Design and Rationale of TRITON-PN, a Phase 3 Study to Evaluate the Efficacy of Nucresiran in Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy

TRITON-PN
HATTR-PN CLINICAL STUDY

Scan to View

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Conclusions

- Nucresiran is an investigational RNAi therapeutic with advanced target specificity that may provide greater clinical benefits and reduced treatment burden vs established standard of care in patients with ATTR through deeper, more sustained TTR knockdown, lower interpatient variability, and less frequent dosing
- TRITON-PN is a global, randomized, open-label, Phase 3 study that will investigate the efficacy, safety, PK, and PD profile of nucresiran in patients with ATTRv-PN
- TRITON-PN will assess the impact of nucresiran on disease-relevant outcomes in patients with ATTRv-PN, such as neurologic impairment, QoL, disability, and serum TTR reduction

Key takeaway

TRITON-PN is a global, randomized, open-label Phase 3 study, assessing the efficacy, safety, PK, and PD profile of nucresiran in patients with ATTRv-PN

Introduction

ATTRv Is a Progressive and Fatal Disease Caused by Pathogenic *TTR* Variants[1,2]

- Misfolded TTR accumulates as amyloid fibrils in multiple organs and tissues, including nerves, resulting in peripheral neuropathy[3]
- ATTRv has an aggressive course in which disease progression is associated with worsening symptom severity, decreased QoL, loss of physical function, and death[1–4]
- Early, targeted treatment of multisystem organ dysfunction is essential to reduce the burden and progression of ATTRv[3]

RNAi Therapeutics Silence the *TTR* Gene

- RNAi therapeutics reduce hepatic production of both variant and wild-type TTR at its source (**Figures 1 and 2**)
- Rapid TTR knockdown with RNAi therapeutics has been shown to improve outcomes for patients with ATTR with polyneuropathy or cardiomyopathy[3,5,6]
- More than 10,000 patients with ATTR have received RNAi therapeutics (patisiran or vutrisiran), some followed for up to 7 years, with more than 25,000 patient-years of treatment exposure as of October 2025[5–12]
- Deeper TTR knockdown offers the potential for further improving outcomes, as has been observed in other forms of amyloidosis[13,14]

Figure 1. Mode of Action of RNAi Therapeutics

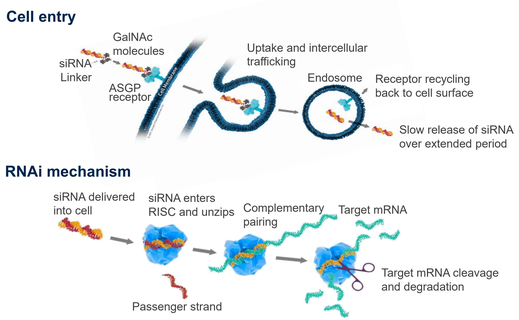
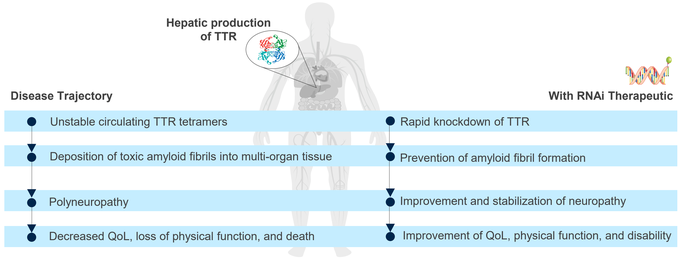


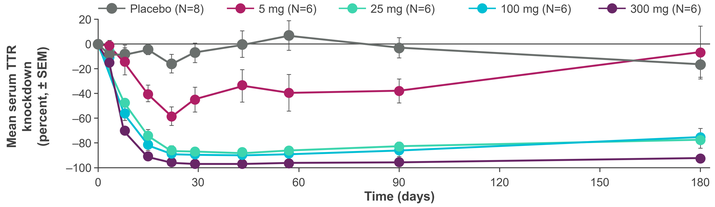
Figure 2. Therapeutic Hypothesis: Rapid, Deep, and Sustained Knockdown of TTR by Nucresiran Will Improve Outcomes and QoL for Patients with ATTRv-PN



Nucresiran Is an Investigational, Third-Generation RNAi Therapeutic

- Nucresiran utilizes IKARIA™, an advanced platform methodology, to identify sequences with improved potency and durability as well as target specificity
- Infrequent dosing every 6 months may also improve patient experience and long-term treatment compliance[15]
- In a Phase 1 study (NCT05661916), a single, 300 mg dose of nucresiran led to rapid >90% TTR knockdown[16]
  - TTR knockdown was maintained over 6 months with very low intersubject variability (**Figure 3**)
  - Encouraging safety and tolerability were observed; the majority of adverse events were mild in severity (none were considered treatment-related) and no safety signals, including hepatic signals, were identified

Figure 3. Nucresiran Phase 1 Results Demonstrate Rapid, Deep, and Sustained TTR Reduction

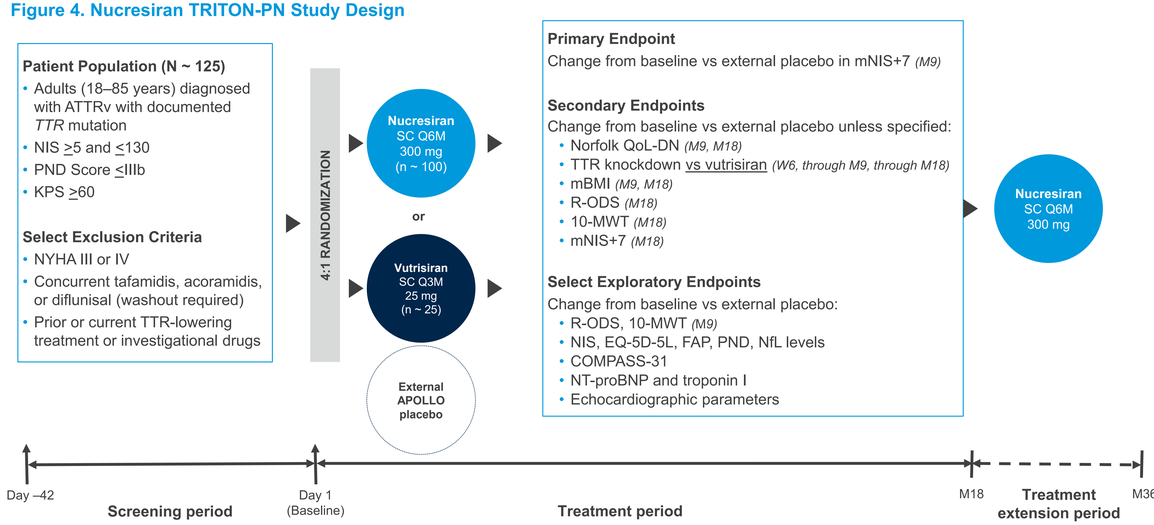


Methods

TRITON-PN is a Global, Randomized, Open-Label, Phase 3 Study to Investigate Nucresiran in Patients with ATTRv-PN

- TRITON-PN (NCT07223203) will randomize patients with ATTRv-PN 4:1 to receive nucresiran or vutrisiran, respectively (**Figure 4**)
- For primary, secondary, and exploratory clinical efficacy endpoints, nucresiran will be compared for superiority against the external placebo control group of the APOLLO study[10]
- For the secondary endpoints of serum TTR reduction, nucresiran will be compared for superiority against the in-study vutrisiran arm
- Upon completion of the 18-month treatment period, patients will be eligible to enter the 18-month treatment extension period

Figure 4. Nucresiran TRITON-PN Study Design



Study Status and Timeline

- The study design, including inclusion and exclusion criteria, have been finalized
- Enrollment of adult patients with ATTRv-PN is expected to begin in 2026

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Abbreviations: 10-MWT, 10-meter walk test; ASGP, asialoglycoprotein; ATTR, transthyretin amyloidosis; ATTRv, variant (hereditary) transthyretin amyloidosis; ATTRv-PN, variant (hereditary) transthyretin amyloidosis with polyneuropathy; COMPASS-31, Composite Autonomic Symptom Score-31; EQ-5D-5L, European Quality of Life-5 Dimensions 5-Levels; FAP, familial amyloidotic polyneuropathy; GalNAc, N-acetylgalactosamine; KPS, Karnofsky performance status; M, month; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment score +7; mRNA, messenger ribonucleic acid; NfL, neurofilament light chain; NIS, neuropathy impairment score; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamic; PK, pharmacokinetic; PND, polyneuropathy disability; Q3M, every 3 months; Q6M, every 6 months; QoL, quality of life; QoL-DN, Quality of Life-Diabetic Neuropathy; RISC, RNA-induced silencing complex; RNAi, RNA interference; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; SEM, standard error of the mean; siRNA, small interfering RNA; TTR, transthyretin; W, week.