TRITON-CM: A Phase 3 Study to Evaluate the Efficacy and Safety of Nucresiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

TRITON-CM
ATTR-CM CLINICAL STUDY

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Conclusions

- **TRITON-CM is a global, randomized, double-blind, event-driven Phase 3 CV outcomes study that will investigate the efficacy and safety of nucresiran in patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM)**
- **Nucresiran is an investigational RNAi therapeutic with advanced target specificity that is capable of rapid, deep, and durable knockdown of transthyretin (TTR) with low interpatient variability**
- **TRITON-CM will test the hypothesis that nucresiran can reduce all-cause mortality and recurrent CV events in patients with ATTR-CM**

Introduction

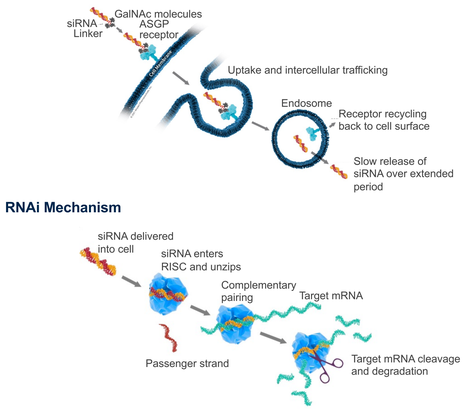
ATTR-CM

- Transthyretin amyloidosis (ATTR) is a progressive and fatal condition caused by deposition of misfolded TTR as amyloid fibrils in multiple tissues[1–3]
- ATTR is classified as either hereditary (hATTR) or wild-type (wtATTR), depending on the presence or absence of amyloidogenic *TTR* gene variants[1–4]
- Accumulation of wild-type or variant TTR amyloid fibrils in the heart leads to cardiomyopathy (ATTR-CM)[2,5]
- ATTR-CM is characterized by progressive heart failure, declines in functional status and quality of life, increased hospitalizations, and reduced survival[6,7]

RNA Interference (RNAi) Therapeutics

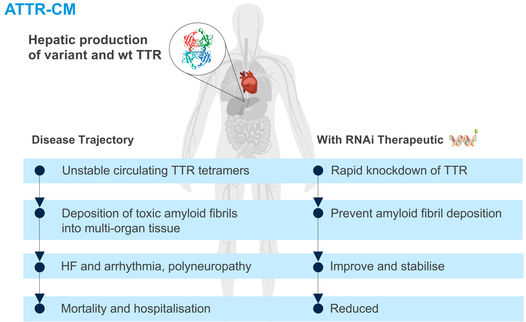
- RNAi therapeutics suppress the hepatic production of TTR by targeting wild-type and variant *TTR* mRNA for degradation (**Figures 1 and 2**)

Figure 1. Mode of Action of RNAi Therapeutics



- Rapid TTR knockdown with RNAi therapeutics improves outcomes for patients with ATTR with polyneuropathy or cardiomyopathy[8–10]
- Most recently, the HELIOS-B study showed that vutrisiran knockdown of TTR improved outcomes for patients with ATTR-CM across multiple domains, including reducing CV events and all-cause mortality and improving functional capacity and quality of life[10]
- The positive effects observed in HELIOS-B add to the growing evidence that RNAi-based therapeutics that knockdown TTR can improve clinical outcomes in ATTR-CM
- Greater TTR knockdown offers the potential for further improving outcomes, as has been observed in other forms of amyloidosis[11,12]

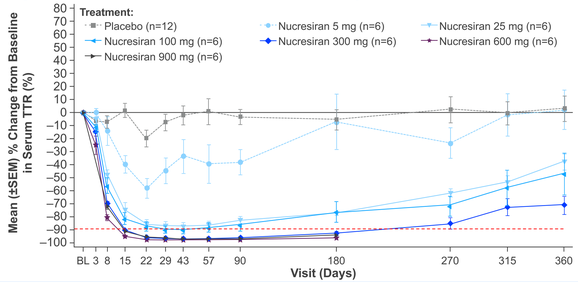
Figure 2. Therapeutic Hypothesis: Rapid and Deep TTR Knockdown by Nucresiran Will Improve Outcomes and Quality of Life for Patients with ATTR-CM



Nucresiran

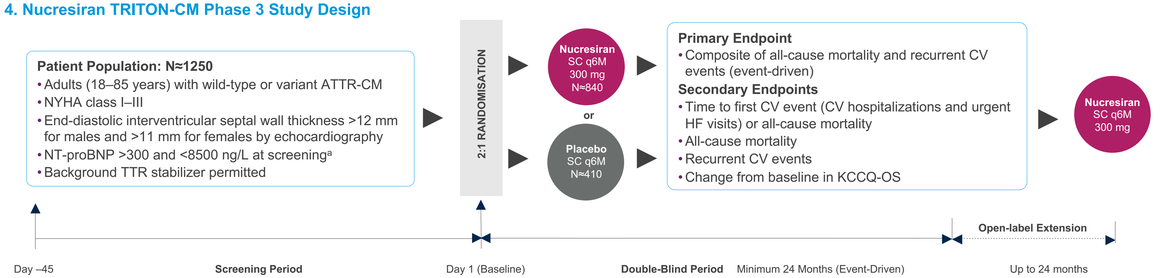
- Nucresiran is an investigational RNAi therapy for ATTR
- Nucresiran utilizes IKARIA™, an advanced platform methodology, to identify sequences with improved potency and durability as well as target specificity
- In a Phase 1 study (NCT05661916), a single, 300 mg dose of nucresiran led to rapid, >90% TTR knockdown by Day 15 and peak knockdown >96% by Day 29, which was maintained for over 6 months with very low intersubject variability[13] (**Figure 3**)
- Encouraging safety and tolerability were observed at all doses in the Phase 1 study
  - The majority of adverse events were mild in severity and none were considered related to treatment
  - No safety signals, including liver-related signals, were identified

Figure 3. TTR Knockdown in the Phase 1 Study of Nucresiran



Methods

Figure 4. Nucresiran TRITON-CM Phase 3 Study Design



Other Key Inclusion Criteria

- Medical history of HF with ≥1 prior hospitalization for HF **OR** clinical evidence[b] of HF that requires treatment with a diuretic
- Demonstration of ATTR cardiomyopathy by one of the following:
  - Documented TTR amyloid deposits in cardiac tissue regardless of MGUS status
  - In the absence of MGUS, ^{99m}Tc scintigraphy with Grade 2 or 3 cardiac uptake
  - In the presence of MGUS, documentation of TTR protein in noncardiac tissue **AND** Grade 2 or 3 cardiac uptake on ^{99m}Tc scintigraphy

Key Exclusion Criteria

- NYHA class IV HF; or NYHA class III heart failure **AND** ATTR Amyloidosis Disease Stage 3[c]
- Polyneuropathy Disability Score ≥IIIa at screening visit[d]
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2
- Non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease
- Received prior TTR-lowering therapy **OR** plan for or anticipate beginning treatment during screening or the first 24 months following randomization

[a]NT-proBNP >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation. [b]Manifested by signs and symptoms of volume overload or elevated intracardiac pressures. [c]Defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min.[13] [d]Requires cane or stick to walk or is wheelchair-bound due to polyneuropathy.

Study Treatments

- Patients will be randomized 2:1 to receive nucresiran 300 mg SC or placebo SC q6M for at least 24 months (**Figure 4**)
- After a minimum of 24 months and the double-blind period has ended OR after completing 5 years in the double-blind period, patients initially randomized to placebo will switch to nucresiran and all patients will receive open-label treatment with nucresiran for up to 24 months during the extension period

Exploratory and Pharmacokinetic/Pharmacodynamic (PK/PD) Endpoints

- Exploratory endpoints include the change from baseline in: cardiac biomarkers (NT-proBNP, troponin I), echocardiographic parameters, NAC stage, NYHA class, EuroQoL-5 Dimensions, neurofilament light chain, and oral diuretic intensification/initiation
- PK/PD endpoints include change from baseline in: serum TTR, plasma PK exposure, and the frequency and titers of anti-drug antibodies

Statistical Analysis

- The analysis timing is event-driven, requiring a prespecified number of primary composite endpoint events
- The composite endpoint of all-cause mortality and recurrent CV events will be analyzed by a modified Anderson–Gill model
- Time to first CV event or all-cause mortality, and time to death from any cause will be analyzed using a log-rank test; hazard ratio will be estimated using a Cox proportional hazards model
- Recurrent CV events will be analyzed using a negative binomial regression model; relative rate ratio will be generated
- Change from baseline in KCCQ-OS will be analyzed using a mixed-effects model of repeated measures approach

Study Status and Timeline

- The study design, including inclusion and exclusion criteria, have been finalized
- Enrolment of adult patients with ATTR-CM is expected to begin in 2025

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Abbreviations: ASGP, asialoglycoprotein; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GalNAc, N-Acetylgalactosamine; hATTR, hereditary ATTR; HCP, healthcare professional; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; MGUS, monoclonal gammopathy of undetermined significance; mRNA, messenger RNA; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamics; PK, pharmacokinetics; q6M, every 6 months; RISC, RNA-induced silencing complex; RNAi, RNA interference; SC, subcutaneous; SEM, standard error of the mean; siRNA, small interfering RNA; Tc, technetium; TTR, transthyretin; wt, wild-type; wtATTR, wild type-ATTR.