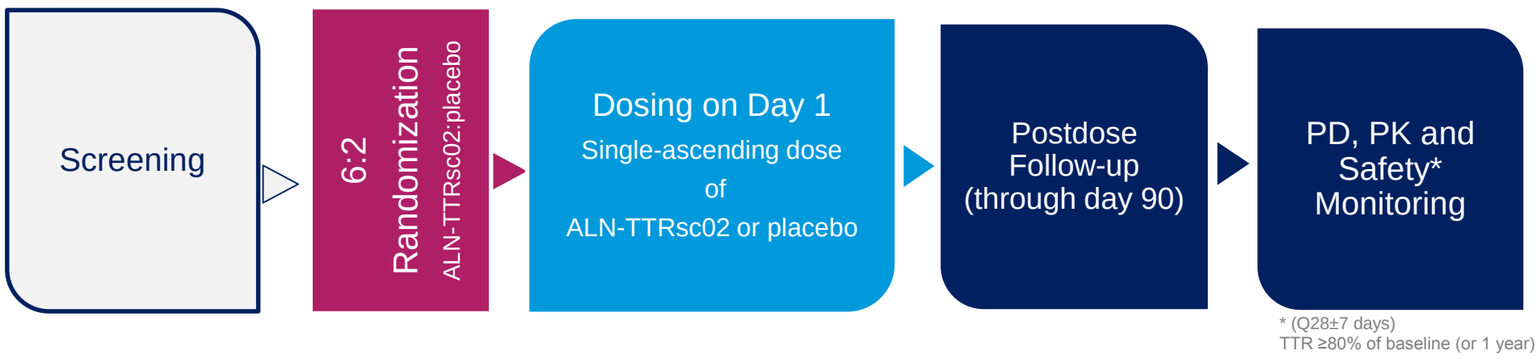


Methods

Phase 1 Study Design

- Phase 1, randomized (single blind), single ascending dose study of ALN-TTRsc02 in healthy volunteers (NCT02797847) (Figure 2)
- Study included cohorts of 8 participants randomized 6:2 to receive a single dose of SC administered ALN-TTRsc02 (5 mg to 300 mg) or placebo
- Primary Objectives: Safety and tolerability of single dose of ALN-TTRsc02 in healthy adult volunteers
- Secondary Objectives: Pharmacodynamics (TTR Levels) and Pharmacokinetics (PK) through 90 days post dose
- PD, PK, and safety monitoring for up to approximately 1 year post dose or until TTR ≥80% of baseline
- A population PK/PD model was developed using longitudinal serum TTR data from this study

Figure 2: Phase 1 Study Design



Results

Study Enrollment

- 80 healthy volunteers including 16 of Japanese descent; 20 in the placebo and 60 in treatment groups (Table 1)

Table 1: Baseline Demographics

		ALN-TTRsc02								
	Placebo (N=20)	5 mg (N=6)	25 mg (N=12)	25 mg Japanese (N=6)	50 mg (N=12)	50 mg Japanese (N=6)	100 mg (N=6)	200 mg (N=6)	300 mg (N=6)	Total ALN-TTRsc02 (N=60)
Median Age, years (range)	31 (20,44)	31 (20,41)	29 (19,42)	31 (27,36)	28 (21,40)	28 (22,31)	35 (19 ,43)	30 (22, 33)	27 (22,43)	28 (19,43)
Gender Male (%)	11 (55%)	4 (67%)	4 (33%)	3 (50%)	5 (42%)	1 (17%)	3 (50%)	3 (50%)	4 (67%)	27 (45%)
Race (%)^										
White	11 (55%)	5 (83%)	9 (75%)	0	7 (58%)	0	3 (50%)	2 (33%)	4 (67%)	30 (50%)
Asian	4 (20%)	1 (17%)	1 (8%)	6 (100%)	2 (17%)	6 (100%)	2 (33%)	1 (17%)	0	19 (32%)
Black or AA	2 (10%)	0	1 (8%)	0	1 (8%)	0	1 (17%)	3 (50 %)	2 (33%)	8 (13%)
Other	3 (15%)	0	1 (8%)	0	2 (17%)	0	0	0	0	3 (5%)
Mean Weight, kg (range)	71 (54,91)	76 (64,99)	75 (52,95)	64 (53, 79)	72 (54.102)	56 (45,69)	68 (56,86)	72 (53,83)	76 (67,82)	70 (45,102)

AA = African American
^ Some subjects selected more than 1 race and are included in classification "Other"

Safety Summary-Overall Population

- No serious adverse events or study discontinuation due to AEs
- AEs reported in 77% of ALN-TTRsc02 and 50% of placebo subjects; mostly mild (Table 2)
- Related AEs in 6 subjects (10%) on ALN-TTRsc02; all mild
  - 4 subjects with mild, transient AEs at the injection site
    - Injection site bruising (50 mg), injection site pain and erythema (200 mg), injection site pain (300 mg)
  - 2 other subjects with related AEs
    - Pruritus and cough (50 mg); nausea and fatigue (200 mg)
- 1 subject at 200 mg with transient ALT elevation >3xULN
  - Event was asymptomatic and not considered an AE by investigator
  - No concurrent changes in bilirubin or alkaline phosphatase
- No clinically significant changes in renal function or hematologic parameters, including platelets
- No clinically significant changes in ECG, vital signs or physical exam

Table 2: Adverse Events by Dose Level

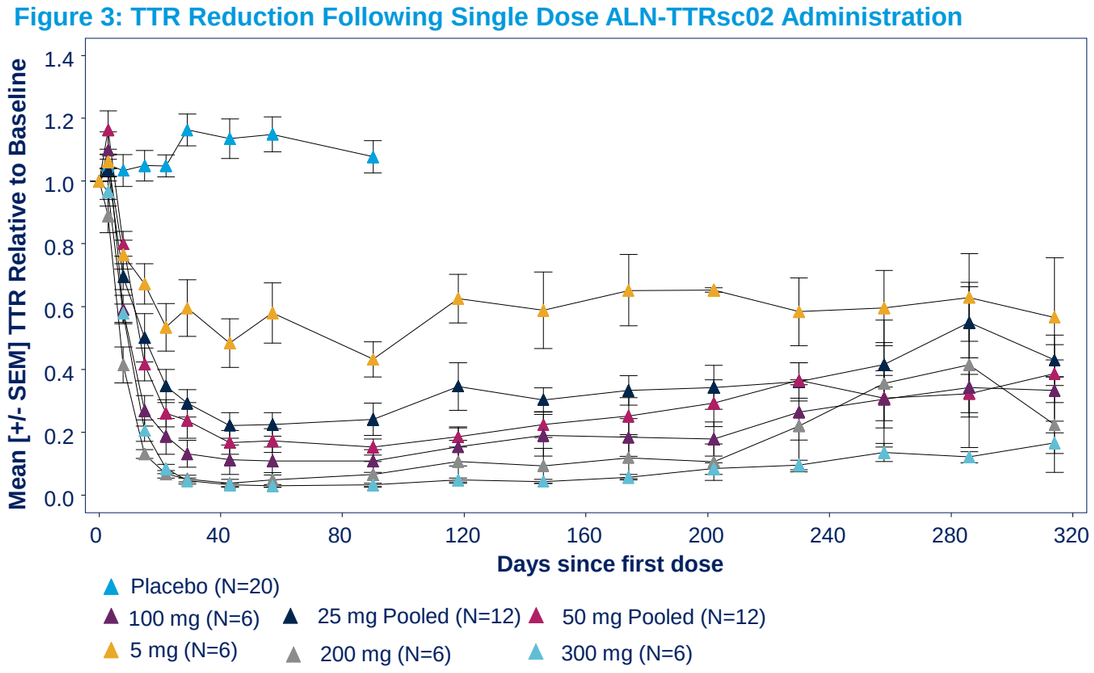
		ALN-TTRsc02^								
	Placebo* (n=20)	5 mg (n=6)	25 mg (n=12)	25 mg Japanese (n=6)	50 mg (n=12)	50 mg Japanese (n=6)	100 mg (n=6)	200 mg (n=6)	300 mg (n=6)	Total ALN-TTRsc02 (n=60)
Any AE (%)	10 (50%)	5 (83%)	10 (83%)	1 (17%)	11 (92%)	5 (83%)	4 (67%)	5 (83%)	5 (83%)	46 (77%)
Nasopharyngitis	6 (30%)	4 (67%)	8 (67%)	0	7 (58%)	4 (67%)	4 (67%)	1 (17%)	3 (50%)	31 (52%)
Headache	0	2 (33%)	2 (17%)	0	0	0	2 (33%)	2 (33%)	2 (33%)	10 (17%)
Diarrhea	0	1 (17%)	0	0	2 (17%)	0	0	1 (17%)	1 (17%)	5 (8%)
Nausea	0	1 (17%)	1 (8%)	0	0	0	0	3 (50%)	0	5 (8%)
Cough	0	0	1 (8%)	0	2 (17%)	1 (17%)	0	0	0	4 (7%)
Fatigue	0	1 (17%)	0	0	0	0	0	1 (17%)	1 (17%)	3 (5%)
Injection site pain	1 (5%)	0	0	0	0	0	0	2 (33%)	1 (17%)	3 (5%)

* Follow up through Day 90; ^ Follow up through Day 314

ALN-TTRsc02 Achieves Robust and Durable Serum TTR Knockdown (KD)

- Mean maximum TTR reduction ranged from 83% to 97% for ALN-TTRsc02 doses of 25 to 300 mg (Figure 3)
- Peak TTR KD and duration increased in a dose dependent manner
- Similar PD effect in Japanese cohorts (data not shown)

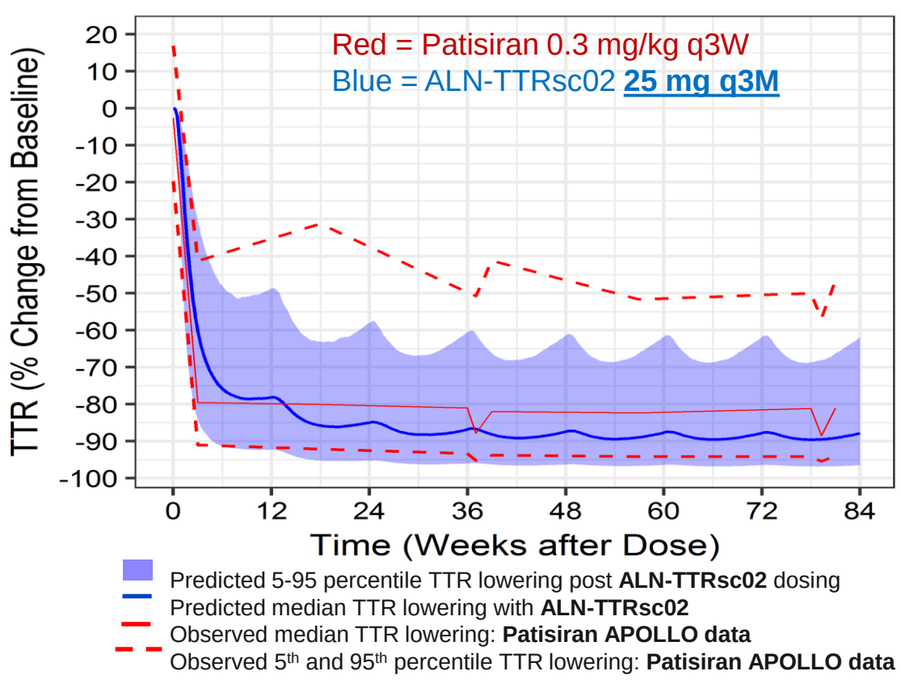
Figure 3: TTR Reduction Following Single Dose ALN-TTRsc02 Administration



Prediction of TTR KD Following Quarterly (Every 3 Months) Dosing of ALN-TTRsc02

- With a 25 mg dose of ALN-TTRsc02 every 3 months, model predicts peak and trough TTR KD of 88% and 90% compared to patisiran, with a peak and trough TTR KD of 81% and 88%, respectively (Figure 4)[14]
- Model predicts reduced inter-individual variability in TTR KD with ALN-TTRsc02 compared to patisiran
- Steady state TTR KD with ALN-TTRsc02 is stable with reduced peak-to-trough fluctuations over the dosing interval compared to patisiran[14]

Figure 4: Model Predicted TTR KD After a 25 Dose of ALN-TTRsc02 Every 3 Months Compared to Observed TTR KD with Patisiran Administration



q3M = quarterly dosing

Summary

- ALN-TTRsc02 was generally well tolerated with no serious adverse events reported and with no AEs leading to treatment discontinuation
- Single doses of ALN-TTRsc02 resulted in robust and durable TTR reduction
- Modelled dosing of 25 mg every 3 months expected to result in similar or better TTR KD compared to patisiran, an investigational RNAi therapeutic
- Targeting hepatic TTR production with ALN-TTRsc02 has the potential to offer quarterly subcutaneous treatment option for patients with ATTR amyloidosis and warrants continued development

Abbreviations: AE, adverse events; ECG, electrocardiogram; FDA, Federal Drug Administration; GI: gastrointestinal; NDA, new drug application; RNAi, RNA interference; SC, subcutaneous; TTR, transthyrethin; WT, wild type. References: 1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57; 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 3. Adams D et al. Neurology. 2015;85(8):675-682; 4. Damy T et al. J Cardiovasc Transl Res. 2015;8(2):117-127; 5. Hawkins PN et al. Ann Med. 2015;47(8):625-638; 6. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 7. Mariani LL et al. Ann Neurol. 2015;78(6):901-16; 8. Swiecicki PL, et al. Amyloid 2015;22(2):123-31; 9. Sattianayagam AJ, et al. Eur Heart J 2012;33;1120; 10. Gertz MA, et al. Mayo Clin Proc 1992;67(5):428-40; 11. Castaño A, et al. Heart Fail Rev 2015;20(2):163–78; 12. Pinney JH, et al. J Am Heart Assoc 2013;2:e000098; 13. Coelho T, et al. Curr Med Res Opin; 14. Adams, D. Orphanet J Rare Dis 2017, 12(Suppl 1):O9 – oral presentation EU ATTR ; 02 Nov; 17. Disclosures: Tracy Zimmermann, Verena Karsten, Clarida Martinez, Amy Chan, Yue Wang, Husain Attarwala, John Vest and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.