CLINICAL STUDY PROTOCOL
ALN-TTRSC02-003
DATED 12 FEBRUARY 2024

Protocol Title:	HELIOS-B: A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Short Title:	HELIOS-B: A Study to Evaluate Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy
Study Drug:	Vutrisiran (ALN-TTRSC02)
EU CT Number:	2023-508366-15
EudraCT Number:	2019-003153-28
IND Number:	141923
Protocol Date:	Original protocol: 22 August 2019 Amendment 1: 28 May 2020 Amendment 2: 18 February 2021 Amendment 3: 13 May 2022 Amendment 4: 22 March 2023 Amendment 5: 12 February 2024
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PPD Senior Director, Clinical Research

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTRSC02-003 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

HELIOS-B: A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Short Title

HELIOS-B: A Study to Evaluate Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

Study Drug

Vutrisiran (ALN- TTRSC02)

Phase

Phase 3

Study Center(s)

The study will be conducted at approximately 150 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of vutrisiran compared to placebo on reducing all-cause mortality and CV events	• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure [HF] visits) in the overall population • Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)
Secondary	
To evaluate the efficacy of vutrisiran compared with placebo treatment on: • Functional capacity • Patient-reported health status and health-related quality of life • All-cause mortality • Severity of clinical heart failure symptoms	The following secondary endpoints will be defined in both the overall population and the vutrisiran monotherapy subgroup: • Change from baseline in 6-MWT • Change from baseline in the KCCQ-OS • All-cause mortality • Change from baseline in NYHA Class

Objectives	Endpoints
Exploratory	
CCI	• CCI
Pharmacodynamics and Pharmacokinetics	
• To characterize the PD effect of vutrisiran on TTR • To characterize plasma PK of vutrisiran • To assess presence of antidrug antibodies (ADA) against vutrisiran	• Change from baseline in serum TTR levels • Plasma PK exposure parameters • Frequency and titers of ADA

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of AEs

Study Design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vutrisiran in approximately 600 patients with ATTR amyloidosis with cardiomyopathy. Approximately 20% of the study population is anticipated to have hereditary ATTR (hATTR) and 80% wild-type ATTR (wtATTR) amyloidosis with cardiomyopathy.

At baseline, patients are either:

- Tafamidis-naïve (see inclusion criterion #4 for definition); or
- Currently receiving tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication in the country of use).

The study consists of 4 periods (Figure 1):

1. **Screening Period:** Up to 45 days during which patients will undergo screening assessments to determine eligibility.
2. **Double-Blind Period (DB Period):**
   - At the start of the DB Period (on Day 1), eligible patients will be randomized in a 1:1 ratio to receive blinded doses of 25 mg of vutrisiran or placebo administered as a subcutaneous (SC) injection once every 3 months (q3M; every 12 weeks ±7 days) for up to 36 months.
     - In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their DB Period and Follow-up Period (see below).
   - Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1).
   - An individual patient's DB Period visits will end after they complete their Month 36 visit, or 30 months after the last patient is randomized, whichever comes first. As such, a patient's last visit during the DB Period may vary from 30 to 36 months after enrollment.
     - The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the Open-Label Extension (OLE) Period will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 33 (Week 144), Day 1 in the OLE Period will occur 156 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 36 (Week 156), Day 1 in the OLE Period will occur on the same day (since study drug is not administered as part of the Month 36 DB visit).
     - The period of DB exposure, defined as the duration prior to first exposure to open-label treatment, will be 144 to 156 weeks (33 to 36 months).

- The primary analysis will be conducted after the last patient has completed the period of DB exposure or otherwise discontinued.

3. **Open-Label Treatment Extension (OLE) Period**

The study has been amended (Amendment 4) to include an OLE Period in lieu of the Open-Label Randomized Treatment Extension Period (previously introduced with Amendment 3). In the OLE Period, all patients will receive the 25 mg q3M vutrisiran regimen.

- Upon entry into the OLE, all eligible patients will transition to receive open-label doses of 25 mg q3M vutrisiran administered as SC injections.
- Patients initially randomized to CCI (under Amendment 3) will transition to receive open-label doses of 25 mg q3M vutrisiran administered as SC injections at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran). Patients initially randomized to 25 mg q3M vutrisiran (under Amendment 3) will continue with the 25 mg q3M regimen.
  - In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their OLE Period and Follow-up Period (see below).
- All patients will undergo assessments as outlined in the Schedule of Assessments for the OLE Period (Table 2).

Note: Patients who do not complete the DB Period may not participate in the OLE Period. Consent must be signed before any procedures are performed in the OLE Period (Table 2).

4. **Follow-Up Period after the last dose of vutrisiran on study:**

- Following completion of the OLE Period (or completion of the DB Period for patients who do not continue into the OLE Period; or their last dose of study drug for patients who discontinue study drug early), patients will commence follow-up visits every 12 weeks for the durations outlined below.
- Prior to unblinding of their treatment from the DB Period, the duration of the Follow-up Period for a patient will be 1 year from their last dose of study drug. For women of child-bearing potential, the duration of the Follow-up Period will be 18 months from their last dose of study drug. Patients will continue vitamin A supplementation during their Follow-up Period.
- After unblinding, all patients who were on placebo, and patients who received vutrisiran whose serum TTR level has returned to ≥80% of baseline or who have completed the Follow-up Period, whichever comes first, may discontinue further follow-up and stop taking vitamin A. Baseline is defined as the last value prior to first vutrisiran dose (ie, prior to the first DB dose for vutrisiran patients in DB Period and prior to the first OLE dose for placebo patients). Patients will be followed for a minimum period as listed below during the Follow-up Period based on the treatment regimen received:
  - All patients whose last dose of study drug was 25 mg vutrisiran/placebo during DB Period or 25 mg vutrisiran during the OLE Period will be followed for a minimum of 90 days after their last dose of study drug.

  - Patients whose last dose of study drug was CCI vutrisiran regimen (under Amendment 3) will be followed for a minimum of CCI after their last dose of study drug during Follow-up Period.

- For any patient who starts a TTR lowering treatment as part of clinical care, and has completed a minimum of 90 or CCI (depending on vutrisiran treatment regimen) of safety follow-up since their last dose of study drug, further follow-up will be discontinued.
- Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1 and Table 2).

Patients may receive vutrisiran on the study until the end of the OLE Period or until one of the following occurs: 1) they meet any of the study discontinuation criteria; 2) vutrisiran is commercially available in the patient's country of residence and vutrisiran is accessible to the patient and the patient has completed their OLE Month 12 Visit; or 3) the vutrisiran development program is discontinued.

Study drug dosing may be allowed outside of the study center (eg, the patient's home) during the DB Period or OLE Period under certain circumstances as specified in Section 5.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in Section 6.

Number of Planned Patients

The planned enrollment for this study is 600 patients.

Diagnosis and Main Eligibility Criteria

This study will enroll adults (≥18 years of age) with a documented diagnosis of ATTR amyloidosis with cardiomyopathy, including those with hATTR or wtATTR amyloidosis and a medical history of HF with at least 1 prior hospitalization for HF.

Study Drug, Dose, and Mode of Administration

Vutrisiran is a subcutaneously (SC) administered *N*-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA), which targets liver-expressed messenger RNA (mRNA) for transthyretin (TTR).

Study drug (vutrisiran or placebo) will be administered using a pre-filled syringe and a needle safety device. The outside of the pre-filled syringe barrel will be masked in such a way as to hide the identity of the study drug contained within.

Starting on Day 1 of the DB Period, patients will receive 25 mg of vutrisiran or placebo administered as a SC injection once every 3 months (q3M; every 12 weeks; ±7 days) for up to 36 months.

Under Amendment 4, all patients in the OLE Period will receive SC injections of vutrisiran 25 mg q3M (every 12 weeks ±7 days) for up to 2 years; patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).

The first dose of study drug should be administered in the clinic on Day 1 of the DB Period (placebo or vutrisiran 25 mg) and Day 1 of the OLE Period (vutrisiran 25 mg). If a patient has tolerated at least 1 dose of study drug in the clinic, subsequent dosing for the remainder of that period may be administered outside the study center (eg, the patient's home) at all other timepoints where allowed by applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare

professional, with oversight by the Investigator. If the patient is unable to come to the study center, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, q3M regimens of study drug (placebo or 25 mg vutrisiran) may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on study drug administration. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.

Reference Treatment, Dose, and Mode of Administration

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration), which will be administered at the same dosing interval and volume as the study drug.

Duration of Treatment and Study Participation

The planned duration of treatment for each patient is up to approximately 60 months (approximately 5 years), inclusive of the 30 to 36-month DB Period and a 24-month OLE Period.

The estimated total time on study for each patient is up to approximately 6 years, including a Screening Period of up to 45 days, a DB Period of up to 36 months, an OLE Period of up to 24 months, and a Follow-up Period of up to 1 year after the last dose of study drug (18 months for women of child-bearing potential).

Statistical Methods

For the DB Period, randomization (1:1) will be stratified by: 1) baseline tafamidis use (yes versus no); 2) ATTR disease type (hATTR versus wtATTR amyloidosis with cardiomyopathy); and 3) New York Heart Association (NYHA) Class I or II and age <75 years versus all other.

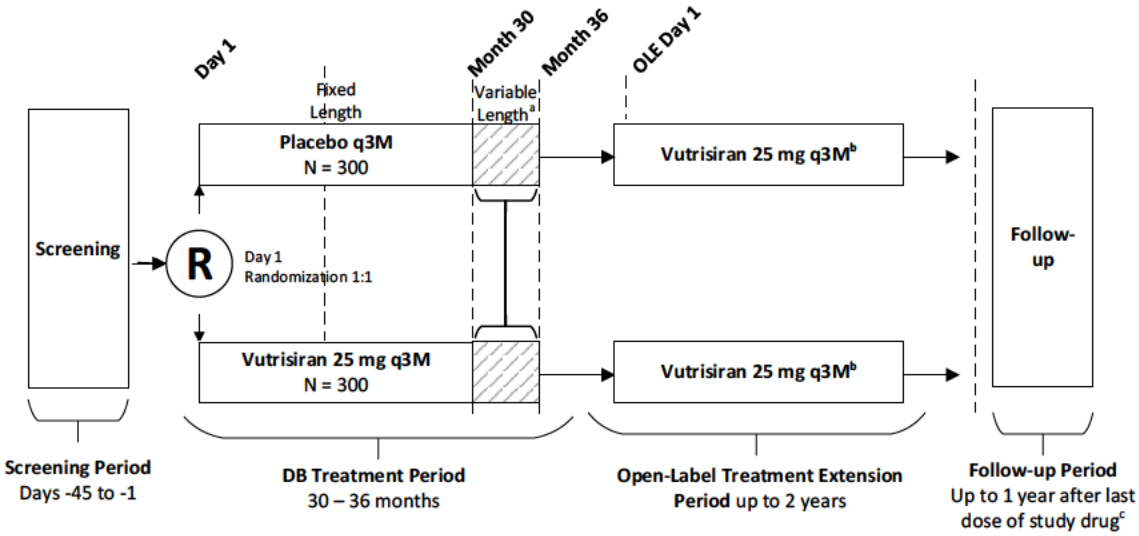
The overall Type I error rate for the two primary endpoints and the secondary endpoints will be controlled at a 2-sided 0.05 significance level using a prespecified multiplicity testing procedure. The two primary endpoints will be tested at a 2-sided 0.05 significance level using the Hochberg testing procedure, ie, if the larger of two p-values is ≤0.05, both null hypotheses will be rejected; otherwise, the smaller of the two p-values will have to be ≤0.025 for the corresponding null hypothesis to be rejected. If both primary endpoints are statistically significant, the full alpha of 0.05 will be passed to test the secondary endpoints defined in both the overall population and the vutrisiran monotherapy subgroup using a pre-specified multiple testing procedure described in the statistical analysis plan (SAP). If one or both of the primary endpoints are not statistically significant, secondary endpoint tests will be performed and the results summarized, but statistical significance will not be inferred.

CCI [redacted]

Patients who undergo heart transplantation and/or left ventricular assist device placement will be treated in the same manner as death in the primary analyses of the primary endpoints and mortality-related endpoint(s).

Safety data will be summarized descriptively.

Figure 1: Study Design



Abbreviations: DB=double-blind; OLE=open-label treatment extension; q3M=every 3 months; SC=subcutaneous.

[a] An individual patient's DB Period visits will end after they complete their Month 36 visit, or 30 months after the last patient is randomized, whichever comes first. As such, a patient's last visit during the DB Period may vary from 30 to 36 months after enrollment (refer to Section 3.1).

[b] The dosing schedule under Amendment 4 is 25 mg vutrisiran every 12 weeks. Upon entry into the OLE Period (OLE Day 1), all eligible patients will receive open-label doses of 25 mg q3M vutrisiran administered as SC injections. Patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).

[c] Following completion of the OLE Period (or completion of the DB Period for patients who do not continue into the OLE Period; or their last dose of vutrisiran for patients who discontinue study drug early), patients will commence follow-up visits as outlined in Section 3.1. For women of child-bearing potential, the duration of the Follow-up Period will be up to 18 months from their last dose of study drug.

Table 1: Schedule of Assessments: Double-Blind (DB) and Follow-Up Periods

Study Week (Month)			Double-Blind Period																	
± Visit Window (Days)	See Table/Section for Details	Screening (D-45 to -1)	W 1 Day 1	W 6 ±7	W 12 (M 3) ±7	W 24 (M 6) ±7	W 36 ±7	W 48 (M 12) ±7	W 60 ±7	W 72 (M 18) ±7	W 84 ±7	W 96 ±7	W 108 (M 24) ±7	W 120 ±7	W 132 (M 30)[a] ±7	W 144[a] ±7	W 156 (M 36)[a] ±7	Pre-tafamidis Drop-in Visit	Early Treatment Discon Visit	Follow-up Period Visits Every 12 Weeks[b] ±10	Early Study Discon Visit
Screening Procedures																					
Informed Consent Form	6.1	X																			
Medical Records Release Form	6.1	X																			
Inclusion/Exclusion Criteria	4.1	X																			
Demographics / Medical History	6.1; Day 1 medical history includes change from Screening	X	X																		
Monoclonal Gammopathy Assessment	Table 6; 6.5.5.1; If available, documented local results may be used to fulfill this inclusion requirement	X																			
FSH Testing	Table 6; 6.5.5.3 To confirm post-menopausal status if applicable	X																			
CCI																					
Efficacy Assessments [c]																					
Vital Status check	6.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6-MWT	6.2.3	X	X			X		X		X			X		X			X	X		X
KCCQ-OS	6.2.4		X			X		X		X			X		X			X	X		X
CCI																					
NYHA Class	6.2.5.4	X				X		X		X			X		X			X	X		X
CCI																					

Table 1: Schedule of Assessments: Double-Blind (DB) and Follow-Up Periods

Study Week (Month)			Double-Blind Period																	
± Visit Window (Days)	See Table/Section for Details	Screening (D-45 to -1)	W 1 Day 1	W 6 ±7	W 12 (M 3) ±7	W 24 (M 6) ±7	W 36 ±7	W 48 (M 12) ±7	W 60 ±7	W 72 (M 18) ±7	W 84 ±7	W 96 ±7	W 108 (M 24) ±7	W 120 ±7	W 132 (M 30)[a] ±7	W 144[a] ±7	W 156 (M 36)[a] ±7	Pre-tafamidis Drop-in Visit	Early Treatment Discon Visit	Follow-up Period Visits Every 12 Weeks[b] ±10	Early Study Discon Visit
CCI																					
Safety Assessments [c]																					
Vital Signs	6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	6.5.2	X						X					X								
Weight	6.5.2	X				X		X		X			X		X		X	X	X		X
Physical Examination (symptom-directed unless noted as full)	6.5.3	Full	X		X	X	X	X		X			X	X	X	X	X	X	X		X
CCI																					
Serum Chemistry Hematology, Urinalysis, Coagulation	Table 6; 6.5.5	X	X	X		X		X		X			X		X		X	X	X	X	X
Additional Chemistry Assessments (CRP and venous lactate)	Table 6; 6.5.5		X					X							X						
LFTs	Table 6; 6.5.5 See Table 7 for additional LFTs indicated for patients with abnormalities listed in 5.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatic Tests	Table 6; 6.5.5	X																			
Immunogenicity (ADA)	Table 6; 6.5.5.2		X		X	X	X	X					X					X		X	
Pregnancy Test	Table 6; 6.5.5.3	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Review/Record Hospitalizations, Urgent HF Visits, and Procedures		----------Continuous----------																			
Adverse Events	6.5.6	----------Continuous----------																			
Concomitant Medications	5.4	----------Continuous----------																			
Check for Concomitant Tafamidis use	5.4.1	----------Continuous----------																			

Table 1: Schedule of Assessments: Double-Blind (DB) and Follow-Up Periods

Study Week (Month)			Double-Blind Period																	
± Visit Window (Days)	See Table/Section for Details	Screening (D-45 to -1)	W 1 Day 1	W 6 ±7	W 12 (M 3) ±7	W 24 (M 6) ±7	W 36 ±7	W 48 (M 12) ±7	W 60 ±7	W 72 (M 18) ±7	W 84 ±7	W 96 ±7	W 108 (M 24) ±7	W 120 ±7	W 132 (M 30)[a] ±7	W 144[a] ±7	W 156 (M 36)[a] ±7	Pre-tafamidis Drop-in Visit	Early Treatment Discon Visit	Follow-up Period Visits Every 12 Weeks[b] ±10	Early Study Discon Visit
Pharmacodynamic Assessments [c]																					
TTR Protein	6.3		X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	
Vitamin A levels	6.3		X					X									X				
CCI [redacted]																					
Pharmacokinetic Assessments																					
Plasma PK	6.4; See Table 3 for detailed predose and postdose timepoints		X				X			X					X						
Study Drug Administration																					
Randomization	3.5; Window: -1 day prior to Day 1		X																		
Study Drug Administration	5.2.2; to be administered after efficacy, safety, and PD assessments during applicable visits		X		X	X	X	X	X	X	X	X	X	X	X	X					

Abbreviations: 6-MWT=6 minute walk test; ADA=antidrug antibodies; AE=adverse event; ATTR=amyloid transthyretin; CRP=C-reactive protein; D=day; DB=Double-blind; Discon=discontinuation; CCI [redacted]; FSH=follicle-stimulating hormone; HF=heart failure; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; CCI [redacted]; LFT=liver function test; M=month; CCI [redacted]; NYHA=New York Heart Association; OLE=open-label extension; PK=pharmacokinetics; PD=pharmacodynamics; CCI [redacted]; QoL-DN=Quality of Life-Diabetic Neuropathy; Tripl=triplicate; TTR=transthyretin; W=week

Notes:

- The investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site or any new trial participant to comply with the protocol given Coronavirus disease 2019 (COVID-19) pandemic limitations.
- Dosing may be allowed outside of the study center (eg, the patient's home) under certain circumstances as specified in Section 5.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in Section 6.
- Patients who discontinue study drug should not be automatically removed from study and be encouraged to remain on the study to complete the remaining assessments as outlined in Section 4.3.1.

- Dosing decisions may be made based on LFT results (Table 6) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used.
- When applicable, pregnancy test results must be known prior to dosing.
- When scheduled at the same time points and where feasible, the assessments of vital signs and CCI should be performed before physical examinations, and blood sample collections.
- In situations where a study visit is unable to be completed at the site (eg, due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug), efficacy, safety, and other assessments may be completed up to 3 months after the time point (ie, up to Study Month 9, Month 15, Month 21, Month 27, or Month 33, respectively) after consultation with the Medical Monitor.

[a] The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the OLE Period will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 33 (Week 144), Day 1 in the OLE Period will occur 156 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 36 (Week 156), Day 1 in the OLE Period will occur on the same day (since study drug is not administered as part of the Month 36 DB visit).

[b] Patients will only enter the Follow-up Period after their last dose of study drug in the DB Period if not continuing into the OLE Period.

[c] When performed on dosing days, the 6-MWT, the KCCQ, safety, and PD assessments will be performed prior to study drug administration. All other efficacy assessments only need to be performed prior to study drug administration on Day 1 of the DB Period and Day 1 of the OLE Period.

Table 2: Schedule of Assessments: Open-Label Treatment Extension (OLE) and Follow-Up Periods

Study Week (Month)		OLE Day 1[a]	OLE W 6	OLE W 12 (M 3)	OLE W 24 (M 6)	OLE W 36	OLE W 48 (M 12)	OLE W 60	OLE W 72 (M 18)	OLE W 84	OLE W 96 (M 24)	Pre-tafamidis Drop-in Visit	Early Treatment Discon Visit	Follow-up Period Visits Every 12 Weeks	Early Study Discon Visit
± Visit Window (Days)	See Table/Section for Details	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			±10	
Informed consent	6.1	X													
Efficacy Assessments[b]															
Vital Status check	6.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KCCQ-OS	6.2.4	X			X		X		X		X	X	X		X
CCI															
NYHA Class	6.2.5.4	X			X		X		X		X	X	X		X
CCI															
Safety Assessments															
Vital Signs	6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	6.5.2	X					X								
Weight	6.5.2	X			X		X		X			X	X		X
Physical Examination (symptom-directed)	6.5.3	X		X	X	X	X		X			X	X		X
CCI															
Serum Chemistry Hematology, Urinalysis, Coagulation	Table 6; 6.5.5	X	X		X		X		X		X	X	X	X	X

Table 2: Schedule of Assessments: Open-Label Treatment Extension (OLE) and Follow-Up Periods

Study Week (Month)		OLE Day 1[a]	OLE W 6	OLE W 12 (M 3)	OLE W 24 (M 6)	OLE W 36	OLE W 48 (M 12)	OLE W 60	OLE W 72 (M 18)	OLE W 84	OLE W 96 (M 24)	Pre-tafamidis Drop-in Visit	Early Treatment Discon Visit	Follow-up Period Visits Every 12 Weeks	Early Study Discon Visit
± Visit Window (Days)	See Table/Section for Details	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			±10	
LFTs	Table 6; 6.5.5 See Table 7 for additional LFTs indicated for patients with abnormalities listed in 5.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ADA)	Table 6; 6.5.5.2	X		X	X		X		X			X		X	
Pregnancy Test	Table 6; 6.5.5.3	X		X[c]	X	X[c]	X	X[c]	X	X[c]	X	X	X		X
Review/Record Hospitalizations, Urgent HF Visits, and Procedures		----------Continuous----------													
Adverse Events	6.5.6	----------Continuous----------													
Concomitant Medications	5.4	----------Continuous----------													
Check for Concomitant Tafamidis use	5.4.1	----------Continuous----------													
Pharmacodynamic Assessments [b]															
TTR Protein	6.3	X	X	X	X	X	X	X	X	X	X	X		X	
Vitamin A levels	6.3	X					X				X				
CCI															
Pharmacokinetic Assessments															
Plasma PK	6.4; See Table 3 for detailed predose and postdose timepoints	X													

Table 2: Schedule of Assessments: Open-Label Treatment Extension (OLE) and Follow-Up Periods

Study Week (Month)		OLE Day 1[a]	OLE W 6	OLE W 12 (M 3)	OLE W 24 (M 6)	OLE W 36	OLE W 48 (M 12)	OLE W 60	OLE W 72 (M 18)	OLE W 84	OLE W 96 (M 24)	Pre-tafamidis Drop-in Visit	Early Treatment Discon Visit	Follow-up Period Visits Every 12 Weeks	Early Study Discon Visit
± Visit Window (Days)	See Table/Section for Details	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			±10	
Study Drug Administration															
Administration of Vutrisiran 25 mg q3M[d]	5.2.2; to be administered after efficacy, safety, and PD assessments during applicable visits	X		X	X	X	X	X	X	X					

Abbreviations: ADA=antidrug antibodies; AE=adverse event; ATTR=amyloid transthyretin; CRP=C-reactive protein; D=day; DB=Double-blind; Discon=discontinuation; CCI ; FSH=follicle-stimulating hormone; HF=heart failure; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; CCI ; LFT=liver function test; M=month; CCI CCI NYHA=New York Heart Association; OLE=open-label extension; PK=pharmacokinetics; PD=pharmacodynamics; CCI ; q3M=once every 3 months; QoL-DN=Quality of Life-Diabetic Neuropathy; SC=subcutaneous; TTR=transthyretin; W=week

Notes:

- **For patients enrolled under Amendment 3, the visit schedule remains the same following implementation of Amendment 4, with no changes to the visit weeks noted in Table 2. For example, if Amendment 4 was implemented after a patient had completed Week 24 under Amendment 3, their first visit under Amendment 4 will be Week 36.**
- **The dosing schedule under Amendment 4 is 25 mg vutrisiran every 12 weeks; however, patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).**
- The investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site or any new trial participant to comply with the protocol given Coronavirus disease 2019 (COVID-19) pandemic limitations.
- Dosing may be allowed outside of the study center (eg, the patient's home) under certain circumstances as specified in Section 5.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in Section 6.
- Patients who discontinue study drug should not be automatically removed from study and be encouraged to remain on the study to complete the remaining assessments as outlined in Section 4.3.1.
- Dosing decisions may be made based on LFT results (Table 6) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used.
- When applicable, pregnancy test results must be known prior to dosing.
- When scheduled at the same time points and where feasible, the assessments of vital signs and CCI should be performed before physical examinations, and blood sample collections.

- In situations where a study visit is unable to be completed at the site (eg, due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug), efficacy, safety, and other assessments may be completed up to 3 months after the time point (ie, up to OLE Month 9, OLE Month 15, OLE Month 21, or OLE Month 27, respectively) after consultation with the Medical Monitor.

[a] For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the OLE Period will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 33 (Week 144), Day 1 in the OLE Period will occur 156 weeks (±7 days) after enrollment in the DB Period. For patients who reach the Month 36 (Week 156) visit of the DB Period prior to the end of the DB Period for the study, this visit will take place on the same day as the Day 1 visit of the OLE Period. When this occurs, patients should complete the Scheduled Assessments for both the Month 36 visit of the DB Period and the Day 1 visit of the OLE Period. However, where these visits take place on the same day, assessments do not need to be repeated twice on the same day (ie, if an assessment is listed for both the Month 36 visit of the DB Period and the Day 1 visit of the OLE Period, the assessment can be performed once). An informed consent form that has been approved by the appropriate Institutional Review Board /Independent Ethics Committee must be signed by the patient before any procedures are performed in the OLE Period.

[b] When performed on dosing days, the KCCQ, safety, and PD assessments will be performed prior to study drug administration. All other efficacy assessments only need to be performed prior to study drug administration on Day 1 of the DB Period and Day 1 of the OLE Period.

[c] Only females of child-bearing potential.

[d] The dosing schedule under Amendment 4 is 25 mg vutrisiran every 12 weeks. Upon entry into the OLE Period (OLE Day 1), all eligible patients will receive open-label doses of 25 mg q3M vutrisiran administered as SC injections. Patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).

Table 3: Pharmacokinetic Time Points for the Double-blind (DB) Period

Study Day	Sampling Time (hh:mm)	Blood PK Sample
Day 1, Week 36, Week 72 (Month 18), and Week 132 (Month 30)	Predose (within 60 minutes before dosing)	X
	04:00 (±30 minutes) after dosing	X

Abbreviations: hh=hours; mm=minutes; PK=pharmacokinetics
Notes: The hour (±range) indicate sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.

Table 4: Pharmacokinetic Time Points for the Open-label Treatment Extension (OLE) Period

Study Day	Sampling Time (hh:mm)	Blood PK Sample
OLE Day 1	03:00 (±30 minutes) after dosing	X
	06:00 (±30 minutes) after dosing	X

Abbreviations: hh=hours; mm=minutes; OLE=open-label extension; PK=pharmacokinetics.
Notes: The hour (±range) indicate sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. See Section 6.4 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6-MWT	6-minute walk test
^{99m}Tc	Technetium
ADA	Antidrug antibody
AE	Adverse event
ALN-65492	Drug substance in vutrisiran (siRNA targeting TTR mRNA)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APOLLO	ALN-TTR02-004 pivotal Phase 3 study of patisiran in patients with hATTR amyloidosis with polyneuropathy
APOLLO-B	ALN-TTR02-011 Phase 3 study of patisiran in patients with ATTR amyloidosis with cardiomyopathy
ASGPR	Asialoglycoprotein receptor
AST	Aspartate aminotransferase
ATTR	Amyloid transthyretin
ATTR-ACT	Phase 3 study of tafamidis in patients with ATTR amyloidosis with cardiomyopathy
BUN	Blood urea nitrogen
CEC	Clinical Events Committee
CHF	Congestive heart failure
COVID-19	Coronavirus disease 2019
CV	Cardiovascular
CT	Computed tomography
DB	Double-blind
DMC	Data Monitoring Committee
DPD-Tc	^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid
CCI	[redacted]
eCRF	Electronic case report form
CCI	CCI [redacted]
ELISA	Enzyme-linked immunosorbent assay
ESC	Enhanced stabilization chemistry
EU	European Union
FAS	Full Analysis Set

Abbreviation	Definition
FSH	Follicle-stimulating hormone
GalNAc	N-acetyl galactosamine containing ligand
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
hATTR	Hereditary ATTR
HAV	Hepatitis A virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HBc	Hepatitis B virus core
HBsAg	Hepatitis B virus surface antigen
HMDP	^{99}Tc-hydroxymethylene diphosphonate
HELIOS-A	ALN-TTRSC02-002 Phase 3 study of vutrisiran in patients with hATTR amyloidosis with peripheral neuropathy
HELIOS-B	ALN-TTRSC02-003 Phase 3 study of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy (focus of this protocol)
HF	Heart failure
HHV-6	Human herpes virus 6
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFE	Immunofixation Electrophoresis
IgG	Immunoglobulin G antibody
IgM	Immunoglobulin M antibody
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection-site reaction
IV	Intravenous(ly)
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	KCCQ Overall Summary
CCI	[redacted]

Abbreviation	Definition
LFT	Liver function test
LNP	Lipid nanoparticle
LV	Left ventricular
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of undetermined significance
MMRM	Mixed-effects model repeated measures
mNIS+7	Modified Neurologic Impairment Score +7
MRI	Magnetic resonance imagery
mRNA	Messenger RNA
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
NYHA	New York Heart Association
OLE	Open-Label Extension
PC	Product complaint
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetic
CCI [redacted]	[redacted]
PPS	Per-Protocol Analysis Set
PT	Preferred term
PYP-Tc	^{99m}Tc-pyrophosphate
q3w	Once every 3 weeks
q3M	Once every 3 months
CCI [redacted]	CCI [redacted]
RBC	Red blood cell
RBP	Retinol binding protein
RNA	Ribonucleic acid
RNAi	RNA interference
RTE	Randomized Treatment Extension
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SC	Subcutaneous
CCI [redacted]	[redacted]
siRNA	Small interfering RNA
SLA	Soluble liver antigen
SMQ	Standardized MedDRA Query
SOC	System organ class
SPEP	Serum Protein Electrophoresis
SUSAR	Suspected unexpected serious adverse reactions
TTR	Transthyretin
ULN	Upper limit of normal
UPEP	Urine Protein Electrophoresis
US	United States
wt	Wild-type
wtATTR	Wild-type ATTR

1. INTRODUCTION

Refer to the vutrisiran Investigator's Brochure (IB) for a detailed overview of transthyretin (TTR)-mediated amyloidosis (ATTR amyloidosis), current treatments, and the clinical development program for vutrisiran.

1.1. Disease Overview

ATTR amyloidosis is a rare, serious, life-threatening, multisystemic disease encompassing hereditary ATTR (hATTR) amyloidosis and wild-type ATTR (wtATTR) amyloidosis, which result from either hereditary (genetic mutation) or nonhereditary (aging) causes, respectively.

TTR, also known as prealbumin, is a tetrameric protein produced by hepatocytes, the choroid plexus, and retina.[Liz 2010] More than 95% of TTR in the circulation is derived from the liver. The primary physiological role of TTR is to serve as a carrier of retinol (also known as vitamin A), which involves TTR binding to the retinol binding protein (RBP): vitamin A complex. However, there is evidence to suggest that vitamin A transport and tissue uptake can occur in the absence of circulating RBP.[Biesalski 1999; Episkopou 1993]

There are over 120 reported TTR genetic mutations associated with hATTR amyloidosis.[Ando 2013; Connors 2003] These inherited mutations in the TTR gene lead to destabilization of the tetrameric protein and disassociation of the TTR subunits into dimers and individual mutant and wild-type (wt) monomers, which subsequently misfold and form amyloid fibrils and plaques in the extracellular space of various tissues.[Hou 2007] Normal, nonmutant wtTTR alone can also be amyloidogenic; this is the basis for the nonhereditary, wtATTR amyloidosis. This is a progressive disease typically seen in patients older than 70 years and is predominantly seen in men.[Westermark 2003] In both hATTR and wtATTR amyloidosis, deposition of TTR amyloid fibrils in various organs results in progressive, chronically debilitating morbidity and mortality. The most common manifestations of ATTR amyloidosis are cardiomyopathy (ie, ATTR amyloidosis with cardiomyopathy) and polyneuropathy (ie, ATTR amyloidosis with polyneuropathy).

In both hereditary and wt disease, cardiac infiltration of the extracellular matrix by TTR amyloid fibrils leads to a progressive increase of ventricular wall thickness and a marked increase in chamber stiffness, resulting in impaired diastolic function. Systolic function is also impaired, typically reflected by abnormal longitudinal strain despite a normal ejection fraction, which is often preserved until late stages of the disease.[Castano 2015; Dungu 2012; Mohty 2013; Ruberg 2012b] Cardiac infiltration by amyloid can also lead to conduction disturbances and arrhythmias. [Adams 2016; Ando 2013; Benson 2007; Connors 2004] ATTR amyloidosis patients with symptomatic heart failure (HF) experience rapid progression of their cardiomyopathy. Based on natural history data, patients typically experience progressive symptoms of HF resulting in hospitalization, with death typically occurring 2.5 to 5 years after diagnosis.[Castano 2015; Damy 2015; Dungu 2012; Hawkins 2015]

1.2. Current Treatments

Historically, palliative/symptomatic therapies directed at specific symptoms, have been the mainstay of treatment despite their limited effectiveness. Recently, several new products for the treatment of ATTR amyloidosis have been approved and have become available in some regions.

Tafamidis, a TTR tetramer stabilizer, is approved for the treatment of patients with early stage hATTR amyloidosis with polyneuropathy in a number of markets, but not in the US.[Hawkins 2015] Diflunisal, a generic, oral nonsteroidal anti-inflammatory drug was shown to reduce neuropathy progression compared with placebo in patients with hATTR amyloidosis in a US National Institutes of Health sponsored study.[Berk 2013] While used off-label in some markets where available, diflunisal is not an approved treatment for hATTR amyloidosis in any market. In the US, diflunisal carries boxed warnings for cardiovascular thrombotic events and gastrointestinal risk (diflusinal package insert 2017). Overall, the data with TTR tetramer stabilizers in hATTR amyloidosis indicate some slowing, but not prevention of neuropathy progression.

More recently, the small interfering ribonucleic acid (siRNA) patisiran, and the antisense oligonucleotide inotersen have been approved for use in patients with hATTR amyloidosis with polyneuropathy in Canada, Japan, EU, US, and other regions on the basis of Phase 3 randomized controlled studies. These novel therapies reduce expression of TTR messenger RNA (mRNA) coding for the circulating amyloidogenic protein, albeit through different mechanisms.[Adams 2018; Benson 2019]

Recently, tafamidis has been approved in some regions for the treatment of patients with ATTR amyloidosis (hereditary and wt) with cardiomyopathy based on results from the Phase 3 ATTR-ACT trial.[Maurer 2018] This study demonstrated that tafamidis treatment over 30 months was associated with lower all-cause mortality and cardiovascular-related hospitalizations compared with placebo treatment. These results support the general therapeutic hypothesis that modifying TTR has the potential to result in beneficial outcomes in patients with ATTR amyloidosis with cardiomyopathy. However, the disease progression that was observed in both treatment arms in ATTR-ACT highlights an important unmet medical need and suggests that a more direct therapeutic mechanism of action, such as specifically targeting the production of the disease-causing protein with an RNAi therapeutic, may be required to halt or reverse the debilitating and ultimately fatal course of the disease.

1.3. RNAi Therapeutics to Reduce TTR Levels

Patisiran is a siRNA targeting hepatic TTR mRNA developed by the Sponsor. Patisiran, which is formulated as a lipid nanoparticle (LNP), is administered every 3 weeks (q3w) by intravenous (IV) infusion and requires use of premedications in order to prevent infusion-related reactions. It is approved for use in patients with hATTR amyloidosis with polyneuropathy in a number of regions, including Canada, the EU, Japan, and the US. These approvals were based on the results of a large, randomized, double-blind, placebo-controlled, Phase 3, Study ALN-TTR02-004 (APOLLO).[Adams 2018] This study demonstrated that patisiran treatment significantly improved neuropathy, quality of life, and a range of disease manifestations relative to placebo in hATTR amyloidosis patients with polyneuropathy across a broad range of disease severity and TTR genotypes.

In additional exploratory analyses, patisiran resulted in favorable impacts on measures of cardiac structure (decrease in mean left ventricular wall thickness), cardiac function (decrease in global longitudinal strain), CCI [redacted] Furthermore, in post-hoc analyses, patisiran was associated with a 46% reduction in the rate of all-cause mortality and cardiac hospitalizations.[Solomon

2019] Currently, patisiran continues to be investigated for the treatment of patients with ATTR amyloidosis with cardiomyopathy in the ongoing Phase 3 Study ALN-TTR02-011 (APOLLO-B).

Previously, the Sponsor investigated another siRNA therapeutic, revusiran that was also conjugated to an *N*-acetylgalactosamine (GalNAc) containing ligand and administered subcutaneously (SC), for use in the treatment of patients with hATTR amyloidosis with cardiomyopathy. However, the revusiran program was discontinued (further details can be found in the vutrisiran Investigator's Brochure).

Presently, the Sponsor is developing a novel synthetic RNAi therapeutic, vutrisiran drug product (ALN-TTRSC02; hereafter referred to as vutrisiran) for SC administration for the treatment of ATTR amyloidosis, including the treatment of patients with ATTR amyloidosis with cardiomyopathy. Vutrisiran utilizes a mechanism similar to patisiran in that RNAi is used to selectively target and degrade TTR mRNA, thus preventing the synthesis of both wt and mutant TTR in the liver, the primary source of circulating TTR. Unlike patisiran, which is formulated as an LNP and administered with an IV infusion, vutrisiran is conjugated to a GalNAc and administered SC. Rapid and efficient uptake of vutrisiran by the liver occurs via the asialoglycoprotein receptor (ASGPR). The ASGPR is a member of the C-type lectin family of receptors that recognizes and binds glycoproteins with terminal galactose or GalNAc residues.[Ashwell 1974] It is expressed on the cell surface of hepatocytes at a high copy number (0.5-1 million per cell) [Baenziger 1980; Schwartz 1980] and facilitates clearance of desialylated glycoproteins from the blood.[Geffen 1992]

Vutrisiran employs a different ratio of chemical modifications to confer increased stability of the siRNA and is thus designed to have greater potency and prolonged duration of action compared to current and previous siRNAs evaluated in the clinic for treatment of this disease. This enables a much lower dose, lower injection volume, and significantly less frequent dosing with vutrisiran compared to other TTR-lowering drugs. Because vutrisiran does not include any LNPs as part of its formulation, no premedications are required.

1.4. Clinical Development of Vutrisiran

Vutrisiran was initially evaluated in a completed Phase 1 study (ALN-TTRSC02-001) in healthy patients, and is currently being investigated in an ongoing Phase 3 study (ALN-TTRSC02-002 [HELIOS-A]) in patients with hATTR amyloidosis with polyneuropathy as described below.

Study ALN-TTRSC02-001 was a Phase 1, randomized, single-blind, placebo-controlled, single-ascending dose study evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of vutrisiran in 80 healthy subjects; 60 subjects received single-doses of vutrisiran (from 5 mg to 300 mg) and 20 subjects received placebo.

Overall, vutrisiran was well tolerated. There were no serious or severe adverse events (AEs) and no subject discontinued from the study due to an AE. Mostly mild, transient, dose-dependent increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in all vutrisiran dose groups, particularly at doses >100 mg. Two subjects had transient, asymptomatic elevations in ALT and/or AST of >3 × the upper limit of normal (ULN). None of the ALT or AST elevations were reported as AEs and none were associated with concurrent bilirubin elevations.

Single SC doses of 25 to 300 mg vutrisiran resulted in robust, and durable reductions in serum TTR protein, with the magnitude and duration of TTR reduction being dose-dependent. At the proposed dose of 25 mg vutrisiran, a single dose resulted in mean maximum TTR reduction of 83%; the nadir was reached at approximately 6 weeks and maintained for 90 days. Based on the results of the Phase 1 Study ALN-TTRSC02-001, vutrisiran 25 mg SC administered once q3M was selected for further development (see Section 1.6 for dose rationale).

HELIOS-A is an ongoing, Phase 3, global, randomized, open-label study to evaluate the efficacy and safety of vutrisiran 25 mg SC q3M in patients with hATTR amyloidosis with polyneuropathy. Enrollment in this study is complete. Patients were randomized 3:1 to receive either 25 mg of vutrisiran (N=122) q3M or 0.3 mg/kg of patisiran (N=42) q3w (as a reference comparator) for 18 months. As of Amendment 4, after the 18-month Treatment Period, all patients transition into the Randomized Treatment Extension (RTE) Period and are randomized 1:1 to receive vutrisiran 25 mg q3M or CCI treatment. The primary endpoint in HELIOS-A is change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) at Month 9 and first key secondary endpoint is change from baseline in the CCI CCI total score at Month 9. The primary endpoint and most secondary endpoints will be comparisons of vutrisiran to the placebo arm of the Phase 3 APOLLO study of patisiran.

Further information on the chemistry, pharmacology, efficacy, and safety of vutrisiran is provided in the current edition of the Investigator's Brochure.

1.5. Study Design Rationale

The proposed Phase 3 ALN-TTRSC02-003 (HELIOS-B) study is a global, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety and PK/PD of vutrisiran in patients with hATTR and wtATTR amyloidosis with cardiomyopathy.

Patients will receive treatment with 25 mg vutrisiran or placebo every 3 months (q3M) during their Double-blind (DB) Period of the study for up to 36 months (see Section 3.1). The primary analysis will be conducted after the last patient has completed the period of DB exposure (defined as the duration prior to first open-label treatment exposure). An Open-label Randomized Treatment Extension Period was added with Amendment 3 in which patients who complete treatment in the DB Period will be randomized to receive either 25 mg vutrisiran q3M or CCI vutrisiran CCI in an open-label fashion. Following implementation of Amendment 4, the Randomized Treatment Extension will be replaced with an Open-Label Extension (OLE) where all patients who complete treatment in the DB Period will receive vutrisiran 25 mg q3M for up to 2 years. A Follow-up Period will commence when patients complete the OLE Period (or complete the DB Period for patients who do not continue into the OLE Period; or their last dose of vutrisiran for patients who discontinue study drug early) and patients will be followed for a period of up to 1 year after their last dose of study drug. See also Section 3.1.

The patient population includes ATTR amyloidosis patients with cardiomyopathy and New York Heart Association (NYHA) class I – III heart failure. However, the study criteria are intended to exclude patients with NYHA Class IV heart failure and patients with advanced NYHA Class III heart failure based on a biomarker based staging system (CCI CCI CCI Gillmore 2018] The population is intended to be broadly representative of patients with ATTR cardiomyopathy while avoiding the highest-risk patients who are unlikely

to have sufficient time on treatment to derive benefit in the context of a clinical trial of limited duration.

Given that tafamidis is prescribed in some, but not all, regions as standard of care in this patient population, at baseline patients will either be on concurrent tafamidis or be considered naïve to tafamidis (Section 4.1; Section 5.4.1). As with any active therapy, initiation of tafamidis in naïve patients during the study (tafamidis drop-in), impacts the ability to accurately quantify the vutrisiran treatment effect relative to placebo, particularly if use is disproportionate between treatment arms. Accordingly, it should be noted that per exclusion criterion #7, tafamidis-naïve patients (per inclusion criterion #4a) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis either during the Screening Period or the first 12 months following randomization should not be enrolled in the trial, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.

The primary objective of the study is to determine the efficacy and safety of vutrisiran for the treatment of cardiomyopathy by evaluating its impact on a composite outcome of mortality and recurrent cardiovascular (CV) events.

The efficacy of vutrisiran will be evaluated in the overall population, which is representative of patients with ATTR cardiomyopathy prescribed tafamidis as standard of care, or those newly diagnosed. Analysis will also be conducted in the vutrisiran monotherapy subgroup which will provide a demonstration of the potential clinical benefit of vutrisiran in the absence of any confounding effect of benefit from concomitant tafamidis.

CV events will include recurrent CV hospitalizations and recurrent non-hospitalized urgent HF visits in accordance with the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials.[Hicks 2018] The primary endpoints will provide definitive evidence of a clinically meaningful impact in the study population. Similar endpoints have been used in numerous heart failure studies, including the recent Phase 3 ATTR-ACT study of the TTR tetramer stabilizer, tafamidis.[Maurer 2018; McMurray 2019] Including urgent HF visits will account for the likelihood that the COVID-19 pandemic may increase current trends to reduce hospitalizations and shift management of clinically comparable heart failure events to outpatient settings.[Hicks 2018] Including urgent HF visits also accounts for regional differences in the criteria for hospitalization, which may be further exacerbated by the COVID-19 pandemic. In addition, data support the equivalence of urgent HF visits to HF hospitalizations for predicting mortality.[Okumura 2016]

As a key secondary objective, the study will also evaluate the efficacy of vutrisiran on functional capacity (6-minute walk test; 6-MWT) and health status and health-related quality of life (Kansas City Cardiomyopathy Questionnaire Overall Summary; KCCQ-OS). The 6-MWT is a clinically relevant assessment of functional capacity that has been used as a primary endpoint in pivotal clinical trials in pulmonary arterial hypertension [Gabler 2012] and has been used in the evaluation of patients with HF.[Bittner 1993; Flynn 2009; Flynn 2012; Mangla 2013; Masoudi 2004; Maurer 2018] The KCCQ-OS has been used as a common assessment in HF interventional studies and has been shown to be an independent predictor of prognosis in HF.[Heidenreich 2006]

Both 6-MWT and KCCQ-OS were shown to rapidly and consistently decline over time in cardiac ATTR amyloidosis patients and, in the tafamidis Phase 3 ATTR-ACT study, these

measures were used to demonstrate a reduction of decline with tafamidis treatment.[Maurer 2018] These data support the use of 6-MWT and KCCQ-OS as clinically relevant endpoints.

The inclusion of placebo as a control for this study allows for a rigorous analysis of the treatment effect of vutrisiran. A placebo control will be especially useful in characterizing the efficacy and safety of vutrisiran in a patient population which is prone to cardiac events.

Assessment of the primary endpoints following a variable 33 to 36 months length of treatment is supported by the tafamidis ATTR-ACT study which demonstrated an impact on outcomes over a similar time period of 30 months. [Maurer 2018] Given the potential for concurrent tafamidis use to reduce the overall vutrisiran treatment effect, a slightly longer length of follow-up has been chosen.

The OLE Period is designed to evaluate the long-term safety and efficacy of vutrisiran.

1.6. Dose Rationale

The vutrisiran regimen of 25 mg q3M SC is proposed for the DB Period of this Phase 3 Study ALN-TTRSC02-003 (HELIOS-B) to be conducted in patients with hATTR or wtATTR amyloidosis with cardiomyopathy. This dose is also being evaluated for the treatment of patients with hATTR amyloidosis with polyneuropathy in the ongoing Phase 3 Study ALN-TTRSC02-002 (HELIOS-A) described in Section 1.4.

CCI

CCI

CCI

CCI [redacted]

CCI [redacted]

1.7. Benefit-Risk Assessment

ATTR amyloidosis with cardiomyopathy is a serious, life-threatening, multisystemic disease characterized by deposition of TTR in various organs, with heart failure (HF) as the most common manifestation. Patients with symptomatic HF due to ATTR amyloidosis experience rapid disease progression, with substantial worsening of CCI [redacted] CCI [redacted] ambulation, and quality of life.[Ruberg 2012a] Without treatment, the disease progresses, resulting in chronically debilitating morbidity and mortality.

As outlined in Section 1.4, data from the vutrisiran Phase 1 clinical study demonstrated potent, dose-dependent inhibition of TTR in healthy patients (Study ALN-TTRSC02-001). Importantly, in the Phase 1 clinical study in healthy patients, single vutrisiran SC doses up to the highest

tested dose (300 mg) were well tolerated. The selected Phase 3 dosing regimen of 25 mg q3M SC is also infrequent, easy to administer, and does not require premedication. Other available TTR lowering agents including patisiran, have demonstrated benefit on both neuropathy and exploratory assessments of cardiomyopathy as well as on quality of life in patients with hATTR amyloidosis. Based on the clinical data with vutrisiran, taken together with clinical efficacy that has been demonstrated with other TTR lowering agents, it is anticipated that TTR reduction with vutrisiran will beneficially impact disease progression in patients with ATTR amyloidosis with cardiomyopathy.

Given the target organ of vutrisiran, the available nonclinical and clinical data, and the mode of administration, important potential risks for vutrisiran are injection-site reactions (ISRs) and liver function test (LFT) abnormalities. During the study, patients will be closely monitored, including evaluation of injections sites. As vutrisiran is targeted for delivery to the liver, there is a potential for development of LFT abnormalities. Patients presenting with any laboratory result considered unacceptable as per exclusion criteria (see Section 4.2) at time of enrollment will be excluded from participation in this study, and LFTs will be routinely monitored throughout the study per the Schedule of Assessments. Criteria for dose withholding, modification and stopping vutrisiran dosing due to LFT abnormalities are provided in Section 5.2.4. An external, independent Data Monitoring Committee (DMC) will monitor and ensure the safety of trial participants (see Section 3.7).

Nonclinical and clinical data with vutrisiran and patisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in severe vitamin A deficiency; transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of retinol binding protein. However, as the vitamin A content of the diet may vary between different individuals, all patients will be instructed to take the recommended daily allowance of vitamin A while on the study (see Section 3.1). Laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation beyond the recommended daily dose during treatment with vutrisiran.

Based on the emerging efficacy and available safety data described above, the benefit-risk assessment supports the evaluation of vutrisiran in hATTR and wtATTR patients with amyloidosis. Detailed information about the known and expected benefits and risks of vutrisiran and additional safety information may be found in the current edition of the vutrisiran Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of vutrisiran compared to placebo on reducing all-cause mortality and CV events	• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure [HF] visits) in the overall population • Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)
Secondary	
To evaluate the efficacy of vutrisiran compared with placebo treatment on: • Functional capacity • Patient-reported health status and health-related quality of life • All-cause mortality • Severity of clinical heart failure symptoms	The following secondary endpoints will be defined in both the overall population and the vutrisiran monotherapy subgroup: • Change from baseline in 6-MWT • Change from baseline in the KCCQ-OS • All-cause mortality • Change from baseline in NYHA Class
Exploratory	
CCI [redacted]	• CCI [redacted]

Objectives	Endpoints
	• CCI [redacted]
Pharmacodynamics and Pharmacokinetics	
• To characterize the PD effect of vutrisiran on TTR • To characterize plasma PK of vutrisiran • To assess presence of antidrug antibodies (ADA) against vutrisiran	• Change from baseline in serum TTR levels • Plasma PK exposure parameters • Frequency and titers of ADA
Safety	
• To evaluate the safety and tolerability of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of AEs

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vutrisiran in approximately 600 patients with ATTR amyloidosis (hATTR or wtATTR) with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR amyloidosis with cardiomyopathy.

At baseline, patients are either:

- Tafamidis-naïve (see inclusion criterion #4 for definition); or
- Currently receiving tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication in the country of use).

The study consists of 4 periods (Figure 1):

1. **Screening Period:** Up to 45 days during which patients will undergo screening assessments to determine eligibility.
2. **Double-Blind (DB) Period:**
   - At the start of the DB Period (on Day 1), eligible patients will be randomized in a 1:1 ratio to receive blinded doses of 25 mg of vutrisiran or placebo administered as a SC injection q3M (every 12 weeks ±7 days) for up to 36 months.
     - In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their DB Period and Follow-up Period (see below).
   - Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1).
   - An individual patient's DB Period visits will end after they complete their Month 36 visit, or 30 months after the last patient is randomized, whichever comes first. As such, a patient's last visit during the DB Period may vary from 30 to 36 months after enrollment.
     - The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the OLE Period will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 33 (Week 144), Day 1 in the OLE Period will occur 156 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 36 (Week 156), Day 1 in the OLE Period will occur on the same day (since study drug is not administered as part of the Month 36 DB visit).
     - The period of DB exposure, defined as the duration prior to first exposure to open-label treatment, will be 144 to 156 weeks (33 to 36 months).
   - The primary analysis will be conducted after the last patient has completed the period of DB exposure or otherwise discontinued.

3. **Open-Label Treatment Extension (OLE) Period**

The study has been amended (Amendment 4) to include an OLE Period in lieu of the Open-Label Randomized Treatment Extension Period (previously introduced with Amendment 3). In the OLE Period, all patients will receive the vutrisiran 25 mg q3M regimen.

- Upon entry into the OLE, all eligible patients will transition to receive open-label doses of 25 mg q3M vutrisiran administered as SC injections.
- Patients initially randomized to CCI (under Amendment 3) will transition to receive open-label doses of 25 mg q3M vutrisiran administered as SC injections at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran). Patients initially randomized to 25 mg q3M vutrisiran (under Amendment 3) will continue with the 25 mg q3M regimen.
  - In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their OLE Period and Follow-up Period (see below).
- All patients will undergo assessments as outlined in the Schedule of Assessments for the OLE Period (Table 2).

Note: Patients who do not complete the DB Period may not participate in the OLE Period. Consent must be signed before any procedures are performed in the OLE Period (Table 2).

4. **Follow-Up Period after the last dose of vutrisiran on study:**

- Following completion of the OLE Period (or completion of the DB Period for patients who do not continue into the OLE Period; or their last dose of vutrisiran for patients who discontinue study drug early), patients will commence follow-up visits every 12 weeks for the durations outlined below.
- Prior to unblinding of their treatment from the DB Period, the duration of the Follow-up Period for a patient will be 1 year from their last dose of study drug. For women of child-bearing potential, the duration of the Follow-up Period will be 18 months from their last dose of study drug. Patients will continue vitamin A supplementation during their Follow-up Period.
- After unblinding, all patients who were on placebo, and patients who received vutrisiran whose serum TTR level has returned to ≥80% of baseline or who have completed the Follow-up Period, whichever comes first, may discontinue further follow-up and stop taking vitamin A. Baseline is defined as the last value prior to first vutrisiran dose (ie, prior to the first DB dose for vutrisiran patients in DB Period and prior to the first OLE dose for placebo patients). Patients will be followed for a minimum period as listed below during the Follow-up Period based on treatment regimen received:
  - All patients whose last dose of study drug was 25 mg vutrisiran/placebo during DB Period or 25 mg vutrisiran during the OLE Period will be followed for a minimum of 90 days after their last dose of study drug.

  - Patients whose last dose of study drug was [redacted] vutrisiran regimen (under Amendment 3) will be followed for a minimum of [redacted] after their last dose of study drug during Follow-up Period.

- For any patient who starts a TTR lowering treatment as part of clinical care, and has completed a minimum of 90 or [redacted] (depending on vutrisiran treatment regimen) of safety follow-up since their last dose of study drug, further follow-up will be discontinued.
- Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1 and Table 2).

Patients may receive vutrisiran on the study until the end of the OLE Period or until one of the following occurs: 1) they meet any of the study discontinuation criteria; 2) vutrisiran is commercially available in the patient's country of residence and vutrisiran is accessible to the patient and the patient has completed their OLE Month 12 Visit; or 3) the vutrisiran development program is discontinued.

Study drug dosing may be allowed outside of the study center (eg, the patient's home) during the DB Period or OLE Period under certain circumstances as specified in Section 5.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in Section 6.

3.2. Duration of Treatment

The planned duration of treatment for each patient is up to approximately 60 months (approximately 5 years), inclusive of the 33 to 36-month DB Period and a 24-month OLE Period.

3.3. Duration of Study Participation

The estimated total time on study for each patient is up to approximately 6 years, including a Screening Period of up to 45 days, a DB Period of up to 36 months, an OLE Period of up to 24 months, and a Follow-up Period of up to 1 year after the last dose of study drug (18 months for women of child-bearing potential).

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if they have:

- completed the DB Period and the Follow-up Period (if the patient does not continue into the OLE Period);
- completed the DB Period, the OLE Period, and the Follow-up Period;
- completed the Early Study Discontinuation Visit; or
- started a TTR-lowering regimen as a part of clinical care

3.4. Number of Planned Patients

The planned enrollment for this study is 600 patients.

3.5. Method of Assigning Patients to Treatment Groups

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRT. The Investigator or his/her designee will contact the IRT to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

Randomization for the DB Period:

Using Interactive Response Technology (IRT), patients will be randomized 1:1 to the vutrisiran or placebo arm. Randomization will be stratified by:

1. Baseline tafamidis use (yes versus no)
2. ATTR disease type (hATTR versus wtATTR amyloidosis with cardiomyopathy)
3. NYHA Class I or II **and** age <75 years versus all other

3.6. Blinding

During the DB Period, all site personnel and patients will be blinded to study drug treatment. Vutrisiran and placebo will be packaged identically. The outside of the pre-filled syringe barrel will be masked in such a way as to hide the identity of the study drug contained within.

All study personnel will be blinded to any clinical laboratory results scheduled as part of the study that could potentially unblind them, including TTR levels, vitamin A levels, PK data, and ADA.

As it could affect the blind, patients and their physicians are prohibited from obtaining pre-albumin and vitamin A levels during the DB Period, other than the blinded assessments scheduled in the study, unless clinically indicated and after consultation with the Medical Monitor.

During the DB Period, Investigators, study personnel, and the Sponsor will remain blinded to treatment assignment until the database lock for the primary analysis.

During the OLE Period, vutrisiran will be administered in an open-label fashion.

3.6.1. Emergency Unblinding

During the DB Period, if the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event taking care not to share any information about unblinded treatment assignment. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the trial master file.

Refer to the IRT instructions for details on emergency unblinding.

3.7. Data Monitoring Committee (DMC)

An independent DMC will oversee the safety and overall conduct of this study. Recommendations by the DMC will be based on the overall assessment of benefit-risk. The DMC will operate under the rules of a charter that will be agreed upon and approved by the DMC members. Details are provided in the DMC Charter.

3.8. Clinical Events Committee (CEC)

During the DB Period, an independent Clinical Events Committee (CEC) will review deaths, hospitalizations, and urgent HF visits blinded to treatment assignment on an ongoing basis for endpoint adjudication. The CEC will make a determination on whether deaths and hospitalizations can be attributed as cardiovascular. Details are provided in the CEC charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age

1. Age 18 (or age of legal consent per local regulations, whichever is older) to 85 years, inclusive.

Patient and Disease Characteristics

2. Documented diagnosis of ATTR amyloidosis with cardiomyopathy, classified as either hATTR amyloidosis with cardiomyopathy or wtATTR amyloidosis with cardiomyopathy:
   a. Hereditary ATTR (hATTR) amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:
      i. Documentation of a TTR pathogenic mutation consistent with hATTR amyloidosis.
      ii. Evidence of cardiac involvement CCI [redacted]
      iii. Amyloid deposits in cardiac or noncardiac tissue (eg, fat pad aspirate, salivary gland, median nerve connective sheath) confirmed by Congo Red (or equivalent) staining **OR** technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc] or ^{99}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) has been excluded.
      iv. If the patient has evidence of a MGUS based on serum and urine protein electrophoresis and serum free light chains (Section 6.5.5.1), documentation of TTR protein in tissue with immunohistochemistry or mass spectrometry is required.

b. Wild-type ATTR (wtATTR) amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

   i. Documentation of absence of pathogenic TTR mutation.
   ii. Evidence of cardiac involvement CCI [redacted]
   iii. Amyloid deposits in cardiac tissue with TTR protein identification by IHC, mass spectrometry, OR technetium (^{99}mTc) scintigraphy (^{99}mTc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99}mTc-pyrophosphate [PYP-Tc], or ^{99}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if MGUS has been excluded.
   iv. If the patient has evidence of a MGUS (Section 6.5.5.1) based on serum and urine protein electrophoresis and serum free light chains, the following is required: documentation of TTR protein in cardiac tissue with immunohistochemistry or mass spectrometry; OR, documentation of TTR protein in noncardiac tissue (eg, fat pad aspirate, salivary gland, median nerve connective sheath) with immunohistochemistry or mass spectrometry AND Grade 2 or 3 cardiac uptake on technetium scintigraphy per item 2biii above.

3. Medical history of HF with at least 1 prior hospitalization for HF (not due to arrhythmia or a conduction system disturbance treated with a permanent pacemaker) **OR** clinical evidence of HF (with or without hospitalization) manifested by signs and symptoms of volume overload or elevated intracardiac pressures (eg, elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that currently requires treatment with a diuretic.
4. Patient meets one of the following criteria:
   a. Tafamidis-naïve and not actively planning to commence treatment with tafamidis during the first 12 months following randomization (per exclusion criterion #7) (Note: in addition to patients who have never taken tafamidis, those who have previously been on tafamidis and have not received any tafamidis for at least 30 days before the Screening Visit will be considered tafamidis-naïve for purposes of this study); or
   b. On tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use)
5. Patient is clinically stable, with no CV-related hospitalizations within 6 weeks prior to randomization, as assessed by the Investigator.
6. Screening CCI [redacted]; in patients with permanent or persistent atrial fibrillation, Screening CCI [redacted]
7. Able to complete ≥150 meters on the 6-MWT at Screening.

CCI [redacted]

Informed Consent

9. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

10. Patient agrees to sign a separate medical records release form, where allowed by local regulations, to allow for the collection of information on vital status, cardiac transplant procedures, left-ventricular assist device placement, and hospitalizations, for the duration of the DB Period of the study (see Section 6.1).

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Has known primary amyloidosis (AL amyloidosis) or leptomeningeal amyloidosis.
2. NYHA Class IV heart failure; or NYHA Class III heart failure AND ATTR Amyloidosis Disease Stage 3 ([redacted]).[Gillmore 2018]

[redacted]

Laboratory Assessments

4. Has any of the following laboratory parameter assessments at Screening:
   a. AST or ALT levels >2.0 × ULN,
   b. Total bilirubin >2.0 × ULN,
   c. International normalized ratio (INR) >1.5 (unless patients were on anticoagulant therapy in which case excluded if INR >3.5).
5. [redacted]
6. Has known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.

Prior/Concomitant Therapy

7. Tafamidis-naïve patients (per inclusion criterion #4a) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis either during the Screening Period or the first 12 months following randomization, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
8. Received prior TTR-lowering treatment (including revusiran, patisiran or inotersen) or participated in a gene therapy trial for hATTR amyloidosis.
9. Is currently taking diflunisal; if previously on this agent, must have at least a 30-day wash-out prior to dosing (Day 1).
10. Is currently taking doxycycline, ursodeoxycholic acid, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 30-day wash-out prior to dosing (Day 1).
11. Unwilling to avoid any concurrent treatment with diflunisal, ursodeoxycholic acid/tauroursodeoxycholate/doxycycline, or TTR lowering agents (eg, patisiran, inotersen)

12. Current or future participation in another investigational device or drug study, scheduled to occur during this study, or has received an investigational agent or device within 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to dosing (Day 1). In the case of investigational TTR stabilizer drugs, washout for 3 months prior to dosing (Day 1) is required; this does not apply to patients who are on tafamidis at baseline (per inclusion criterion #4).
13. Requires treatment with or is unwilling to avoid any concurrent treatment with non-dihydropyridine calcium channel blockers (eg, verapamil, diltiazem).

Medical Conditions

14. Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease (eg, prior myocardial infarction with documented history of cardiac enzymes and ECG changes) that the Investigator feels is a significant contributor or the predominant cause of the patient's heart failure.
15. Unstable congestive heart failure (CHF) (including patients who require adjustment of existing diuretics or addition of new diuretics at time of Screening for purposes of achieving optimal management of CHF).
16. Had acute coronary syndrome or unstable angina within the past 3 months.
17. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.
18. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
19. Has persistent elevation of systolic (>170 mmHg) or diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.
20. Has untreated hypo- or hyperthyroidism.
21. Has an active infection requiring systemic antiviral, antiparasitic or antimicrobial therapy that will not be completed prior to dosing (Day 1).
22. Prior or anticipated (during the first 12 months after randomization) heart, liver or other organ transplant or implantation of left-ventricular assist device.
23. History of multiple drug allergies or history of allergic reaction to any component of or excipient in the study drug.
24. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability.
25. Has other medical conditions or comorbidities (eg, malignancy, neuropsychiatric disorder etc…) which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.

Contraception, Pregnancy, and Breastfeeding

26. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.6.1.
27. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol Use

28. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
29. History of alcohol abuse, within the last 12 months before Screening, in the opinion of the Investigator.
30. History of illicit drug abuse within the past 5 years that in the opinion of the Investigator would interfere with compliance with study procedures or follow-up visits.

4.3. Removal from Study Drug or Assessment

Patients are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the eCRF and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience (including, at a minimum, information on vital status, cardiac transplant

procedures, left-ventricular assist device placement and hospitalizations for the duration of the DB Period of the study) is captured in the final analyses.

If the patient discontinues study drug early, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including efficacy endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue early from study drug during their treatment in the DB Period will be encouraged to:

- Return for an Early Treatment Discontinuation Visit (Table 1);
- Remain on the study and complete all remaining DB Period visits at months 6, 12, 18, 24, 30 and 36, (excluding PK assessments), or until 30 months after the last patient is randomized, whichever is earlier; and
- Complete safety assessments, per the Follow-up Period in the Schedule of Assessments (Table 1) as outlined in Section 3.1.

Patients who discontinue early from study drug during their treatment in the OLE Period will be encouraged to:

- Return for an Early Treatment Discontinuation Visit (Table 2);
- Complete safety assessments, per the Follow-up Period in the Schedule of Assessments (Table 2) as outlined in Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study at any time. A patient considering stopping participation in the study should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments, or alternatively may complete any minimal assessments for which the patient consents as described in Section 4.3.1. If a patient still chooses to discontinue study drug and stop participation in any follow-up before the completion of their treatment in the DB Period (defined in Section 3.1) or OLE Period, every effort should be made to have the patient return for the Early Study Discontinuation Visit within 4 weeks (+1 week) of the last dose of study drug (Table 1 and Table 2).

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples) until the time of withdrawal according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Patients who undergo heart transplant or implantation of a left-ventricular assist device are considered to have reached the primary endpoint (treated as death equivalent for primary analysis) and should be discontinued from the study.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.4.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient misses a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes (for the patient) to continue in the study, and/or should continue in the study.

- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, the site should make a minimum of 3 documented telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator should make every effort to search publicly available records (where permitted and allowed by local law) to ascertain survival status and collect information related to cardiac transplant procedures, or left-ventricular assist device placement. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the administration and storage of study drug (vutrisiran and placebo) will be provided in the Pharmacy Manual and the detailed Instructions for Use for the pre-filled syringe. In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their DB Period, OLE Period, and Follow-up Period as outlined in Section 3.1.

5.2.1. Description

The siRNA drug substance ALN-65492 is a chemically synthesized double-stranded oligonucleotide targeting TTR that is covalently linked to a ligand containing 3 GalNAc residues. CCI [redacted]

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Study drug (vutrisiran or placebo) will be administered using single-use prefilled syringes. Each prefilled syringe will be filled with either a 25 mg dose of vutrisiran or placebo with a fill volume of 0.5 mL. Each pre-filled syringe includes a needle safety device which will be engaged to cover the exposed needle after injection.

See the Pharmacy Manual for further details of solution concentration and fill volume.

5.2.2. Dose and Administration

Detailed instructions for administration are provided in the Pharmacy Manual. Detailed Instructions for Use for the pre-filled syringe will also be provided.

Starting on Day 1 of the DB Period, patients will receive 25 mg of vutrisiran or placebo administered as a SC injection q3M (every 12 weeks ±7 days) for up to 36 months.

Under Amendment 4, all patients will receive SC injections of 25 mg of vutrisiran q3M (every 12 weeks ±7 days) for up to 2 years during the OLE Period.

The first dose of study drug should be administered in the clinic on Day 1 of the DB Period (placebo or 25 mg of vutrisiran) and Day 1 of the OLE Period (25 mg of vutrisiran). If a patient has tolerated at least 1 dose of study drug in the clinic, subsequent dosing for the remainder of that period may be administered outside the study site (eg, the patient's home) at all other timepoints where allowed by applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare professional, with oversight by the Investigator.

If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, study drug (placebo or 25 mg vutrisiran) may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on study drug administration. This measure (self- or caregiver administration) is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.

The SC injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained.

Additional details, including detailed instructions for study drug administration, can be found in the Pharmacy Manual. In addition, instructions and procedures related to administration of study drug by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

Missed doses of Study Drug

If a patient does not receive a dose of study drug within the specified dosing windows, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered as close to the scheduled dosing date as possible with a maximum 8-week delay (to be considered a delayed dose). For patients initially randomized to CCI (under Amendment 3), delays beyond 8 weeks may be allowable, but must be discussed with the Medical Monitor. Thereafter, the dose will be considered missed and not administered. If a dose is missed or is administered with a delay, the next dose will resume following the original schedule. In cases in which a dose is delayed in this manner for issues related to the COVID-19 pandemic, the Medical Monitor should be informed as soon as possible, but prior consultation is not required. In all cases, the dose should be administered as close as possible to the scheduled timepoint.

Every effort should be made to avoid missed doses of study drug. If a patient misses a dose for reasons unrelated to the COVID-19 pandemic, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue dosing in the study (see also Section 4.3).

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.4. LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on LFT results (Table 6) collected at the previous visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used. All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic if central laboratory collection is not possible, then a local laboratory may be used. These local laboratory results must be sent to the site for review by the Investigator and entry into the clinical database.
2. For any ALT or AST elevation >3× ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 5.
3. For any ALT or AST elevation >3× ULN:
    a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days. If a central laboratory result is not possible due to COVID-19, a local laboratory may be used for monitoring in consultation with the Medical Monitor; all local laboratory results must be sent to the clinical site for entry into the clinical database.
    b. Perform assessments per Table 6 and Table 7.
    c. If an alternative cause is found, provide appropriate care.
4. For any ALT or AST elevation >3× ULN that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2× ULN or INR ≥1.5 without alternative cause, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3× ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2× ULN or INR ≥1.5, see Table 5.

Table 5: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action
>3× to 5× ULN	• May continue dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor LFTs at least every two weeks • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing
>5× to 8× ULN	• Hold dosing until recovery to ≤1.5× ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor LFTs at least weekly until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5× ULN following resumption of dosing, permanently discontinue dosing
>8× ULN	• Permanently discontinue dosing after confirmation of the transaminase value at the central laboratory. • Monitor LFTs at least weekly until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.5. Dose Preparation, Handling, and Storage

Staff at each clinical study center**,** or the home healthcare professional, will be responsible for preparation of study drug, according to procedures detailed in the Pharmacy Manual. In cases where study drug is administered outside the study center, dosing may be prepared by the home healthcare professional or patient/caregiver according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Study drug will be refrigerated at approximately [5±3°C] until dose administration.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage and preparation details will be provided in the Pharmacy Manual and Patient/Caregiver Storage and Administration Instructions.

5.2.6. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements.

During the DB Period, the outside of the pre-filled syringe barrel will be masked in such a way as to hide the identity of the study drug contained within (Section 3.6).

Additional details will be available in the Pharmacy Manual.

5.2.7. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used or partially unused pre-filled syringes must be disposed of immediately as specified in the Instructions for Use for the pre-filled syringe.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Product Complaints

5.3.1. Definition

A product complaint (PC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product and its packaging after it is released for distribution.

A PC may be detected prior to use of study drug, during use, or after use. A PC is typically non-medical in nature; however, it is possible that complaints could be associated with an AE. Examples of a PC include, but are not limited to: illegible label, missing label, damaged syringe, empty syringe, contamination of product, and malfunction of syringe needle safety device.

5.3.2. Reporting

For PCs, the Sponsor or its designee should be notified within 24 hours. PCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6 instructions on reporting PCs will also be detailed in the Pharmacy Manual.

In situations where a dose is being administered by a patient or caregiver, instructions to report to the study site any issues that could fall under a PC are outlined in the Patient/Caregiver Storage and Administration Instructions. The study site should then notify the Sponsor or designee within 24 hours of being informed per above instructions.

5.4. Concomitant Medications

Use of concomitant medications will be recorded on the patient's eCRF as specified in the Schedule of Assessments (Table 1). This includes all prescription medications, herbal

preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins (including vitamin A supplementation) and topical medications are permitted.

However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

All patients will take the recommended daily allowance of vitamin A during their DB Period, OLE Period, and Follow-up Period as outlined in Section 3.1.

Use of the following medications/treatments are prohibited during study participation (Section 4.2):

- any investigational agent other than study drug
- diflunisal
- ursodeoxycholic acid/tauroursodeoxycholate/doxycycline (Doxycycline is permitted if being taken for short-term treatment of infection. Also see exclusion criterion 10).
- TTR lowering agents (eg., patisiran, inotersen)
- Non-dihydropyridine calcium channel blockers (eg, verapamil, diltiazem); given they are widely recognized to be contraindicated in this patient population

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.4.1. Concomitant Tafamidis Use

Per inclusion criterion #4, at baseline patients are either: 1) tafamidis-naïve (defined in inclusion criterion #4a) or 2) currently on tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use). The number of patients enrolled on concomitant tafamidis at baseline will be monitored and may result in enrollment limitations in certain regions to permit enrollment of tafamidis-naïve patients (no baseline concomitant tafamidis) to ensure the study is sufficiently powered and to ensure the ability to accurately quantify the vutrisiran monotherapy effect relative to placebo.

Patients who are on tafamidis at baseline as per inclusion criteria are encouraged, if it is medically appropriate in the opinion of the Investigator, to remain on tafamidis for the duration of the study. For patients on tafamidis at baseline, the reason why the patient was enrolled while already receiving tafamidis (in the opinion of the Investigator) will be recorded in the eCRF. Although data with the combination of vutrisiran and TTR tetramer stabilizers, such as tafamidis, are not available, the concomitant use of vutrisiran and TTR stabilizers is likely to have an acceptable safety and tolerability profile. This assessment is based on complementary mechanisms of actions of the 2 agents which would not suggest additional safety concerns when used concomitantly. In addition, vutrisiran and TTR stabilizers have non-overlapping

pharmacokinetic and drug metabolism properties, which would not result in PK drug-drug interactions. Further, clinical data on the concomitant use of patisiran with TTR tetramer stabilizers indicated no drug-drug interaction in the Phase 2 Study ALN-TTR02-003, and the overall safety profile of patisiran in patients who used concomitant TTR stabilizers was consistent with that observed in patients who did not use concomitant TTR stabilizers.

While initiating on-label use of tafamidis in previously naïve patients during the study (tafamidis drop-in) is not prohibited in countries where tafamidis is commercially available in this patient population, it could impact the ability to accurately quantify the vutrisiran treatment effect relative to placebo. Accordingly, it should be noted that per exclusion criterion #7, tafamidis-naïve patients (per inclusion criterion #4a) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis either during the Screening Period or the first 12 months following randomization, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis, should not be enrolled in the trial.

Patients will be monitored for tafamidis use from Screening to completion of the study as indicated in the Schedule of Assessments (Table 1 and Table 2). If, during the study, the Investigator decides to begin on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in a patient who is tafamidis-naïve at baseline (ie, tafamidis drop-in), prior to commencing concomitant tafamidis the Investigator will perform assessments (including primary and select secondary efficacy assessments) at the Pre-tafamidis Drop-in Visit as outlined in the Schedule of Assessments (Table 1 and Table 2).

In all cases, the Pre-tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis. Thereafter, the patient will continue with all assessments per the Schedule of Assessments (Table 1 and Table 2). Any efficacy assessments performed within the previous 45 days do not need to be repeated at this visit. In addition, at the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the eCRF.

5.5. Treatment Compliance

Compliance with study drug administration will be verified by study staff.

5.6. Other Requirements

5.6.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose and until the end of their Follow-up Period (defined in Section 3.1).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.

- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of child-bearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements or at the request of the Sponsor, as described in the corresponding patient informed consent forms.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3).

5.6.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study as indicated in Section 4.2.

6. STUDY ASSESSMENTS

The schedule of study assessments for the DB Period is provided in Table 1 and Table 3 (pharmacokinetic time points); the schedule of study assessments for the OLE Period is provided in Table 2 and Table 4.

When performed on dosing days, the 6-MWT, the KCCQ, safety, and PD assessments will be performed prior to study drug administration. All other efficacy assessments only need to be performed prior to study drug administration on Day 1 of the DB Period and Day 1 of the OLE Period. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure allow, routine assessments may be performed outside of the study center (eg, the patient's home) by a trained healthcare professional at all timepoints. These assessments include the following: vital signs, physical exam, weight, CCI pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications. All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic when central laboratory assessments are not possible, then a local laboratory may be used. If a local laboratory is used, TTR and vitamin A levels should not be tested until after unblinding of treatment assignments (see Section 3.6). These local lab results must be sent to the site for review by the Investigator and entry into the clinical database. Wherever possible, AE collection associated with visits outside of the clinic will be collected by qualified site staff through verbal contact with the patient.

With the exception of patients unable to come to the site (eg, due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study site), at a minimum, patients should visit the site for the scheduled dosing and assessments for the Week 12 (Month 3) visit of the DB Period within the study visit window and for efficacy assessments as detailed below.

If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must, at a minimum, verbally contact the patient within the expected window for each study visit to collect relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).

All efficacy assessments associated with the following DB Period visits should be conducted at the study center: Month 6, Month 12, Month 18, Month 24, and Month 30. In addition, dosing and efficacy assessments scheduled for Day 1 of the OLE Period should be conducted at the study center. In situations where a study visit is unable to be completed at the site (eg, due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug), efficacy, safety, and other assessments may be completed up to 3 months after the time point (ie, up to Study Month 9, Month 15, Month 21, Month 27, or Month 33, respectively) after consultation with the Medical Monitor.

Further details with regard to visits performed outside of the clinic are provided in the Study Reference Manual.

6.1. Screening Assessments

See the Schedule of Assessments (Table 1) for a list of Screening visit assessments.

The investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site or any new trial participant to comply with the protocol given COVID-19 pandemic limitations.

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient before the Screening procedures are initiated. All patients will be given a copy of the signed and dated ICF.

Due to the inclusion of all-cause mortality in the primary endpoint analysis, a Medical Records Release Form will be also required of all patients where allowed by local regulations, for the purpose of obtaining information on vital status, cardiac transplant procedures, left-ventricular assist device placement (Section 6.2.2), and hospitalizations (Section 6.2.1) from patients for the duration of the DB Period of the study. This information will be obtained by the patient's physician through contacting the patient or family or from death registries. The signing of this medical records release form is in addition to the ICF and will apply even if the patient discontinues from the study early. Also see Section 4.3.2.1 for the collection of vital status after withdrawal of consent and Section 4.3.3 for patients who are lost to follow-up.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Medical history will be collected during Screening (including any cardiac disorders, any eye disorders or previous ophthalmology test results, and prior medications). Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration. Documented technetium scintigraphy and/or tissue biopsy testing for amyloidosis performed prior to study enrollment should be collected and recorded as part of medical history.

Information on prior medications, hospitalization, and procedures through 1 year prior to first dose should be collected and recorded.

The diagnostic tests required to confirm eligibility per inclusion criterion 2 are intended to be historical, as part of the patient's clinical care and diagnosis, and will not be performed as part of the study except as described below.

If a diagnostic result that confirms ATTR Amyloidosis is not available at Screening for the assessment of eligibility (Section 4.1, inclusion criterion 2a/b), testing may be conducted at a laboratory or diagnostic center selected by the site, in consultation with the Medical Monitor, in countries in which this test is not standard of care. For TTR mutation testing, a blood sample may be drawn at Screening and sent for genotype testing at the central lab, in countries in which genotyping is not available at a local laboratory.

CCI [redacted]

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during Screening provided that the patient can be evaluated for eligibility and randomized within the allowed Screening Period. Qualifying LFTs (AST, ALT and bilirubin) CCI [redacted] are an exception to this rule and may not be repeated unless there is clear evidence of a laboratory error after discussion with the Medical Monitor.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued), in conjunction with the decision of the Medical Monitor(s), may be allowed to rescreen after a minimum of 5 days have elapsed from their last screening assessment. All patients who are rescreened will be re-consented (ICF and the medical records release form). If a patient is rescreened within the 45-day Screening window, please consult the medical monitor to determine which screening procedures must be repeated. If rescreening occurs outside of the 45-day Screening window, all screening procedures must be repeated.

For patients who do not meet LFT CCI [redacted] criteria, rescreening patients once may be permitted with consultation of the Medical Monitor after a minimum of 5 days have elapsed from a patient's last laboratory screening assessment.

Patients who failed Screening due to situations related to the COVID-19 pandemic may be allowed to rescreen after consultation with the Medical Monitor.

6.2. Efficacy Assessments

See the beginning of Section 6 for procedures to follow in situations in which an efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study site.

6.2.1. Deaths, Hospitalizations, and Urgent Heart Failure Visits

All deaths, hospitalizations and urgent HF visits will be recorded throughout the study as part of SAE and AE monitoring (see Section 6.5.6) and per the Schedules of Assessments (Table 1 and Table 2). Vital status checks are described in Section 6.2.2.

All deaths, hospitalizations, and urgent HF visits will be adjudicated by an independent CEC (see Section 3.8).

6.2.2. Vital Status Check

Vital status checks will be performed at the timepoints specified in the Schedules of Assessments (Table 1 and Table 2). Given that heart transplantation or left-ventricular assist device implantation procedures will be considered deaths for the purposes of the primary analysis, vital status checks should include checking for the occurrence of these procedures.

Also see Section 4.3.2.1 for the collection of vital status after withdrawal of consent and Section 4.3.3 for patients who are lost to follow-up.

6.2.3. 6-Minute Walk Test (6-MWT)

Full details regarding the 6-MWT are provided in the relevant study manual.

The 6-MWT is an assessment of functional exercise capacity. The 6-MWT will be administered by staff trained in the procedure per the relevant study manual. When possible, the staff administering the 6-MWT will be different from the Investigator or designee managing the care of the patient. In all cases these staff must be qualified by the central 6-MWT vendor.

The 6-MWT will be performed at each of the timepoints specified in the Schedule of Assessments (Table 1).

At Screening, the 6-MWT will be administered for study eligibility purposes (per inclusion criterion #7 [Section 4.1]). Before conducting the 6-MWT at Screening, the site staff will familiarize the patient with the purpose and conduct of the 6-MWT, as described in detail in the relevant study manual. Familiarization can be repeated at other timepoints if deemed helpful.

When performed on dosing days, the 6-MWT will be performed prior to study drug administration.

Patients who are hospitalized during the study should wait at least 2 weeks after hospitalization before completing a 6-MWT assessment; less time post-hospitalization may be permitted if, in the opinion of the Investigator, the patient is unencumbered due to the recent hospitalization.

In addition, if a patient is not feeling well due to an external factor (eg, flu, sprained ankle, pulled back muscle) at a visit when the 6-MWT will be performed, the test should not be done and should be rescheduled for another day, if possible within the permitted visit window (±7 days).

For each 6-MWT assessment, the site should make every effort to have this assessment performed by the same assessor and to perform the test at approximately the same time of day. If the test is interrupted or deemed unusable by the 6-MWT core laboratory, the 6-MWT should be repeated as soon as possible within the allowed visit window.

A patient may also require additional unscheduled measurements or measurements associated with the Pre-tafamidis Drop-in Visit or Early Treatment Discontinuation Visit (Table 1). To avoid repeated assessments within a short period of time, a 6-MWT will only be performed if the most recent assessment was performed more than 45 days before.

6.2.4. Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ [Green 2000] is a 23-item self-administered questionnaire developed to independently measure the patient's perception of health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life within a 2-week recall period.

The KCCQ quantifies 6 domains (symptoms, physical function, quality of life, social limitation, self-efficacy, and symptom stability) and 2 summary scores (clinical and overall summary [OS]).

The KCCQ questionnaire will be completed at the timepoints specified in the Schedules of Assessments (Table 1 and Table 2). When performed on dosing days, the KCCQ questionnaire will be administered prior to study drug administration.

6.2.5. Cardiac Assessments

Manifestations of cardiac amyloid involvement will be assessed via CCI [redacted] CCI [redacted] NYHA class as described below.

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.2.5.4. New York Heart Association (NYHA) Class

NYHA class is a clinical assessment of symptoms resulting from HF and is assessed according to the table in Section 10.2. NYHA class will be evaluated at the timepoints specified in the Schedules of Assessments (Table 1 and Table 2). The score collected at Screening will be used to determine eligibility.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.3. Pharmacodynamic Assessments

In this study, serum samples for measurement of TTR levels and vitamin A levels will be collected for the assessment of PD effects. TTR levels will be determined by a validated enzyme-linked immunosorbent assay (ELISA). Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

For this assessment, blood samples will be collected prior to dosing according to the timepoints specified in the Schedules of Assessments (Table 1 and Table 2).

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of plasma vutrisiran PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments (Table 1 and Table 2). A detailed schedule of time points for the collection of blood samples for PK analysis is provided in the Schedule of Assessments (Table 3 and Table 4).

Plasma concentration of vutrisiran will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Study Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, ECG findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by the Sponsor's Medical Monitors and Medical Monitors at the designated contract research organization, and in addition by an independent DMC as described in Section 3.7.

Routine safety assessments and collection of relevant safety information may be collected outside of the study center where applicable country and local regulations and infrastructure allow (beginning of Section 6).

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedules of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured predose, when applicable. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated or supine position, after the patient has rested comfortably for approximately 10 minutes. Blood pressure should be taken using the same arm, when possible. Body temperature in degrees Celsius will be obtained via oral, tympanic, or infrared methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital signs assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice (as applicable).

Vital signs results will be recorded in the eCRF.

6.5.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedules of Assessments (Table 1 and Table 2) and will be recorded in the eCRF.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedules of Assessments (Table 1 and Table 2); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status. In situations in which symptom-directed physical examinations cannot be performed during a home visit, they may be deferred to the next on-site visit.

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

CCI [redacted]

6.5.5. Clinical Laboratory Assessments

Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedules of Assessments (Table 1 and Table 2). These assessments will be evaluated by a central laboratory unless otherwise indicated.

LFTs must be reviewed by the Investigator prior to each dose of study drug.

Dosing decisions may be made based on LFT results (Table 6) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used. Specific instructions for transaminase elevations are provided in Section 6.5.5.4.

For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested.

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of assessments all laboratory assessments specified in Table 6 which are performed at the clinic or outside the clinic (eg, the patient's home), should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions. The only exception for central laboratory testing is related to the COVID-19 pandemic as described in the beginning of Section 6.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Carbon dioxide
Creatinine CCI	Chloride
Bicarbonate	
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Additional Chemistry Assessments	
C-reactive protein	Venous lactate
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Hepatic Tests (only at Screening)	
Hepatitis A, including: HAV antibody IgM and IgG	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Hepatitis C, including: HCV antibody HCV RNA PCR – qualitative and quantitative assays	Hepatitis E, including: HEV antibody IgM and IgG

Immunogenicity (see Section 6.5.5.1)	
Antidrug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only, at Screening only)
Monoclonal Gammopathy Assessment (only at Screening if applicable, see Section 6.5.5.1)	
Serum protein electrophoresis (SPEP) with immunofixation electrophoresis (IFE) (or documented local results)	Serum free light chains (or documented local results)
Urine protein electrophoresis (UPEP) with Immunofixation electrophoresis (IFE) (or documented local results)	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CCI FSH= follicle-stimulating hormone; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HBsAg=hepatitis B virus surface antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; HEV=hepatitis E virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid; MDRD=modification of diet in renal disease; SPEP with IFE=serum protein electrophoresis with Immunofixation Electrophoresis.

6.5.5.1. Assessment for Monoclonal Gammopathy including MGUS

As part of the determination of a diagnosis of ATTR amyloidosis, excluding evidence of a monoclonal gammopathy at Screening (Table 1) may be necessary (inclusion criterion #2). Laboratory assessments associated with this are indicated in Table 6. If available, documented local results obtained prior to Screening may be used to fulfill this inclusion requirement.

Abnormal findings, such as a monoclonal band (M-spike), on SPEP with IFE or serum free light chains with an abnormal kappa-to-lambda ratio that are suggestive of an alternative diagnosis, such as light chain amyloidosis, will require confirmatory testing using mass spectrometry or immunohistochemistry for confirmation of TTR protein deposition. Specifications for testing samples will be provided in the study laboratory manual. The determination of whether abnormal findings are suggestive of light chain amyloidosis may be assessed by a clinician experienced in the diagnosis of amyloidosis.

6.5.5.2. Immunogenicity

Blood samples (serum) for ADA testing will be collected at the timepoints specified in the Schedules of Assessments (Table 1 and Table 2). On dosing days, ADA sample collection is within 1 hour before dosing.

ADA will be assessed using a validated ELISA method.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Study Laboratory Manual.

6.5.5.3. Pregnancy Testing

Pregnancy tests will be performed for females of child-bearing potential at the timepoints specified in the Schedules of Assessments (Table 1 and Table 2) and at any time pregnancy is suspected.

A serum pregnancy test will be performed at Screening and urine or serum pregnancy tests will be performed thereafter. The results of the pregnancy test must be known before study drug administration. More frequent pregnancy testing may be performed where required per local requirements.

Patients who are pregnant at Screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

In situations where a study visit is unable to be completed at the site due to the COVID-19 pandemic impacting activities at the study site or patient ability or willingness to access the site, pregnancy testing may be performed by a healthcare professional or the patient/caregiver (and confirmed by the site) where applicable country and local regulations and infrastructure allow.

Follicle-stimulating hormone testing will be performed in all post-menopausal women to confirm suspected post-menopausal status.

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM and IgG	Parvovirus B19
HAV antibody IgM	HHV-6
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All Extended Hepatic Panel assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the International Council on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3 × ULN
- Severe or serious injection site reactions (ISRs); ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of vutrisiran.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to eCRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc.).

If patients develop ocular symptoms suggestive of vitamin A deficiency, for example reduced night vision or night blindness, the Investigator should consult with the Medical Monitor, and consider referral to an ophthalmologist if, in the opinion of the Investigator, it is medically appropriate. Any information collected during an ophthalmological assessment should be recorded in the eCRF and reports or images of ophthalmological assessments should be collected as well.

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. SAEs must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study drug that occurs after a patient withdraws from the study, the Investigator shall report the SAE to the Sponsor or designee within 24 hours of first awareness of the event.

If the Investigator becomes aware of an SAE in a patient with a suspected causal relationship to the study drug that occurs after the end of the study, the Investigator shall report the SAE to the Sponsor within 24 hours of first awareness of the event using the paper SAE form.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Clinical Trials Regulation (EU) No 536/2014 (CTR), and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through the end of their Follow-up Period (defined in Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding

the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled to not breastfeed for 90 days after the last dose of study drug (q3M treatment arm) or CCI after the last dose of study drug if the patient was initially randomized to the CCI dose regimen (under Amendment 3) and their last dose was CCI vutrisiran.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose Reporting

An overdose is defined as any dose of study drug administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. When an overdose is suspected, the Investigator should inform the Medical Monitor.

6.5.7. COVID-19 Data Collection

Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.

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7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before study unblinding for the primary analysis. The SAP will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

Enrollment (randomization) of 600 patients was planned CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

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7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses for the primary analysis, conducted at the completion of the DB Period (Section 3.1). Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

Additional analyses and data summaries will be outlined in the SAP.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS):** All patients who were randomized and received any amount of study drug (vutrisiran or placebo).
- **Vutrisiran Monotherapy Subgroup FAS:** All patients who were not on tafamidis at the study baseline in the FAS.
- **Safety Analysis Set:** All patients who received any amount of study drug.
- **Vutrisiran Monotherapy Subgroup Safety Analysis Set:** All patients who were not on tafamidis at the study baseline in the Safety Analysis Set.
- **PK Analysis Set:** All patients who received at least one full dose of study drug and have at least one non-missing postdose PK assessment and evaluable PK data.
- **PD Analysis Set:** All patients who received at least one full dose of study drug and have an evaluable baseline and at least one evaluable postbaseline sample for TTR assessment.

The FAS and vutrisiran monotherapy subgroup FAS will be used for the analysis of efficacy endpoints. Safety analyses will be based on the Safety Analysis Set and vutrisiran monotherapy subgroup Safety Analysis Set. PK and PD analyses will be based on PK Analysis Set and PD Analysis Set, respectively.

All by-treatment analyses based on the FAS and vutrisiran monotherapy subgroup FAS will be according to the randomized treatment arm. Safety analyses will be analyzed according to the treatment actually received.

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for the primary and secondary efficacy endpoints. Efficacy subgroup analyses will be conducted for age group (<75 versus ≥75), baseline tafamidis use (Yes versus No) (overall population endpoints only), ATTR disease type (hATTR; wtATTR) and NYHA Class (I/II; III). Safety subgroup analyses will be conducted for at least the following variables: age group, gender, race, geographic region, and NYHA class. Additional variables may be included and the details will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized by treatment arm.

7.2.5. Efficacy Analyses

The overall Type I error rate for the two primary endpoints and the secondary endpoints will be controlled at a 2-sided 0.05 significance level using a prespecified multiplicity testing procedure. The two primary endpoints will be tested at a 2-sided 0.05 significance level using the Hochberg testing procedure, ie, if the larger of two p-values is ≤0.05, both null hypotheses will be rejected; otherwise, the smaller of the two p-values will have to be ≤0.025 for the corresponding null hypothesis to be rejected. If both primary endpoints are statistically significant, the full alpha of 0.05 will be passed to test the secondary endpoints defined in both the overall population and the vutrisiran monotherapy subgroup using a pre-specified multiple testing procedure described in the statistical analysis plan (SAP). If one or both of the primary endpoints are not statistically significant, secondary endpoint tests will be performed and the results summarized, but statistical significance will not be inferred. CCI [redacted]

7.2.5.1. Primary Endpoints

The two primary endpoints of all-cause mortality and recurrent CV events in (1) the overall population and (2) the vutrisiran monotherapy subgroup CCI [redacted]

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Sensitivity analyses will be conducted and details will be provided in the SAP.

7.2.5.2. Secondary Endpoints

The secondary endpoints will be analyzed in both the overall population and the vutrisiran monotherapy subgroup.

The longitudinal endpoints, 6-MWT and KCCQ-OS, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline over 30 months. CCI [redacted]

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The change from baseline in NYHA class at Month 30 will be dichotomized into two categories: stable or improved versus worsened. This binary outcome will be analyzed using a logistic regression model with treatment, baseline NYHA class, and CCI CCI as covariates. For the overall population analysis, the model will also include baseline tafamidis use and baseline tafamidis use-by-treatment as covariates.

Sensitivity analyses for these secondary endpoints will be conducted and details will be provided in the SAP.

7.2.5.3. Exploratory Endpoints

Analysis of the exploratory endpoints (Section 2) will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Tabulated summary statistics and graphical displays of observed values, changes and percentage changes from baseline in PD biomarkers (TTR) will be presented in a longitudinal manner.

7.2.7. Pharmacokinetic Analysis

Tabulated summary statistics and graphical displays of the plasma concentrations of vutrisiran will be presented. In addition, population pharmacokinetic analysis will be performed to describe the plasma pharmacokinetics and evaluate the impact of relevant covariates, such as, weight, gender, race, age, renal function, hepatic function, and disease severity on plasma PK. Summary tables and figures and inferential statistics will be generated.

7.2.8. Safety Analyses

All safety summaries will be by treatment arm. The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by the Anatomical Therapeutic Chemical classification system and Preferred Term (PT).

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. The frequency and percentage of patients with AEs, SAEs, related AEs, and AEs leading to discontinuation will be summarized by SOC and PT. By patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Shift tables from baseline grade (or category) to the worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical examination findings and 12-lead ECG data will be presented in by-patient listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized. The impact of ADA on PK, PD, efficacy and safety endpoints will be explored. Details will be described in the SAP.

7.2.10. Interim Analysis

No interim analysis is planned.

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8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent and Medical Records Release Form

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient. A medical records release form will be also required of all patients where

allowed by local regulations, for the purpose of obtaining information on vital status, cardiac transplant procedures, left-ventricular assist device placement (Section 6.2.2), and hospitalizations (Section 6.2.1) from patients who discontinue early from the study.

The signing of this medical records release form is in addition to the ICF.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study (except those that support the need to remove an apparent immediate hazard to the patient). The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6.4. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are randomized under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the

Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons

designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

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10. APPENDICES

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10.2. New York Heart Association Class (NYHA)

Class	Symptomatology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

CCI

[redacted]

10.4. Amendment History

10.4.1. Amendment 5 Summary of Changes

The primary purpose for this global protocol amendment is to expand the analysis of the existing primary endpoint to both the overall population and the vutrisiran monotherapy subgroup (defined as the subgroup of patients not on tafamidis at study baseline). Changes included in this amendment concern the method of data analyses and do not impact study execution or the patient experience.

Establishing the efficacy of vutrisiran in the overall population is important because it is representative of current treatment practice, wherein many patients with ATTR amyloidosis (hereditary and wt) with cardiomyopathy are prescribed tafamidis as it is the only currently approved treatment available.

The rationale for analyzing the primary endpoint in the vutrisiran monotherapy subgroup is to enable demonstration of the potential clinical benefit of vutrisiran without any confounding effect of benefit from tafamidis. Patients already prescribed tafamidis for the approved cardiomyopathy indication were permitted to enroll in HELIOS-B, and there was no eligibility requirement that these patients needed to have manifested disease progression on tafamidis. Thus, patients on tafamidis at baseline, comprising approximately 40% of the enrollment into

HELIOS-B, are likely to have been receiving some degree of CV benefit from this medication throughout the trial. For this reason, the results from a pre-specified analysis in the vutrisiran monotherapy subgroup would provide the clearest demonstration of the potential clinical benefit of vutrisiran, without any confounding effect of benefit from concomitant tafamidis.

This amendment also restructures the existing secondary and exploratory endpoints such that specific endpoints were moved from exploratory to secondary and from secondary to exploratory based on the rationale below.

Changes included with Amendment 5 are outlined below:

Section(s)	Description of Change	Brief Rationale
Section 1.5; Section 2; Section 7.2.5; Synopsis	The primary endpoint is the composite of all-cause mortality and recurrent CV events. Amendment 5 will add a (dual) primary endpoint to test this composite endpoint (composite of all-cause mortality and recurrent CV events) in both the overall population and the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline).	The primary endpoint will be analyzed in the overall population, since that is representative of current treatment practice, wherein many patients with ATTR-CM are prescribed tafamidis as it is the only currently approved treatment available. Patients already prescribed tafamidis for the approved cardiomyopathy indication were permitted to enroll in HELIOS-B, and there was no eligibility requirement that these patients needed to have manifested disease progression on tafamidis. Thus, patients on tafamidis at baseline are likely to have been receiving some degree of CV benefit from this medication throughout the trial. For this reason, the results from a pre-specified analysis in the vutrisiran monotherapy subgroup would provide the clearest demonstration of the potential clinical benefit of vutrisiran, without any confounding effect of benefit from concomitant tafamidis.
	Restructured specific secondary and exploratory endpoints, CCI [redacted] a new secondary endpoint of change from baseline in NYHA class, and deletion of recurrent CV events. CCI [redacted]	The relocation or addition of specific secondary and exploratory endpoints have been made to optimize the study design in light of emerging external data in ATTR-CM from other clinical trials in the disease space. Recurrent CV events was removed from the secondary endpoints list because data will be available and analyzed as part of the primary analysis. The changes impact the placement of the endpoints within the endpoint structure and addition of

Section(s)	Description of Change	Brief Rationale
	CCI [redacted]	exploratory endpoints based on assessments already being collected on study; there have been no changes to the way these endpoints are collected on study.
	CCI [redacted]	CCI [redacted]
Section 3.1; Section 3.2; Synopsis	Clarified the potential duration of exposure during the DB Period with revisions to the following bullet points: • An individual patient's DB Period visits will end after they complete their Month 36 Visit, or 30 months after the last patient is randomized, whichever comes first. As such, a patient's last visit during the DB Period may vary from 30 to 36 months after enrollment. – The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the Open-Label Extension (OLE) Period will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 33 (Week 144), Day	Revised to better explain the potential variability for the duration of exposure during the DB Period based on the timing of an individual patient's last visit in the DB Period, and to clarify timing of the primary analysis. There are no changes to the patients' schedule of assessments or to the patient experience in the study.

Section(s)	Description of Change	Brief Rationale
	1 in the OLE Period will occur 156 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 36 (Week 156), Day 1 in the OLE Period will occur on the same day (since study drug is not administered as part of the Month 36 DB visit). – The period of DB exposure, defined as the duration prior to first exposure to open-label treatment, will be 144 to 156 weeks (33 to 36 months). • The primary analysis will be conducted after the last patient has completed the period of DB exposure or otherwise discontinued.	
Section 5.4.1	For patients on tafamidis at baseline, the reason why the patient was enrolled while already receiving tafamidis (in the opinion of the Investigator) will be recorded in the eCRF.	To align with Protocol Administrative Letter 6, dated 08 September 2023.
Section 6.2.5	CCI [redacted]	CCI [redacted]
Sections 6.5.6.4 and 6.5.6.5	Clarified requirements for reporting SAEs after patient withdrawal or end of study.	To align with EU CTR (No 536/2014), Article 41.
Section 7.1; Section 7.2; Synopsis	The power and its assumptions were updated in Section 7.1.	CCI [redacted]

Section(s)	Description of Change	Brief Rationale
		CCI [redacted]
	Defined new analysis sets: vutrisiran monotherapy subgroup FAS; vutrisiran monotherapy subgroup Safety Analysis Set.	Additional analysis sets and analysis plans were added for the vutrisiran monotherapy subgroup to reflect the endpoints change in the protocol amendment 5.
	CCI [redacted]	CCI [redacted]
	CCI [redacted]	CCI [redacted]
	CCI [redacted]	CCI [redacted]

Section(s)	Description of Change	Brief Rationale
		CCI [redacted]
	Added analysis details for NYHA class. CCI [redacted]	To reflect the endpoint changes in the protocol amendment 5.

10.4.2. Amendment 4 Summary of Changes

The primary purpose for this protocol amendment is to transition all patients in the CCI once CCI vutrisiran arm of the extension period to receive 25 mg once every 3 months (q3M) vutrisiran for the remainder of their dosing visits in the study.

The HELIOS-A and HELIOS-B studies are evaluating a CCI vutrisiran dosing regimen in comparison to a 25 mg q3M vutrisiran dosing regimen in their extension periods for patients with hereditary ATTR (hATTR) amyloidosis with polyneuropathy and cardiomyopathy, respectively. Based on 9-month data from the extension period of the HELIOS-A study in patients with hATTR amyloidosis with polyneuropathy, the clinical efficacy and safety profiles of the CCI regimen were comparable to the 25 mg q3M regimen as presented in the Investigator's Brochure Edition 5 Addendum. Non-inferiority in percent serum transthyretin (TTR) reduction between CCI and 25 mg q3M was established; however, some degree of TTR recovery was noted at the end of the CCI dosing interval.

After consideration, the Sponsor has made a business decision to discontinue clinical development of the CCI regimen.

Changes to the protocol are outlined below.

Changes Related to the Removal of the CCI Dosing Regimen

- The study design has been revised to transition all patients receiving CCI to 25 mg q3M vutrisiran, and will include an Open-label Treatment Extension (OLE) Period in lieu of the Randomized Treatment Extension Period. This change led to modification of the study design figure, revision to the schedules of assessments (Table 2 and Table 4), and other relevant adjustments throughout the protocol.
- Clarified that the minimum duration of follow-up post unblinding will be based on whether the patients last dose was 25 mg or CCI.
- Replaced Randomized Treatment Extension (RTE) Period with OLE Period throughout the protocol.

Additional Changes:

- Deleted pharmacokinetic (PK) collection at the early discontinuation/termination visits during the OLE Period (Table 2) to align with the Double-Blind Period (Table 1) and alleviate confusion since the PK sample is not required if patients discontinue study drug after the OLE Day 1 visit.
- Clarified the duration of the Double-Blind Period relative to patients starting in the OLE Period.
- Removed use of a case report form for reporting product complaints.
- CCI

CCI [redacted]

– CCI [redacted]

A detailed summary of changes is provided in Table 8. The following changes are not detailed: administrative changes, corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

Table 8: Protocol Amendment 4 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Amendment 4 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Remove reference to the RTE Period and the CCI *dosing regimen, clarify the duration of the Double-Blind Period relative to a patient starting in the OLE Period, and adjust follow-up time between dosing.*

The primary change occurs in Section 3.1 Summary of Study Design

Revised text:

The study consists of 4 periods (Figure 1):

1. Screening Period: Up to 45 days during which patients will undergo screening assessments to determine eligibility.
2. Double-Blind (DB) Period:
   - At the start of the DB Period (on Day 1), eligible patients will be randomized in a 1:1 ratio to receive blinded doses of 25 mg of vutrisiran or placebo administered as a SC injection q3M (every 12 weeks ±7 days) for up to 36 months.
     - In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their DB Period and Follow-up Period (see below).
   - Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1).
   - An individual patient's DB Period will end after they complete their Month 36 Visit, or 30 months after the last patient is randomized, whichever comes first. As such, the length of each patient's intended treatment during the DB Period may vary from 30 to 36 months.
   - The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. ~~For those patients, the Day 1 visit of their Open-label Treatment Extension (OLE) Period should be 3 months after their last planned visit (at Month 30 or Month 33 [±7 days]).~~ **For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the Open-Label Extension (OLE) Period will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 33 (Week 144), Day 1 in the OLE Period will occur 156 weeks (±7 days) after enrollment in the DB Period**.
   - The primary analysis will be conducted after the last patient has completed the Month 30 Visit or otherwise discontinued.
3. Open-Label ~~Randomized~~ Treatment Extension (**OLE** ~~RTE~~) Period

The study has been amended (Amendment 4) to include an OLE Period in lieu of the Open-Label Randomized Treatment Extension Period (previously introduced with Amendment 3). In the OLE Period, all patients will receive the 25 mg q3M vutrisiran regimen.

- ~~On or before the date of their last planned visit of the DB Period, patients will be randomized to treatment in RTE Period as described below and receive their first dose of open-label vutrisiran at this visit (RTE Day 1).~~
- ~~At the start of~~ **Upon entry into** the **OLE Period** ~~(RTE Day 1)~~, eligible patients will ~~be randomized in a 1:1 ratio~~ **transition** to **receive open-label doses of 25 mg q3M vutrisiran** ~~or~~ CCI **administered as SC injections**.
- **Patients initially** randomized **to** CCI **(under Amendment 3) will transition** to receive open-label doses of 25 mg **q3M** vutrisiran administered as SC injections **at their next scheduled dosing visit (24 weeks after their last dose of** CCI **vutrisiran). Patients initially randomized to 25 mg q3M vutrisiran (under Amendment 3) will continue with the 25 mg q3M regimen**.
  - In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their ~~RTE~~ **OLE** Period and Follow-up Period (see below).
- **All** patients will undergo assessments as outlined in the Schedule of Assessments for the ~~RTE~~ **OLE** Period (Table 2).

Note: Patients who do not complete the DB Period may not participate in the ~~RTE~~ **OLE** Period. Consent must be signed before any procedures are performed in the ~~RTE~~ **OLE** Period (Table 2).

4. Follow-Up Period after the last dose of vutrisiran on study:
   - Following completion of the ~~RTE~~ **OLE** Period (or completion of the DB Period for patients who do not continue into the ~~RTE~~ **OLE** Period; or their last dose of vutrisiran for patients who discontinue study drug early), patients will commence follow-up visits every 12 weeks for the durations outlined below.
   - Prior to unblinding of their treatment from the DB Period, the duration of the Follow-up Period for a patient will be 1 year from their last dose of study drug. For women of child-bearing potential, the duration of the Follow-up Period will be 18 months from their last dose of study drug. Patients will continue vitamin A supplementation during their Follow-up Period.
   - After unblinding, all patients who were on placebo, and patients who received vutrisiran whose serum TTR level has returned to ≥80% of baseline or who have completed the Follow-up Period, whichever comes first, may discontinue further follow-up and stop taking vitamin A. Baseline is defined as the last value prior to first vutrisiran dose (ie, prior to the first DB dose for vutrisiran patients in DB Period and prior to the first **OLE** dose for placebo patients). Patients will be followed for a minimum period as listed below during the Follow-up Period based on treatment regimen received:

  - All patients **whose last dose of** study drug **was** 25 mg vutrisiran/placebo during DB Period or 25 mg vutrisiran during the ~~RTE~~ **OLE** Period will be followed for a minimum of 90 days after their last dose of study drug.
  - **Patients whose last dose of study drug was** CCI vutrisiran regimen **(under Amendment 3)** will be followed for a minimum of CCI after their last dose of study drug during Follow-up Period.

- For any patient who starts a TTR lowering treatment as part of clinical care, and has completed a minimum of 90 or CCI (depending on vutrisiran treatment regimen) of safety follow-up since their last dose of study drug, further follow-up will be discontinued.
- Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1 and Table 2).

Patients may receive vutrisiran on the study until the end of the ~~RTE~~ **OLE** Period or until one of the following occurs: 1) they meet any of the study discontinuation criteria; 2) vutrisiran is commercially available in the patient's country of residence and vutrisiran is accessible to the patient and the patient has completed their ~~RTE~~ **OLE** Month 12 Visit; or 3) the vutrisiran development program is discontinued.

Study drug dosing may be allowed outside of the study center (eg, the patient's home) during the DB Period or ~~RTE~~ **OLE** Period under certain circumstances as specified in Section 5.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in Section 6.

Sections also reflecting this change:

- Synopsis
- Table 2, Schedule of Assessments: Open-Label Treatment Extension (OLE) and Follow-Up Periods

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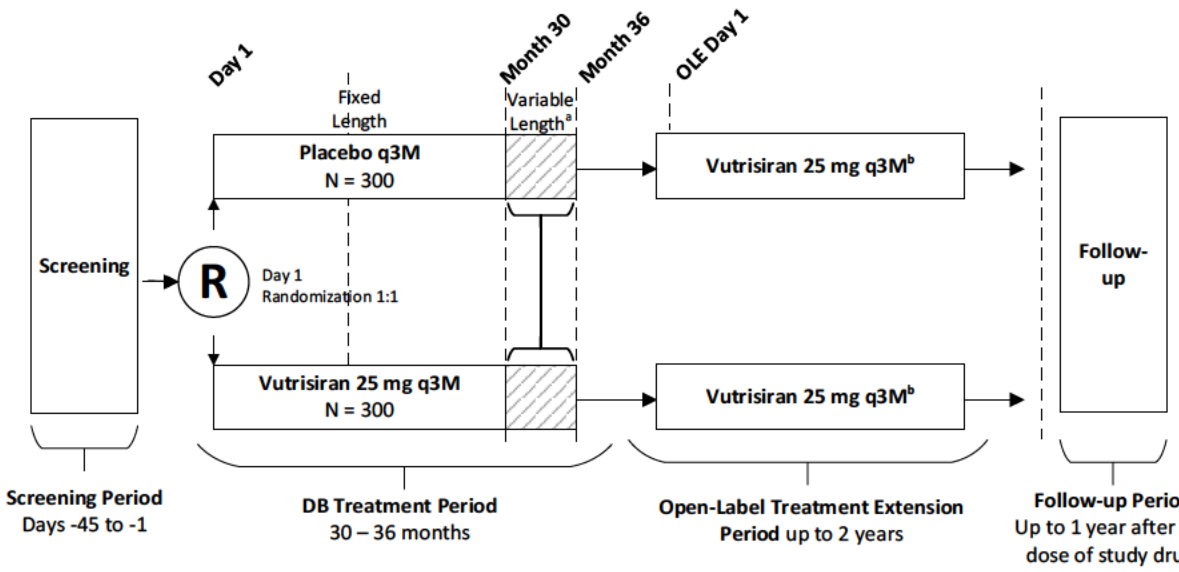
Purpose: Update the study design figure to reflect Amendment 4

The primary change occurs in Synopsis

Revised figure:



[a] An individual patient's DB Period will end after they complete the Month 36 Visit, or 30 months after the last patient is randomized, whichever comes first. As such, the length of each patient's intended treatment during the DB Period may vary from 30 to 36 months.

[b] **The dosing schedule under Amendment 4 is 25 mg vutrisiran every 12 weeks. Upon entry into the OLE Period (OLE Day 1), all eligible patients will receive open-label doses of 25 mg q3M vutrisiran administered as SC injections. Patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).**

[c] Following completion of the **OLE** Period (or completion of the DB Period for patients who do not continue into the **OLE** Period; or their last dose of vutrisiran for patients who discontinue study drug early), patients will commence follow-up visits as outlined in Section 3.1. For women of child-bearing potential, the duration of the Follow-up Period will be up to 18 months from their last dose of study drug.

Purpose: To clarify the Schedules of Assessments

The primary change occurs in Synopsis, Table 1 and Table 2

Revised text:

- CCI [redacted]
- Deleted PK collection at the Early Termination/Early Study Discontinuation visits (Table 2)
- Additional bulleted notes beneath Table 2:

  - **For patients enrolled under Amendment 3, the visit schedule remains the same following implementation of Amendment 4, with no changes to the visit weeks noted in Table 2. For example, if Amendment 4 was implemented after a patient had completed Week 24 under Amendment 3, their first visit under Amendment 4 will be Week 36.**
  - **The dosing schedule under Amendment 4 is 25 mg vutrisiran every 12 weeks; however, patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).**

- Revised footnote a, Table 2:
  - [a] **For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the OLE will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 33 (Week 144), Day 1 in the OLE will occur 156 weeks (±7 days) after enrollment in the DB Period. For patients who reach the Month 36 (Week 156)** visit of the DB Period prior to the end of the DB Period for the study, this visit will take place on the same day as the Day 1 visit of the **OLE** Period. When this occurs, patients should complete the Scheduled Assessments for both the Month 36 visit of the DB Period and the Day 1 visit of the **OLE** Period. However, where these visits take place on the same day, assessments do not need to be repeated twice on the same day (ie, if an assessment is listed for both the Month 36 visit of the DB Period and the Day 1 visit of the **OLE** Period, the assessment can be performed once). An informed consent form that has been approved by the appropriate Institutional Review Board /Independent Ethics Committee must be signed by the patient before any procedures are performed in the **OLE** Period.

- Added footnote d, Table 2:
  - [d] **The dosing schedule under Amendment 4 is 25 mg vutrisiran every 12 weeks. Upon entry into the OLE Period (OLE Day 1), all eligible patients will receive open-label doses of 25 mg q3M vutrisiran administered as SC injections. Patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).**

Purpose: To clarify the impact to study design rationale based on Amendment 4.

The primary change occurs in Section 1.5, Study Design Rationale

Revised text:

Patients will receive treatment with 25 mg vutrisiran or placebo every 3 months (q3M) during their Double-blind (DB) Period of the study for up to 36 months. The primary analysis will be conducted 30 months after the last patient is randomized. As such, the length of each patient's intended treatment during the DB Period may vary from 30 to 36 months. ~~In addition, an~~ **An** Open-label **Randomized Treatment Extension** Period ~~(hereafter referred to as the RTE Period)~~ was added with Amendment 3 in which patients who complete treatment in the DB Period will be randomized to receive either 25 mg vutrisiran q3M or CCI in an open label fashion. **Following implementation of Amendment 4, the Randomized Treatment Extension will be replaced with an Open-Label Treatment Extension where all patients who complete treatment in the DB Period will receive vutrisiran 25 mg q3M for up to 2 years.** A Follow-up Period will commence when patients complete the **OLE** Period (or complete the DB Period for patients who do not continue into the **OLE** Period; or their last dose of vutrisiran for patients who discontinue study drug early) and patients will be followed for a period of up to 1 year after their last dose of study drug. See also Section 3.1.

The ~~RTE~~ **OLE** Period is designed to evaluate the **longterm** ~~efficacy,~~ safety and efficacy ~~, PK, and PD of the~~ CCI ~~dosing regimen in comparison to the 25 mg q3M dosing regimen~~ of vutrisiran.

Purpose: Remove modeling statements and planned analysis for the CCI *dose regimen*

The primary change occurs in Section 1.6, Dose Rationale

Revised text:

The vutrisiran regimen of 25 mg q3M SC is proposed for the DB Period of this Phase 3 Study ALN-TTRSC02-003 (HELIOS-B) to be conducted in patients with hATTR or wtATTR amyloidosis with cardiomyopathy. ~~In addition to the 25 mg q3M dose, a dose of~~ CC ~~SC given~~ CCI ~~is included as a treatment arm during the RTE Period. These doses are~~ **This dose is** also being evaluated for the treatment of patients with hATTR amyloidosis with polyneuropathy in the ongoing Phase 3 Study ALN-TTRSC02-002 (HELIOS-A) described in Section 1.4.

~~In addition to the 25 mg dose of vutrisiran, modeling and simulation predict that the~~ CCI ~~and 25 mg q3M regimens of vutrisiran achieve comparable average TTR reductions with the same cumulative annual dose (100 mg). Addition of the~~ CCI ~~dose in the RTE Period of this study will provide data to further assess the extent of TTR reduction and the overall safety, PD, and efficacy of a~~ CCI ~~dose compared to a 25 mg q3M dose of vutrisiran.~~

Purpose: Remove justification for addition of CCI *dosing regimen.*

The primary change occurs in Section 1.7, Benefit-Risk Assessment

Deleted text:

~~Patients with ATTR amyloidosis often suffer substantial loss in ambulatory ability and mobility that significantly impact activities of daily living and can make healthcare visits challenging. The addition of a CCI dose regimen aims to further minimize the need for frequent healthcare visits and further mitigate patient burden. This is consistent with global trends toward decreased healthcare encounters, the importance of which has been further highlighted by the COVID-19 pandemic~~.

Purpose: To remove description of the process for randomization during the treatment extension.

The primary change occurs in Section 3.5, Method of Assigning Patients to Treatment Groups

Deleted text:

~~Randomization for the RTE Period:~~

~~Using Interactive Response Technology (IRT), patients will be randomized 1:1 to the 25 mg vutrisiran q3M or CCI arm. Randomization will be stratified by:~~

1. ~~Tafamidis use (yes versus no) (assessed on Day 1 of the RTE Period)~~
2. ~~ATTR disease type (hATTR versus wtATTR amyloidosis with cardiomyopathy)~~
3. ~~NYHA Class I or II and age <75 years versus all other (assessed on Day 1 of the RTE Period)~~

Sections also reflecting this change:

- Synopsis

Purpose: Remove description of the CCI dose.

The primary change occurs in Section 5.2.1, Description (of study drug)

Deleted text:

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Study drug (vutrisiran or placebo) will be administered using single-use prefilled syringes. Each prefilled syringe will be filled with either a 25 mg dose of vutrisiran or placebo with a fill volume of 0.5 mL. ~~Two pre-filled syringes (each with a 25 mg dose of vutrisiran and a volume of 0.5 mL) will be administered sequentially for patients randomized to the CCI dose during the RTE Period.~~ Each pre-filled syringe includes a needle safety device which will be engaged to cover the exposed needle after injection.

Purpose: Specify dose administration for patients enrolled under Amendment 3 and those under Amendment 4.

The primary change occurs in Section 5.2.2, Dose and Administration

Revised text:

Starting on Day 1 of the DB Period, patients will receive 25 mg of vutrisiran or placebo administered as a SC injection q3M (every 12 weeks ±7 days) for up to 36 months.

~~Starting on Day 1 of the RTE Period~~ **Under Amendment 4**, **all** patients will receive SC injections of 25 mg of vutrisiran q3M (every 12 weeks ±7 days) ~~or~~ CCI for up to 2 years **during the OLE Period**.

The first dose of study drug should be administered in the clinic on Day 1 of the DB Period (placebo or 25 mg of vutrisiran) and Day 1 of the **OLE** Period (25 mg of vutrisiran ~~or~~ CCI ~~of vutrisiran~~). If a patient has tolerated at least 1 dose of study drug in the clinic, subsequent dosing for the remainder of that period may be administered outside the study site (eg, the patient's home) at all other timepoints where allowed by applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare professional, with oversight by the Investigator.

If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, ~~q3M regimens of~~ study drug (placebo or 25 mg vutrisiran) may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on study drug administration. This measure (self- or caregiver administration) is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing. ~~The~~ CCI ~~vutrisiran regimen introduced in the RTE Period must be administered by a healthcare professional.~~

Missed doses of Study Drug

If a patient does not receive a dose of study drug within the specified dosing windows, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered as close to the scheduled dosing date as possible with a maximum 8-week delay (to be considered a delayed dose). For patients ~~in the~~ **initially randomized to** CCI ~~treatment arm~~ **(under Amendment 3)**, delays beyond 8 weeks may be allowable, but must be discussed with the Medical Monitor.-Thereafter, the dose will be considered missed and not administered. If a dose is missed or is administered with a delay, the next dose will resume following the original schedule. In cases in which a dose is delayed in this manner for issues related to the COVID-19 pandemic, the Medical Monitor should be informed as soon as possible, but prior consultation is not required. In all cases, the dose should be administered as close as possible to the scheduled timepoint.

Sections also reflecting this change:

- Synopsis

Purpose: Clarify Patient/Caregiver Storage and Administration Instructions

The primary change occurs in 5.2.5, Dose Preparation, Handling, and Storage

Deleted Text:

Staff at each clinical study center, or the home healthcare professional, will be responsible for preparation of study drug, according to procedures detailed in the Pharmacy Manual. In cases where study drug is administered outside the study center, dosing may be prepared by the home healthcare professional or patient/caregiver ~~(patient/caregiver is applicable to the 25 mg q3M dose only)~~ according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Purpose: Removed use of a case report form for reporting product complaints

The primary change occurs in 5.3.2, Reporting

Revised Text:

For PCs, the Sponsor or its designee should be notified within 24 hours ~~using the appropriate eCRF~~.

Purpose: Clarified pregnancy reporting for any patients who received CCI *under Amendment 3.*

The primary change occurs in Section 6.5.6.7, Pregnancy Reporting

Revised text:

If a female patient becomes pregnant during the study through the end of their Follow-up Period (defined in Section 3.1), the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled to not breastfeed for 90 days after the last dose of study drug (q3M treatment arm) or CCI after the last dose of study drug CCI **if the patient was initially randomized to the** CCI **dose regimen (under Amendment 3) and their last dose was** CCI **vutrisiran.**

Purpose: Remove reference to a planned descriptive comparison of 25 mg q3M versus CCI .

The primary change occurs in Section 7.2, Statistical Methodology

Revised text:

Additional data summaries to help understand any impact of the COVID-19 pandemic and ~~any descriptive comparison of ALN-TTRSC02 25 mg q3M and~~ CCI ~~dose regimens during the RTE Period~~ **OLE Period data analyses** on efficacy, PD, and safety assessments will be outlined in the SAP.

Purpose: Remove planned interim analysis.

The primary change occurs in Section 7.2.10, Interim Analysis

Revised text:

CCI

No interim analysis is planned.

Sections also reflecting this change:

- Table of Abbreviations
- Section 7, Statistics

10.4.3. Amendment 3 Summary of Changes

The primary purpose for this protocol amendment is to add an Open-label Randomized Treatment Extension (RTE) Period to allow a descriptive comparison of 2 vutrisiran dosing regimens administered during the RTE Period.

During the RTE period, patients will be randomized 1:1 to receive treatment with 1 of 2 different treatment regimens for up to 2 years. Patients in one arm will receive 25 mg vutrisiran once every 3 months (q3M). Patients in the other arm will receive an alternative dosing regimen CCI This amendment will enable a descriptive comparison of the alternate dosing regimen with the current dosing regimen with respect to safety, pharmacodynamic (PD), pharmacokinetic (PK), and efficacy. The proposed CCI regimen is the same cumulative annual dose (100 mg) relative to the 25 mg q3M and the dosing regimens are predicted to have similar safety, transthyretin (TTR) reduction (PD), and efficacy.

The CCI regimen, being administered only twice a year, is a potentially important alternative option for patient care that may further reduce treatment burden for patients and caregivers. Patients with ATTR amyloidosis often suffer substantial loss in ambulation and mobility that significantly impact activities of daily living and can make healthcare visits challenging. The ongoing coronavirus disease 2019 (COVID-19) pandemic has demonstrated the potential benefit of a less frequent dosing option for patients with ATTR amyloidosis to minimize the need for healthcare visits and mitigate the associated risk of missed doses for a serious and life-threatening condition. The addition of the CCI regimen aims to provide an option that can reduce treatment visits by half (from 4 to 2 times a year) and further mitigate patient burden, consistent with global trends toward decreased healthcare encounters. The benefit of reduced healthcare encounters, while highlighted recently by the COVID-19 pandemic, will substantially benefit patients post-pandemic as well.

The rationale for the CCI regimen of vutrisiran is based on predictions from modeling and simulation of TTR reduction data from the Phase 1 vutrisiran study (ALN-TTRSC02-001) and data through Month 18 from the Phase 3 ALN-TTRSC02-002 (HELIOS-A) study in patients with hATTR amyloidosis with polyneuropathy. The safety, PD, PK, and efficacy of the vutrisiran CCI regimen is also being explored in patients with hATTR with polyneuropathy in the RTE of the ongoing HELIOS-A study.

In addition to achieving the same cumulative annual dose of 100 mg as tested in the treatment period in HELIOS-A, observed data from the single-dose Phase 1 study (ALN-TTRSC02-001) and PK/PD modeling show that the CCI and 25 mg q3M regimens of vutrisiran are expected to achieve comparable average TTR reductions (see Table 9).

- The CCI regimen is expected to achieve slightly higher median peak lowering with lower variability compared with the 25 mg q3M regimen (89.3 % vs 87.8%).
- The 25 mg q3M and CCI regimens are predicted to achieve median trough TTR reduction of 86.4% and 82.5% which are similar to the observed median trough TTR reductions of 81.2% for patisiran at Month 18 of the APOLLO study. [Adams 2018]
- Importantly, the steady state average TTR lowering of both 25 mg q3M and CCI CCI are expected to be similar (87.1% vs 86.7%).

The TTR lowering expected with 25 mg q3M or CCI dosing regimens of vutrisiran is similar to that observed with patisiran in APOLLO, and hence is expected to translate into similar clinical efficacy.

Table 9: Summary of Observed and Predicted Median TTR Reductions (%) for CCI 25 mg q3M Vutrisiran, and 0.3 mg/kg q3W Patisiran Regimens

	Vutrisiran (Model-predicted)		HELIOS-A Vutrisiran (Observed)	APOLLO Patisiran[c] (Observed)
Serum TTR % change from baseline	**25 mg q3M[a]**	**CCI**	**25 mg q3M**	**0.3 mg/kg q3W**
Peak	-87.8 (-97.8, -51.7)	-89.3 (-97.9, -57.0)	-90.8[d] (-97.7, -63.4)	-88.5 (-95.4, -56.8)
Trough	-86.4 (-97.7, -43.7)	-82.5 (-97.5, -31.4)	-86.2[e] (-97.3, -41.8)	-81.2 (-94.2, -49.9)
Average	-87.1 (-97.7, -48.6)	-86.7 (-97.7, -46.9)	-86.9[f] (-97.5, -42.1)	-83.1 (-93.7, -56.5)

Abbreviations: q3M=once every 3 months; CCI ; q3W=once every 3 weeks; TTR=transthyretin.
The numbers in table are median and 5th and 95th percentiles of simulations (vutrisiran) or observed data (patisiran)

[a] The average TTR reduction was computed over a dosing interval (Month 15 to Month 18), while peak and trough TTR reduction was at Week 66 and Week 72, respectively.
[b] The average TTR reduction was computed over a dosing interval (Month 12 to Month 18), while peak and trough TTR reduction was at Week 56 and Week 72, respectively.
[c] For APOLLO observed data (Month 18), the peak and trough percent TTR change was at Month 18 and Day 546, respectively, while the average percent TTR change represents the mean of assessments at Day 546, Month 18 and Day 567.
[d] Day 211 and Day 547 samples for vutrisiran.
[e] Day 253 and Day 505 samples for vutrisiran.
[f] Represents the mean of assessments between Month 6 and Month 9 (Day 169, 211 and 253) and Month 15 to Month 18 (Day 421, 465 and 505) for vutrisiran.

Importantly, the available safety data in healthy volunteers, as well as exposure-response modeling, suggest the two regimens will result in similar safety profiles. In the Phase 1 study, vutrisiran demonstrated an acceptable safety profile at single doses up to 300 mg. The data to date in HELIOS-A also support that vutrisiran continues to have an acceptable safety profile.

In summary, the adjustment of the study design to include an RTE Period will facilitate a descriptive comparison of safety, PD, PK, and efficacy of the CCI regimen relative to the 25 mg q3M dose regimen. The CCI regimen has the same annual dose (100 mg) and an expected therapeutic effect and safety comparable to the 25 mg q3M regimen.

Changes to the protocol are outlined below.

Changes Related to the Addition of the RTE Period and a CCI Dosing Regimen

- Patients must sign an informed consent form for the RTE Period before any procedures can be performed in the RTE Period.
- The study design has been revised to include the open-label RTE Period described above. This includes modification of the study design figure, addition of new schedules of assessments for the RTE Period (Table 2 and Table 4), and other relevant modifications throughout the protocol.

- The schedule of assessments for the Double-blind (DB) Period has been modified to reflect the addition of the RTE Period. The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. For those patients, the Day 1 visit of their RTE Period should be 3 months after their last planned visit (at Month 30 or Month 33 [±7 days]).
- Patients will now enter the Follow-up Period after completing treatment in the RTE Period (or completion of the DB Period for patients who do not continue into the RTE period; or their last dose of vutrisiran for patients who discontinue study drug early).
- Guidance was added for minimum safety follow-up for all patients and contraceptive requirements after the last dose of study drug in the RTE:
  - For patients who receive 25 mg vutrisiran q3M, minimum safety follow-up will be 90 days and women of childbearing potential should continue contraception for 90 days after the last dose of study drug. This is consistent with the original guidance with respect to patients receiving q3M treatment with 25 mg vutrisiran or placebo in the DB Period.
  - For patients who receive CCI [redacted] in the RTE Period, minimum safety follow-up will be CCI [redacted] and women of childbearing potential should continue contraception for CCI [redacted] after the last dose of study drug.
- Previous wording that the Sponsor would provide access to vutrisiran through an open-label extension in the case in which there were no commercially available treatment options was removed, as the RTE Period now provides continued access.

Additional Changes:

- Revised guidance to specify that efficacy assessments other than the 6-MWT and the KCCQ only need to be performed prior to study drug administration on Day 1 of the DB Period and Day 1 of the RTE Period. This change will decrease the burden of study visits on patients by allowing patients' time to be used more efficiently. Given the pathophysiology of ATTR amyloidosis, the mechanism of action of vutrisiran, and long duration of its PD effect, the results of these efficacy assessments would not be expected to be impacted by receiving a dose of study drug administered earlier on the same day.
- Specified that starting a TTR-lowering regimen meets the criteria for end of study for an individual patient.
- Removed wording that the Sponsor may perform a sample size re-assessment (SSR) 3 months prior to having the last patient randomized to preserve study power in the event of a higher-than-expected tafamidis drop-in rate or imbalance between treatment arms. The sponsor observed low tafamidis drop-in rate (<1%) as of May 2021 and made the decision to not conduct an SSR. As a result, an SSR was not conducted, and enrollment was completed in August 2021.
- Clarified guidance on safety and other assessment delays when a study visit is unable to be completed at the site (previously only efficacy assessments were specified). Also included requirement for consultation with the Medical Monitor.

- Updated liver function test (LFT) monitoring and pregnancy reporting text to align with updates made to the Sponsor protocol template reflecting current Sponsor standards.
- Clarified definitions of the PK Analysis Set and PD Analysis Set to include all patients who received at least 1 complete dose of study drug. Removed Per-Protocol Analysis Set.

A detailed summary of changes is provided in Table 10. The following changes are not detailed: administrative changes, corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

Table 10: Protocol Amendment 3 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 3 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: To add the Randomized Treatment Extension (RTE) Period.

The primary change occurs in Section 3.1, Summary of Study Design

Revised text:

The study consists of ~~3~~ **4** periods (Figure 1):

6. **Screening Period:** Up to 45 days during which patients will undergo screening assessments to determine eligibility.
7. **Double-Blind (DB) Period ~~(DB Period)~~:**
   - At the start of the DB Period **(on Day 1)**, eligible patients will be randomized in a 1:1 ratio to receive **blinded doses of** 25 mg of vutrisiran or placebo administered as a SC injection q3M for up to 36 months.
     - In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their DB Period and Follow-up Period (see below).
   - Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1).
   - An individual patient's DB Period will end after they complete their Month 36 Visit, or 30 months after the last patient is randomized, whichever comes first. As such, the length of each patient's intended treatment during the DB Period may vary from 30 to 36 months.
   - **The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. For those patients, the Day 1 visit of their RTE Period should be 3 months after their last planned visit (at Month 30 or Month 33 [±7 days]).**
   - The primary analysis will be conducted after the last patient has completed the Month 30 Visit or otherwise discontinued.
8. **Open-Label Randomized Treatment Extension (RTE) Period**
   - **On or before the date of their last planned visit of the DB Period, patients will be randomized to treatment in RTE Period as described below and receive their first dose of open-label vutrisiran at this visit (RTE Day 1).**
   - **At the start of the RTE Period (RTE Day 1), eligible patients will be randomized in a 1:1 ratio to receive open-label doses of 25 mg of vutrisiran q3M or** CCI **administered as SC injections for up to 2 years.**

  - **In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their RTE Period and Follow-up Period (see below).**

- **Patients will undergo assessments as outlined in the Schedule of Assessments for the RTE Period (Table 2).**

Note: Patients who do not complete the DB Period will not participate in the RTE Period. Consent must be signed before any procedures are performed in the RTE (Table 2).

9. Follow-Up Period after the last dose of vutrisiran on study:

- Following **completion of the RTE Period (or completion of the DB Period for patients who do not continue into the RTE Period; or** their last dose of vutrisiran ~~in the DB Period,~~ **for patients who discontinue study drug early),** patients will commence follow-up visits every 12 weeks for the durations outlined below.
- Prior to unblinding **of their treatment from the DB Period**, the duration of the Follow-up Period for a patient will be 1 year from their last dose of study drug. For women of child-bearing potential, the duration of the Follow-up Period will be 18 months from their last dose of study drug. Patients will continue vitamin A supplementation during their Follow-up Period.
- After unblinding, all patients who were on placebo, and patients who received vutrisiran whose serum TTR level has returned to ≥80% of baseline or who have completed the Follow-up Period, whichever comes first, may discontinue further follow-up and stop taking vitamin A~~; all patients will be followed for a minimum of 3 months~~. **Baseline is defined as the last value prior to first vutrisiran dose (ie, prior to the first DB dose for vutrisiran patients in DB Period and prior to the first RTE dose for placebo patients). Patients will be followed for a minimum period as listed below during the Follow-up Period based on treatment regimen received:**
  - **All patients who received only a q3M study drug regimen (25 mg vutrisiran/placebo during DB Period and/or 25 mg vutrisiran during the RTE Period) will be followed for a minimum of 90 days after their last dose of study drug.**
  - **All patients who received the** CCI **vutrisiran regimen (during the RTE Period) will be followed for a minimum of** CCI **after their last dose of study drug during Follow-up Period.**
- For any patient who starts a TTR lowering treatment as part of clinical care, and has completed a minimum of ~~3 months~~ **90 or** CCI **(depending on vutrisiran treatment regimen)** of safety follow-up **since their last dose of study drug**, further follow-up will be discontinued.
- Patients will undergo assessments as outlined in the Schedule of Assessments (Table 1 **and Table 2**).

~~Upon completion of the DB Period for each individual patient, in the case where there are no commercially available treatment options, the Sponsor will aim to provide access to vutrisiran via the means available (eg, open-label extension study, named patient sales programs, charitable access programs, or other means).~~

Patients may receive vutrisiran on the study until the end of the RTE Period or until one of the following occurs: 1) they meet any of the study discontinuation criteria; 2) vutrisiran is commercially available in the patient's country of residence and vutrisiran is accessible to the patient and the patient has completed their RTE Month 12 Visit; or 3) the vutrisiran development program is discontinued.

Study drug dosing may be allowed outside of the study center (eg, the patient's home) during the DB Period or RTE Period under certain circumstances as specified in Section 5.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in Section 6.

Sections also reflecting this change:

- Synopsis
- Study Design Figure 1
- Schedule of Assessments, Table 1, Table 2, and Table 4
- Section 1.4, Clinical Development of Vutrisiran
- Section 1.5, Study Design Rationale
- Section 1.6, Dose Rationale
- Section 1.7, Benefit-Risk Assessment
- Section 3.2, Duration of Treatment
- Section 3.3, Duration of Study Participation
- Section 3.3.1, Definition of End of Study for an Individual Patient
- Section 3.5, Method of Assigning Patients to Treatment Groups
- Section 3.6, Blinding
- Section 4.3.1, Discontinuation of Study Drug or Declining Procedural Assessments
- Section 4.3.2.1, Patient Stops Participation in the Study

- Section 5.2 (and subsections within), Study Drug
- Section 5.4 (and subsections within), Concomitant Medications
- Section 6 (and subsections within), Study Assessments
- Section 7.2, Statistical Methodology

Purpose: To specify that efficacy assessments other than the 6-MWT and KCCQ only need to be performed prior to study drug administration on Day 1 of the DB Period and Day 1of the RTE Period.

The primary change occurs in Section 6, Study Assessments

Revised text:

When performed on dosing days, ~~efficacy~~ **the 6-MWT, the KCCQ**, safety, and PD assessments will be performed prior to study drug administration. **All other efficacy assessments only need to be performed prior to study drug administration on Day 1 of the DB Period and Day 1 of the RTE Period.**

Sections also reflecting this change:

- Schedule of Assessments, Table 1 and Table 2

Purpose: To specify starting a TTR-lowering regimen meets end of study criteria for an individual patient.

The primary change occurs in Section 3.3.1, Definition of End of Study for an Individual Patient

Revised text:

A patient is considered to have reached the end of the study if they have:

- completed the DB Period and the Follow-up Period **(if the patient does not continue into the RTE Period);** ~~or~~
- **completed the DB Period, the RTE Period, and the Follow-up Period;**
- completed the Early Study Discontinuation Visit; **or**
- **started a TTR-lowering regimen as a part of clinical care**

~~Note that a patient is considered to have completed the study only if they have completed the DB Period and the Follow-up Period.~~

Purpose: To remove wording that the sponsor may perform a sample size re-assessment (SSR).

The primary change occurs in Section 3.4, Number of Planned Patients

Revised text:

CCI [redacted]

Section also reflecting this change:

- Section 7.2.10, Sample Size Re-estimation

Purpose: To add liver function test monitoring guidance in situations where transaminase levels are >8 x upper limit of normal.

The primary change occurs in Section 5.2.4, LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing, Table 5

Added text:

• Permanently discontinue dosing after confirmation of the transaminase value at the central laboratory.

• Monitor LFTs at least weekly until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly

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Purpose: To clarify contraception requirements.

The primary change occurs in Section 5.6.1, Contraception

Revised text:

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose~~, throughout study participation, and for 90 days after the last dose of study drug~~ **and until the end of their Follow-up Period (defined in Section 3.1)**.

Purpose: To clarify guidance on safety and other assessment delays when a study visit is unable to be completed at the site.

The primary change occurs in Section 6, Study Assessments

Revised text:

In situations where ~~an efficacy assessment~~ **a** study visit is unable to be completed at the site **(eg,** due to the COVID~~-~~-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug**)**, efficacy**, safety, and other** assessments may be completed up to 3 months after the time point (ie, up to Study Month 9, Month 15, Month 21, Month 27, or Month 33, respectively) **after consultation with the Medical Monitor**.

Sections also reflecting this change:

- Schedule of Assessments, Table 1 and Table 2

Purpose: To clarify pregnancy reporting requirements.

The primary change occurs in Section 6.5.6.7, Pregnancy Reporting

Revised text:

If a female patient becomes pregnant during the study through **the end of their Follow-up Period (defined Section 3.1)** ~~90 days following the last dose of study drug, or through their last visit in the study (whichever is later),~~ the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled to not breastfeed for 90 days after the last dose of study drug **(q3M treatment arm) or** CCI [redacted]

Purpose: To clarify the definitions of the PK analysis set and PD analysis and to remove the Per-Protocol Analysis Set.

The primary change occurs in newly added Section 7.2.1, Populations to be Analyzed

Revised Text:

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS):** all patients who were randomized and received any amount of study drug (vutrisiran or placebo).
- ~~**Per-Protocol Analysis Set (PPS):** all patients in the FAS set who do not have major violations of inclusion/exclusion criteria or other protocol deviations considered to impact the interpretation of the primary efficacy analysis. Classification of patients into (or exclusions from) the PPS will be determined prior to database lock and study unblinding.~~
- **Safety Analysis Set:** includes all patients who received any amount of study drug.
- **PK Analysis Set:** All ~~randomized~~ patients who received ~~any amount of study drug~~ **at least one full dose of vutrisiran** and have at least ~~1 post dose blood sample for~~ **one non-missing postdose** PK ~~parameters and have evaluable PK data~~ **assessment**.
- **PD Analysis Set:** All patients who received ~~any amount of study drug and who have an evaluable baseline and at least 1 evaluable post-baseline serum TTR measurement will be included in the PD analyses~~ **at least one full dose of study drug**.

The FAS will be used for the analysis of all efficacy endpoints. ~~The primary endpoint will also be analyzed for the PPS.~~ Safety analyses will be based on the Safety Analysis Set. PK and PD analyses will be based on PK Analysis Set and PD Analysis Set, respectively.

Purpose: To clarify subgroup analyses.

The primary change occurs in Section 7.2.2, Examination of Subgroups

Revised Text:

Subgroup analyses will be conducted for the primary and selected secondary efficacy endpoints. ~~Subgroup~~ **Efficacy subgroup analyses will be conducted for age group (<75 versus ≥75), baseline tafamidis use (Yes verse No), ATTR disease type (hATTR; wtATTR) and NYHA Class (I/II; III). Safety subgroup** analyses will be conducted for at least the following variables: age group, gender, race, geographic region, and NYHA class. Additional variables may be included and the details will be provided in the SAP.

References

Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):11-21.

10.4.4. Amendment 2 Summary of Changes

The primary purpose for this protocol amendment is to make the following changes briefly summarized below:

- CCI [redacted]
- Adjusted the inclusion criterion for considering patients as tafamidis-naïve for the purposes of the study (inclusion criterion 4a). Previously indicated these patients should have had ≤30 days total of prior tafamidis use with no tafamidis use for the past 6 months. The protocol now indicates patients may also be considered tafamidis-naïve for the purposes of the study if they have not received any tafamidis for at least 30 days before the Screening Visit. The timeframe of requiring at least 30 days prior to Screening is considered sufficient time to allow washout of any pharmacodynamic effects of tafamidis on TTR stabilization. Changes were also made to align the exclusion criterion related to patients planning to initiate tafamidis during the trial (exclusion criterion 7) with the change to inclusion criterion 4 outlined above.
- Adjusted the inclusion criterion related to the diagnosis of wild-type ATTR (wtATTR) amyloidosis (inclusion criterion 2biv), to allow non-cardiac tissue biopsy to be used for confirming the diagnosis of wtATTR amyloidosis in patients with evidence of monoclonal gammopathy of undetermined significance provided that they also have evidence of cardiac amyloid deposition on technetium scintigraphy as per the criteria in inclusion criterion 2biii. Cardiac tissue biopsy also remains as an option for confirming the diagnosis. This change was made to accommodate regional differences in diagnostic evaluations and does not reflect any change in the intended patient population. The change is consistent with recent literature, which support the potential use of non-cardiac tissue biopsies to negate the need for invasive cardiac biopsies in patients who have shown Grade 2 or Grade 3 cardiac uptake on technetium scintigraphy, and with the diagnostic approach used in other studies of cardiac amyloidosis (eg, ATTR-ACT). [Dorbala 2019; Maurer 2019; Maurer 2018; Witteles 2019]
- Additional clarifications were made that align with the original scope of the changes to the assessment of monoclonal gammopathy outlined in HELIOS-B Protocol Administrative Letter 3 dated 10 September 2020.

Several additional changes are being implemented as outlined below:

- Added further guidance confirming rules already in place that specify when performed on dosing days, efficacy, safety, and PD assessments will be performed prior to study drug administration.
- Added a visit window of ±10 days for visits during the Follow-up Period.

- To protect blinding, added an instruction that TTR and vitamin A levels should not be tested when a local laboratory must be used when use of a central laboratory is not possible due to COVID-19 restrictions. This is consistent with the instructions on Vitamin A testing in Section 3.6 (Blinding) of the protocol.
- Added instructions to indicate that all patients who are rescreened must be reconsented and that if a patient is within the 45-day screening window, the medical monitor should be contacted to determine which screening procedures should be repeated.
- Adjusted requirements for vital sign collection to indicate they can be collected after approximately 10 minutes of rest and that blood pressure should be taken from the same arm when possible. CCI [redacted]
- Added the guidance that symptom-directed physical examinations may be deferred to the next on-site visit, when they cannot be performed during a home visit.
- In addition to the requirement that pregnancies be reported through 90 days following the last dose of study drug, further clarified that pregnancies should also be reported through a patient's last study visit (whichever is later). This change was made to ensure pregnancy reporting continues during the Follow-up Period.
- Simplified process of overdosing reporting to indicate that when an overdose is suspected, the Investigator should inform the Medical Monitor. Removed instructions about recording an actual dose associated with an overdose in the electronic case report form.
- Made edits to the summary of the HELIOS-A study in the introduction to align with recent study protocol amendments and completion of enrollment.

A detailed summary of changes is provided in Table 11. The following changes are not detailed: administrative changes, changes associated with administrative letters ([between protocol amendments 1 and 2), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

Table 11: Protocol Amendment 2 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 2 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Removed limit of 30% on enrollment of patients receiving tafamidis at study entry. Adjusted determination of sample size section accordingly.

The primary changes occur in Section 3.1. (Summary of Study Design) and Section 7.1. (Determination of Sample Size)

Revised text:

3.1. Summary of Study Design (relevant text)

At baseline, patients are either:

- Tafamidis-naïve (see inclusion criterion #4 for definition); or
- Currently receiving tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication in the country of use). ~~This group will be capped at 30% of total enrollment in the study.~~

7.1. Determination of Sample Size

CCI [redacted]

CCI [redacted]

Section(s) also reflecting this change:

- PROTOCOL SYNOPSIS
- Section 1.5. (Study Design Rationale)
- Section 5.4.1. (Concomitant Tafamidis Use)
- Section 7.2.10. (Sample Size Re-estimation)

Purpose: Adjusted the inclusion criterion for considering patients as tafamidis-naïve for the purposes of the study (inclusion criterion 4a).

The primary change occurs in Section 4.1. (Inclusion Criteria)

Revised text (relevant text):

4. Patient meets one of the following criteria:
    a. Tafamidis-naïve and not actively planning to commence treatment with tafamidis during the first 12 months following randomization (per exclusion criterion #7) (Note: in addition to patients who have never taken tafamidis, those who have previously been on tafamidis ~~for ≤30 days total~~ and have not received any tafamidis ~~in~~**for at least 30 days before** the ~~past 6 months~~**Screening Visit** will be considered tafamidis-naïve for purposes of this study); or
    b. On tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use)

Section(s) also reflecting this change:

- Section 4.2. (Exclusion Criteria)
- Section 5.4.1. (Concomitant Tafamidis Use)

Purpose: Adjusted the inclusion criterion related to the diagnosis of wild-type ATTR amyloidosis (inclusion criterion 2biv)

The primary change occurs in Section 4.1. (Inclusion Criteria)

Revised text (relevant text):

2. Documented diagnosis of ATTR amyloidosis with cardiomyopathy, classified as either hATTR amyloidosis with cardiomyopathy or wtATTR amyloidosis with cardiomyopathy:

b. Wild-type ATTR (wtATTR) amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

iv. If the patient has evidence of a MGUS **(Section 6.5.5.1)** based on serum and urine protein electrophoresis and serum free light chains**, the following is required**: documentation of TTR protein in cardiac tissue with immunohistochemistry or mass spectrometry ~~is required~~**; OR, documentation of TTR protein in noncardiac tissue (eg, fat pad aspirate, salivary gland, median nerve connective sheath) with immunohistochemistry or mass spectrometry AND Grade 2 or 3 cardiac uptake on technetium scintigraphy per item 2biii above.**

Purpose: Additional clarifications were made that align with the original scope of the changes to the assessment of monoclonal gammopathy outlined in HELIOS-B Protocol Administrative Letter 3 dated 10 September 2020.

The primary change occurs in Section 6.5.5.1. (Assessment for Monoclonal Gammopathy including MGUS)

Revised text:

As part of the determination of a diagnosis of ATTR amyloidosis, excluding evidence of a monoclonal gammopathy at Screening (Table 1) may be necessary (inclusion criterion #2). Laboratory assessments associated with this are indicated in Table 4. If available, documented local results obtained ~~within 1 year~~ prior to Screening may be used to fulfill this inclusion requirement.

Abnormal findings, such as a monoclonal band (M-spike), on SPEP with IFE or serum free light chains with an abnormal kappa-to-lambda ratio **that are suggestive of an alternative diagnosis, such as light chain amyloidosis,** will require confirmatory testing using mass spectrometry or immunohistochemistry for confirmation of TTR protein deposition. Specifications for testing samples will be provided in the study laboratory manual.

The determination of whether abnormal findings are suggestive of light chain amyloidosis may be assessed by a clinician experienced in the diagnosis of amyloidosis.

Section(s) also reflecting this change:

- Table 1 (Schedule of Assessments)
- Table 4 (Clinical Laboratory Assessments)

Purpose: Added further guidance confirming rules already in place that specify when performed on dosing days, efficacy, safety, and PD assessments will be performed prior to study drug administration.

The primary changes occur in Table 1 (Schedule of Assessments)

Moved the rows related to study drug administration and randomization to the end of the Schedule of Assessments.

Added a link to Table 2 to direct reviewers the detailed schedule for predose and postdose PK samples that were already in place.

Added note to cell in the "Study Drug Administration" row and the "See Table/Section for Details" column: 5.2.2**; to be administered after efficacy, safety, and PD assessments during applicable visits**

Modified the following existing footnote and moved it to the top of the footnote list. Also added references to this footnote in the Efficacy Assessments, Safety Assessments and Pharmacodynamic Assessments rows:

[a] When performed on dosing days, efficacy, safety, and PD assessments will be performed prior to study drug administration. ~~Unless otherwise specified, assessments are to be performed prior to dosing.~~

Section(s) also reflecting this change:

- Section 6 (Study Assessments)
- Section 6.2.4. (Kansas City Cardiomyopathy Questionnaire [KCCQ])

Purpose: Added a visit window of ±10 days for visits during the Follow-up Period.

The primary change occurs in Table 1 (Schedule of Assessments)

Added text: ±10-day window added to the column titled "Follow-up Period Visits Every 12 Weeks"

Purpose: To protect blinding, added an instruction that TTR and vitamin A levels should not be tested when a local laboratory must be used when use of a central laboratory is not possible due to COVID-19 restrictions.

The primary change occurs in Section 6 (Study Assessments)

Revised text (relevant text only): All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic when central laboratory assessments are not possible, then a local laboratory may be used. **If a local laboratory is used, TTR and vitamin A levels should not be tested (see Section 3.6).**

Purpose: Added instructions to indicate that all patients who are rescreened must be reconsented and that if a patient is within the 45-day screening window, the medical monitor should be contacted to determine which screening procedures should be repeated.

The primary change occurs in Section 6.1.2. Rescreening

Revised text (relevant text only):

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued), in conjunction with the decision of the Medical Monitor(s), may be allowed to rescreen after a minimum of 5 days have elapsed from their last screening assessment. ~~A patient~~ **All patients who are rescreened** will be re-consented (ICF and the medical records release form~~), if~~**). If a patient is rescreened within the 45-day screening window, please consult the medical monitor to determine which screening procedures must be repeated. If** rescreening occurs outside of the 45-day screening window~~. In this case~~, all screening procedures must be repeated.

Purpose: Adjusted requirements for vital sign collection to indicate they can be collected after approximately 10 minutes of rest and that blood pressure should be taken from the same arm when possible. Confirmed that triplicate ECGs will be only conducted at Screening.

The primary changes occur in the following sections (relevant revised text indicated):

6.5.1. Vital Signs

Vital signs should be measured predose in the seated or supine position, after the patient has rested comfortably for **approximately** 10 minutes. Blood pressure should be taken using the same arm**, when possible**.

CCI [redacted]

[redacted]

Purpose: Added the guidance that symptom-directed physical examinations may be deferred to the next on-site visit, when they cannot be performed during a home visit.

The primary change occurs in Section 6.5.3. (Physical Examination)

Added text: **In situations in which symptom-directed physical examinations cannot be performed during a home visit, they may be deferred to the next on-site visit.**

Purpose: In addition to the requirement that pregnancies be reported through 90 days following the last dose of study drug, further clarified that pregnancies should also be reported through a patient's last study visit (whichever is later).

The primary change occurs in Section 6.5.6.7. (Pregnancy Reporting)

Revised text: If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, **or through their last visit in the study (whichever is later),** the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy.

Purpose: Simplified process of overdosing reporting to indicate that when an overdose is suspected, the Investigator should contact the Medical Monitor within 24 hours to discuss the event. Removed instructions about recording an actual dose associated with an overdose in the electronic case report form.

The primary change occurs in Section 6.5.6.8. (Overdose Reporting)

Revised text:

An overdose is defined as any dose **of study drug** administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. ~~The Investigator will decide whether a dose is to be~~

~~considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.~~ **When an overdose is suspected, the Investigator should inform the Medical Monitor**.

~~All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.~~

Purpose: Made edits to the summary of the HELIOS-A study in the introduction to align with recent study protocol amendments and completion of enrollment.

The primary change occurs in Section 1.4. (Clinical Development of Vutrisiran)

Revised text:

HELIOS-A is an ongoing, Phase 3, global, randomized, open-label study to evaluate the efficacy and safety of vutrisiran 25 mg SC q3M in patients with hATTR amyloidosis with polyneuropathy. ~~The~~ **Enrollment in this** study is ~~expected to enroll 160 patients for~~ **complete, and treatment in** the 18-month treatment period~~, including 120 patients treated with~~ **is ongoing. Patients were randomized 3:1 to receive either 25 mg of** vutrisiran ~~and 40 patients treated with~~**(N=122) q3M or 0.3 mg/kg of** patisiran **(N=42) q3w (as a** reference comparator) **for 18 months.** The ~~co-~~primary ~~endpoints~~**endpoint** in HELIOS-A ~~are changes~~**is change** from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) CCI [redacted] ~~. This study also aims to evaluate patient mortality and hospitalization as a secondary endpoint, in addition to other secondary and exploratory endpoints~~ **at Month 9**. The primary endpoint and most secondary endpoints will be comparisons of vutrisiran to the placebo arm of the Phase 3 APOLLO study of patisiran.

Purpose: Administrative changes, changes associated with administrative letters ([between protocol amendments 1 and 2/since the original protocol was finalized]), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

These changes are not listed individually.

References

Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2-Evidence Base and Standardized Methods of Imaging. J Card Fail. 2019 Nov;25(11):e1-e39.

Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019 Sep;12(9):e006075.

Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007-16.

Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, et al. Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice. JACC Heart Fail. 2019 Aug;7(8):709-16.

10.4.5. Amendment 1 Summary of Changes

The primary purpose for this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators at active study centers (Canada, Latvia, Lithuania, Slovenia, and US) in a Dear Investigator Letter dated 07 April 2020 to assure the safety of study participants while minimizing risks to study integrity amid the COVID-19 pandemic. These changes were to be immediately adopted by the investigator site per the Dear Investigator Letter and are in line with guidance from both the European Medicines Agency and the United States Food and Drug Administration on the conduct of clinical trials during the COVID-19 pandemic.[EMA 2020; FDA 2020]

This protocol amendment also incorporates several other changes including: modification of study endpoints, changes in inclusion/exclusion criteria based on feedback from regulators and sites, and allowance for diagnostic testing in countries where necessary screening tests are not standard of care. A detailed summary of protocol changes is provided in Table 12 and Table 13; the changes will not be implemented until appropriate Health Authority and Ethics Committee (EC) and/or Institutional Review Board (IRB) approval.

Urgent Safety Measures due to the Impact of the COVID-19 Pandemic

Urgent Safety Measures were implemented by the Sponsor, as mentioned above, to ensure the safety of study participants and the integrity of study data in response to the impact of the COVID-19 pandemic. The changes are outlined below.

- **Study Drug Dosing at a Location other than the Study Center (eg, the patient's home)**

  Administration of study drug will be permitted outside the study center (eg, the patient's home) by a home healthcare professional at all timepoints provided the patient has tolerated at least 1 dose of study drug administered in the study center (previously required study drug administration in the study center for all dosing visits).

- **Dosing Outside the Study Center by Patient or Caregiver**

  Following appropriate training on study drug administration, dosing may be permitted by the patient or caregiver at all dosing timepoints under the oversight of the Investigator and following consultation with the Medical Monitor. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing. In addition, added references to patient/caregiver instructions for administration, storage of study drug, and reporting of product complaints.

- **Expanded Dosing Window After Which a Dose Will be Considered Delayed**

  If a patient does not receive a dose of study drug within the specified dosing window, the dose may be administered with up to an 8-week delay (previously 6 weeks) to be considered a delayed dose. If the delay in dose is related to COVID-19, the Medical Monitor should be informed of any delayed doses (previously consultation with the Medical Monitor was required prior to administration of the delayed dose).

This change has been implemented to provide greater flexibility amid travel and other restrictions related to the COVID 19 pandemic, in order to minimize the number of missed doses on study. Given the long activity of vutrisiran resulting in sustained suppression of TTR as observed in Phase 1 study, an occasional delay of 8 weeks in dosing is expected to have minimal impact on the TTR suppression (decrease of only 7% in TTR suppression relative to vutrisiran original scheduled dosing) as predicted by the Sponsor's PK/PD modeling. Resumption of dosing as per the original dosing schedule is expected to be tolerated based on the safety data from the Phase 1 study which evaluated, and demonstrated an acceptable safety profile, at doses as high as 300 mg (12× higher than the therapeutic dose of 25 mg administered quarterly).

- **Screening Patients**

  The requirement that the Investigator notify the Sponsor before screening patients was added to allow an assessment of the ability of the study center or any new trial participant to comply with the protocol given the COVID-19 limitations.

  In addition, patients who failed screening due to situations related to the COVID-19 pandemic may be allowed to rescreen after consultation with the Medical Monitor.

- **Assessments Performed Outside the Study Center**

  Routine assessments may be performed outside of the study center (eg, the patient's home) by a trained healthcare professional at all timepoints. These assessments include the following: vital signs, physical exam, weight, ECGs, pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications. Wherever possible, AE collection associated with visits outside of the clinic will be collected by qualified site staff through verbal contact with the patient. All laboratory samples should be sent to the central laboratory. Exception added that local laboratory assessments are permitted in cases when assessment at central laboratory is not possible due to complications related to the COVID-19 pandemic.

  With the exception of patients unable to come to the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study site, at a minimum, patients should visit the site for the scheduled dosing and assessments for the Week 12 (Month 3) visit within the study visit window and for efficacy assessments as detailed below.

  If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must verbally contact the patient to collect relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).

- **Elimination of the Week 18 Visit**

  The Week 18 visit, including all associated assessments, has been removed.

  This change was implemented to reduce the frequency of patient visits to the study center, and therefore reduce potential exposure to COVID-19, while maintaining

continuity of study drug dosing. The removal of the Week 18 visit is considered appropriate as the visit is a non-dosing visit and not necessary for safety monitoring. After Week 12, the patients will have study visits every 12 weeks. The current safety profile for vutrisiran from the ongoing HELIOS-A study supports removal of the Week 18 visit. As per the protocol, Investigators will always be required to report any known adverse events, hospitalizations or changes in vital status that occur between Week 12 and Week 24 as they would between any other study visits.

- **Liver Function Tests (LFTs)**

  Removed the requirement for a pre-dose LFT assessment within 14 days of each dose. Dosing decisions may be made based on LFT results collected at the previous dosing visit (up to 14 weeks prior to dosing) or screening, as applicable; in all cases the most recently available LFTs should be used.

  These changes were implemented in order to limit the number of times a patient needs to visit the site/interact with home healthcare professionals and reduce potential exposure to COVID-19. The changes are based on the available safety data from the prior Phase 1 study (ALN-TTRSC02-001) and the ongoing HELIOS-A study (ALN-TTRSC02-002), which support that vutrisiran continues to have an acceptable safety profile.

  In the HELIOS-A study, as of 08 April 2020, 120 patients had received a total of 305 doses of vutrisiran 25 mg every 3 months (mean 2.5 doses, range: 1-5 doses). This provides a mean exposure of 130.4 days (range: 1 to 339 days) and most patients (101 out of 120) have had at least 2 doses of vutrisiran. No subjects in the ongoing HELIOS-A study have had laboratory elevations of >3×ULN for ALT or AST and no subjects have required interruption of study drug due to elevations in liver transaminases, bilirubin or adverse hepatic events. Thus, with increasing exposure in HELIOS-A, vutrisiran continues to have an acceptable hepatic safety profile.

  The Sponsor acknowledges that liver transaminase elevations remain an important potential risk based on the mechanism of action of vutrisiran, as well as findings in pre-clinical studies and early-phase clinical trials. The specific rules for monitoring and dosing in the setting of transaminase elevations outlined in the protocol are unchanged (Section 5.2.4 Table 3 [Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified]).

  Given the available safety data for vutrisiran, the degree of risk of COVID-19 exposure related to the additional visits is considered in excess of the degree of risk mitigation obtained by more frequent LFT monitoring. With the current changes, a robust LFT monitoring schedule of every 12 weeks, is maintained and the results will be regularly reviewed by the Medical Monitor and the Data Monitoring Committee (DMC). Continuous monitoring of adverse events will also allow for detection of any clinically relevant events and additional LFTs may be obtained at any time at the discretion of the investigator.

- **Use of Local Laboratories for Analysis due to COVID-19**

  Confirmed that the intention during normal operations is that all laboratory samples are sent to a central laboratory. Added an exception that in situations related to the COVID-19 pandemic when central laboratory assessments are not possible, a local laboratory may be used. These local lab results must be sent to the site for review by the Investigator and entry into the clinical database.

- **Addition of Infrared to the List of Acceptable Body Temperature Collection Methods**

  Added as a non-contact method of temperature collection to limit contact between patients and study or home healthcare professionals.

- **Performance of Efficacy Assessments and Delays Due to COVID-19**

  Clarified that all efficacy assessments associated with the following visits should be conducted at the study center: Month 6, Month 12, Month 18, Month 24, and Month 30. In situations where an efficacy assessment study visit is unable to be completed at the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, efficacy assessments may be completed up to 3 months after the time point (ie, up to Study Month 9, Month 15, Month 21, Month 27, or Month 33, respectively).

  This change was implemented to allow for collection of critical efficacy data while limiting unnecessary patient exposure to COVID 19 and to ensure, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic.

- **Collection of Information Related to COVID-19**

  Information related to the impact of the COVID-19 pandemic on patient participation in the study will be collected for each patient in order to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data.

- **Updates to Study Administration Text**

  Text was updated to provide clarification of Investigator responsibilities regarding communication of new study information to patients and IRB/IECs.

Changes Not Related to Urgent Safety Measures

The following additional changes are being implemented as outlined below, and a detailed summary is provided in Section 2.2.

- **Objectives and Endpoints**

  The primary and secondary objectives and endpoints were revised to include non-hospitalized urgent heart failure (HF) visits (urgent HF visits). Urgent HF visits must satisfy criteria developed by the Standardized Data Collection for Cardiovascular Trials Initiative and the US Food and Drug Administration[Hicks 2017] and will be adjudicated by the independent Clinical Events Committee (CEC).

Specifically, the primary composite endpoint of "all-cause mortality and recurrent CV hospitalizations" will be changed to "all-cause mortality and recurrent CV events." Recurrent CV events includes CV hospitalizations and urgent HF visits.

Similarly, the composite secondary endpoint of "all-cause mortality and recurrent all-cause hospitalizations" will be revised to also include urgent HF visits. The secondary endpoint of "recurrent CV hospitalizations will be revised to "recurrent CV events" to include urgent HF visits.

Including urgent HF visits will account for the likelihood that the COVID-19 pandemic may increase current trends to reduce hospitalizations and shift management of clinically comparable heart failure events to outpatient settings.[Hicks 2017] Including urgent HF visits also mitigates regional differences in the criteria for hospitalization, which may be further exacerbated by the COVID-19 pandemic. Urgent HF visits are well defined endpoints in regulatory guidances (CPMP/EWP/235/95, Rev.2, Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure, Committee for Medicinal Products for Human Use, 2017; Guidance for Industry, Treatment for Heart Failure: Endpoints for Drug Development, US Food and Drug Administration, 2019).

- **Exclusion of deaths and hospitalizations due to COVID-19**

  Deaths and hospitalizations due to COVID-19 will be excluded from all-cause deaths and hospitalizations, respectively, in the primary analyses of primary and applicable secondary endpoints.

  As of April 29, 2020, according to the World Health Organization, the COVID-19 pandemic has led to over 3,000,000 confirmed cases and over 200,000 deaths worldwide.[WHO 2020] The effects of the pandemic on global health are unprecedented and due to the novel SARS-CoV2 circulating in a population with no prior immunity.[Jin 2020] As the COVID-19 pandemic will have a confounding effect on the number of death and hospitalization events in the study, we will exclude events due to COVID-19 from analyses for all-cause deaths or hospitalizations.

- **Allowance for Diagnostic Testing at Screening**

  Confirmed that diagnostic tests required to confirm eligibility per inclusion criterion 2 are intended to be historical and will not be performed as part of the study. However, an allowance was added for diagnostic testing in countries where necessary screening tests are not standard of care. This will enable diagnostic testing to confirm transthyretin amyloidosis with cardiomyopathy in the event these results are not available for the assessment of eligibility. This change is necessary to accommodate enrollment in regions of the world where certain diagnostic tests may not be standard of care.

- **Revised Subgroup Analysis Description**

  Based on feedback from a regulatory authority, added a statement that subgroup analyses will be conducted for at least the following variables: age group, gender, race, geographic region, and NYHA class.

In addition, the following inclusion and exclusion criteria were modified based on feedback from regulators and Investigators that the prior criteria would unnecessarily exclude patients with ATTR cardiomyopathy for whom the risk benefit profile favors inclusion in the study. In addition, clarification is provided for some criteria.

- **Inclusion Criterion 2b, iv, Evidence of MGUS as part of diagnosis of Wild-type ATTR (wtATTR) amyloidosis with cardiomyopathy**

  Clarified that documentation of TTR protein in cardiac tissue with immunohistochemistry or mass spectrometry is required. Clarification provided to maintain consistency with Inclusion Criterion 2b, iii.

- **Inclusion Criterion 4b, Tafamidis Use at Study Entry**

  Clarified that tafamidis treatment at study entry must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use.

- **Inclusion Criterion 6,** CCI

  The inclusion criterion for CCI

  CCI

- **Exclusion Criterion 4, Liver Function Tests at Screening (AST/ALT and Total Bilirubin)**

  The exclusionary threshold for AST/ALT levels at Screening was increased to >2.0 × upper limit of normal (ULN; previously >1.5 × ULN). The exclusionary threshold for total bilirubin at Screening was increased to >2.0 × ULN for all patients (previously >1.5 × ULN for all patients; with patients with Gilbert's syndrome being eligible if total bilirubin was <2×ULN)

  These changes are based on feedback from Investigators to include more patients who are representative of the overall population of patients treated for ATTR cardiomyopathy. The modifications will avoid excluding patients who have heart failure which may be associated with mild elevations in bilirubin or liver transaminases. In addition, as outlined above, data from the ongoing HELIOS-A study demonstrate that vutrisiran has an acceptable hepatic safety profile.

- **Exclusion Criterion 9, Diflunisal Use**

  The required diflunisal wash-out period was reduced to at least 30-days prior to dosing (Day 1) (previously was at least 3 months), as this was determined to be a

reasonable amount of time to avoid any confounding effects from diflunisal on the baseline assessments.

- **Exclusion Criteria 10 and 11, Prohibited TTR lowering agents**

  Added ursodeoxycholic acid to the list of TTR lowering agents to be avoided during the study. The exclusion now excludes patients unwilling to avoid any concurrent treatment with diflunisal, ursodeoxycholic acid/ tauroursodeoxycholate/ doxycycline , or TTR lowering agents (eg, patisiran, inotersen).

- **Exclusion Criterion 23, History of Drug Allergies/Reaction to Study Drug**

  Exclusion criteria widened to include a history of allergic reaction to any component of or excipient in the study drug based on a request from a regulatory authority.

- **Doxycycline Use**

  Added a clarification that doxycycline use is permitted if taken for short-term treatment of infection; use of doxycycline is otherwise excluded.

The following changes are not detailed: administrative changes, changes associated with administrative letters (since the original protocol was finalized), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

Protocol Amendment 1 Detailed Summary of Changes

Table 12: Protocol Amendment 1 Urgent Safety Measure COVID-19-related Changes to be Adopted Immediately

The primary section(s) of the protocol affected by the changes in Protocol Amendment 1 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: The following changes were made related to administration of study drug:

- *Expanded study drug Dosing Outside the Study Center*
- *Study Drug Dosing at a Location other than the Study Center (eg, the patient's home)*
- *Dosing Outside the Study Center by Patient or Caregiver*
- *Expanded Dosing Window After Which a Dose Will be Considered Delayed*
- *Modified other dose, administration, and product complaint sections to match new administration strategy*

The primary changes occur in Section 5.2.2 (Dose and Administration)

5.2.2. Dose and Administration

Detailed instructions for administration are provided in the Pharmacy Manual. Detailed Instructions for Use for the pre-filled syringe will also be provided.

Starting on Day 1, patients will receive 25 mg of vutrisiran or placebo administered as a SC injection q3M (every 12 weeks ±7 days) for up to 36 months. ~~Study drug will be administered under the supervision of the Investigator or designee.~~

If a patient has tolerated at least 1 dose of study drug in the clinic, subsequent dosing may be administered outside the study site (eg, the patient's home) at all timepoints where allowed by applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare professional, with oversight by the Investigator. If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, study drug may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on study drug administration. This measure (self- or caregiver administration) is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.

The SC injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained.

Additional details, including detailed instructions for study drug administration, can be found in the Pharmacy Manual. **In addition, instructions and procedures related to administration of study drug by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.**

Missed doses of Study Drug

If a patient does not receive a dose of study within the specified dosing windows, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered as close to the scheduled dosing date as possible with a maximum ~~6 week~~ **8-week** delay (to be considered a delayed dose). Thereafter, the dose will be considered missed and not administered. If a dose is missed or is administered with a delay, the next dose will resume following the original schedule. **In cases in which a dose is delayed in this manner for issues related to the COVID-19 pandemic, the Medical Monitor should be informed as soon as possible, but prior consultation is not required. In all cases, the dose should be administered as close as possible to the scheduled timepoint.**

Every effort should be made to avoid missed doses of study drug. If a patient misses a dose, **for reasons unrelated to the COVID-19 pandemic,** the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue dosing in the study (see also Section 4.3).

Sections also reflecting this change:

- Synopsis
- Table 1, Schedule of Assessments
- Section 3.1 Summary of Study Design
- Section 5.2.5, Dose Preparation, Handling, and Storage
- Section 5.3.2, Reporting

Purpose: The requirement that the Investigator notify the Sponsor before screening patients was added to allow an assessment of the ability of the study center or any new trial participant to comply with the protocol given the COVID-19 limitations.

The primary changes occur in Section 6.1 (Screening Assessments)

Added text: **The investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site or any new trial participant to comply with the protocol given COVID-19 pandemic limitations.**

Purpose: The following changes have been made relating to expanding the ability to perform assessments outside of the study center:

- *Clarified and expanded on language already in the protocol related to performing routine assessments outside of the clinic (eg, at home) at all timepoints. These assessments include the following: vital signs, physical exam, weight, ECGs, pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications.*
- *Confirmed that the intention during normal operations is that all laboratory samples are sent to a central laboratory. Added an exception that in situations related to the COVID-19 pandemic when central laboratory assessments are not possible, a local laboratory may be used. These local lab results must be sent to the site for review by the Investigator and entry into the clinical database.*
- *Added guidance that with the exception of patients unable to come to the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study site, at a minimum, patients should visit the site for the scheduled dosing and assessments for the Week 12 (Month 3) visit within the study visit window and for efficacy assessmentsas detailed below.*
- *If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must verbally contact the patient to collect relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).*
- CCI [redacted].
- *Added option for pregnancy testing by the patient or caregiver in situations a study visit is unable to be completed at the site due to the COVID-19 pandemic*

The primary changes occur in Section 6 (Study Assessments), CCI [redacted]), and Section 6.5.6.2 (Pregnancy Testing)

6. STUDY ASSESSMENTS

~~During the study, where applicable country and local regulations and infrastructure allow, assessments that may be conducted by a qualified home healthcare professional include but are not limited to: blood draws, vital signs, physical exam, collection of information regarding hospitalizations, procedures and concomitant medications. Wherever possible, AE collection associated with visits outside of the clinic will be collected by a phone call from qualified site staff. Further details with regard to visits performed outside of the clinic are provided in the Study Manual.~~

Where applicable country and local regulations and infrastructure allow, routine assessments may be performed outside of the study center (eg, the patient's home) by a trained healthcare professional at all timepoints. These assessments include the following: vital signs, physical exam, weight, CCI pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications. All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic when central laboratory assessments are not possible, then a local laboratory may be used. These local lab results must be sent to the site for review by the Investigator and entry into the clinical database. Wherever possible, AE collection associated with visits outside of the clinic will be collected by qualified site staff through verbal contact with the patient.

With the exception of patients unable to come to the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study site, at a minimum, patients should visit the site for the scheduled dosing and assessments for the Week 12 (Month 3) visit within the study visit window and for efficacy assessments as detailed below.

If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must, at a minimum, verbally contact the patient within the expected window for each study visit to collect relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).

All efficacy assessments associated with the following visits should be conducted at the study center: Month 6, Month 12, Month 18, Month 24, and Month 30. In situations where an efficacy assessment study visit is unable to be completed at the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, efficacy assessments may be completed up to 3 months after the time point (ie, up to Study Month 9, Month 15, Month 21, Month 27, or Month 33, respectively).

Further details with regard to visits performed outside of the clinic are provided in the Study Reference Manual.

CCI

CCI

6.5.5.3. Pregnancy Testing *(applicable text only)*

Added text:

In situations where a study visit is unable to be completed at the site due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center, pregnancy testing may be performed by a healthcare professional or the patient/caregiver (and confirmed by the site) where applicable country and local regulations and infrastructure allow.

Sections also reflecting this change:

- Synopsis
- Table 1, Schedule of Assessments
- Section 3.1 Summary of Study Design
- Section 4.3.3. Lost to Follow-Up
- Section 6.2. Efficacy Assessments
- Section 6.5. Safety Assessments
- Section 6.5.5. Clinical Laboratory Assessments

Purpose: The Week 18 visit, including all associated assessments, has been removed.

- Elimination of the Week 18 Visit

The primary changes occur in Table 1 (Schedule of Asessments)

Description of change: The Week 18 visit, including all associated assessments, has been deleted.

Purpose: The following changes were made related to performance of liver function tests:

- *Removed the requirement for a pre-dose LFT assessment within 14 days of each dose.*
- *Dosing decisions may be made based on LFT results collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used.*

The primary changes occur in Table 1 and Section 5.2.4 (LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing)

Table 1 (Schedule of Assessments) – footnotes:

- ~~LFTs before the first dose of study drug (Day 1): Day 1 predose LFT does not need to be performed if there are available LFT results within 14 days of first dose.~~
- ~~LFTs after the first dose of study drug (Day 1): LFTs must be obtained with results available within 14 days before each clinic visit on which vutrisiran dosing is scheduled. LFTs can be analyzed locally, but if a local assessment is drawn, a sample must also be drawn for analysis at the central laboratory.~~
- **Dosing decisions may be made based on LFT results (Table 4) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used.**

5.2.4. LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

Revised text (relevant text only)

1. ~~LFT results (Table 4) are to be obtained within 14 days prior to study drug dosing and results are to be reviewed prior to each dose of study drug.~~ **Dosing decisions may be made based on LFT results (Table 4) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used.** ~~Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.~~ **All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic if central laboratory collection is not possible, then a local laboratory may be used. These local laboratory results must be sent to the site for review by the Investigator and entry into the clinical database.**
2. For any ALT or AST elevation >3× ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3× ULN:

   a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days. **If a central laboratory result is not possible due to COVID-19, a local laboratory may be used for monitoring in consultation with the Medical Monitor; all local laboratory results must be sent to the clinical site for entry into the clinical database.**

   b. Perform assessments per Table 4 and Table 5.

   c. If an alternative cause is found, provide appropriate care.

Sections also reflecting this change:

- Section 6.5.5, Clinical Laboratory Assessments

Purpose: Addition of Infrared to the List of Acceptable Body Temperature Collection Methods.

The primary change occurs in Section 6.5.1 (Vital Signs)

Revised text:

Body temperature in degrees Celsius will be obtained via oral ~~or~~**,** tympanic, **or infrared** methods.

Purpose: Made the following changes related to performance of efficacy assessments and delays due to COVID-19:

- *Clarified that all efficacy assessments associated with the following visits should be conducted at the study center: Month 6, Month 12, Month 18, Month 24, and Month 30.*
- *Specified that in situations where an efficacy assessment study visit is unable to be completed at the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, efficacy assessments may be completed up to 3 months after the time point (ie, up to Study Month 9, Month 15, Month 21, Month 27, or Month 33, respectively).*

The primary change occurs in Section 6 (Study Assessments)

Added text:

All efficacy assessments associated with the following visits should be conducted at the study center: Month 6, Month 12, Month 18, Month 24, and Month 30. In situations where an efficacy assessment study visit is unable to be completed at the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, efficacy assessments may be completed up to 3 months after the time point (ie, up to Study Month 9, Month 15, Month 21, Month 27, or Month 33, respectively).

Sections also reflecting this change:

- Synopsis
- Table 1 Schedule of Assessments
- Section 3.1 Summary of Study Design

Purpose: Added collection of information related to the impact of the COVID 19 pandemic on patient participation in the study for each patient.

The primary change occurs in newly added Section 6.5.7 (COVID-19 Data Collection)

Added text:

Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.

Sections also reflecting this change:

- Section 7.2 Statistical Methodology

Purpose: Updated study administration text.

The primary change occurs in Section 8.1.1, Informed Consent and Medical Records Release Form and Section 8.1.2, Ethical Review

8.1.1. Informed Consent and Medical Records Release Form *(relevant changed text only)*

Added text:

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

8.1.2. Ethical Review *(relevant changed text only)*

Added text:

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study **(except those that support the need to remove an apparent immediate hazard to the patient)**.

Table 13: Protocol Amendment 1 Changes Not Related to Urgent Safety Measures to be Implemented After Regulatory Authority and Ethics Committee Approval

Purpose: The primary and secondary objectives and endpoints were revised to include non-hospitalized urgent heart failure (HF) visits (urgent HF visits).

The primary changes occur in Section 2 (OBJECTIVES AND ENDPOINTS)

Objectives	Endpoints
Primary	
• To evaluate the efficacy of vutrisiran compared to placebo on reducing all-cause mortality and CV ~~-related hospitalizations~~ **events**	• Composite outcome of all-cause mortality and recurrent CV ~~hospitalizations~~ **events (CV hospitalizations and urgent HF visits)**
Secondary	
CCI [redacted]	• Change from baseline in 6-MWT • Change from baseline in the KCCQ-OS • CCI [redacted] • CCI [redacted] • CCI [redacted] • All-cause mortality • CCI [redacted]

Sections also reflecting this change:

- Synopsis
- Section 1.5 (Study Design Rationale)
- Section 3.8 (Clinical Events Committee (CEC))
- Section 7.1 (Determination of Sample Size)
- Section 7.2.5.1 (Primary Endpoint)
- Section 7.2.5.2 (Secondary Endpoints)

Purpose: Deaths and hospitalizations due to COVID-19 will be excluded from all-cause deaths and hospitalizations, respectively, in the primary analyses of primary and applicable secondary endpoints

The primary change occurs in Section 7.2.5 (Efficacy Analyses):

Added text: Deaths and hospitalizations due to COVID-19 will be excluded from all-cause deaths and hospitalizations, respectively, in the primary analyses of primary and applicable secondary endpoints.

Sections also reflecting this change:

- Synopsis

Purpose: Added allowance for diagnostic testing in countries where necessary screening tests are not standard of care.

The primary change occurs in Section 6.1 (Screening Assessments):

Added text:

The diagnostic tests required to confirm eligibility per inclusion criterion 2 are intended to be historical, as part of the patient's clinical care and diagnosis, and will not be performed as part of the study except as described below.

If a diagnostic result that confirms ATTR Amyloidosis is not available at Screening for the assessment of eligibility (Section 4.1, inclusion criterion 2a/b), testing may be conducted at a laboratory or diagnostic center selected by the site, in consultation with the Medical Monitor, in countries in which this test is not standard of care. For TTR mutation testing, a blood sample may be drawn at Screening and sent for genotype testing at the central lab, in countries in which genotyping is not available at a local laboratory.

Purpose: Added a statement that subgroup analyses will be conducted for at least the following variables: age group, gender, race, geographic region, and NYHA class.

The primary change occurs in Section 7.2.2:

Revised text:

Subgroup analyses ~~may~~ **will** be conducted for the primary and selected secondary efficacy endpoints. ~~List of subgroup variables and endpoints for which subgroup analysis will be performed, as well as methodology for interaction test (if needed), will be provided in the SAP.~~ **Subgroup analyses will be conducted for at least the following variables: age group, gender, race, geographic region, and NYHA class. Additional variables may be included and the details will be provided in the SAP.**

Purpose: Inclusion Criterion 2b, iv, Clarified that documentation of TTR protein in cardiac tissue with immunohistochemistry or mass spectrometry is required. Clarification provided to maintain consistency with Inclusion Criterion 2b, iii.

The primary change occurs in Section 4.1, Inclusion Criteria

Revised text:

2b, iv. If the patient has evidence of a MGUS based on serum and urine protein electrophoresis and serum free light chains, documentation of TTR protein in **cardiac** tissue with immunohistochemistry or mass spectrometry is required.

Purpose: Inclusion Criterion 4b, Clarified that tafamidis treatment at study entry must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use. Changes made throughout the protocol to maintain a consistent statement.

The primary changes occurs in Section 4.1 (Inclusion Criteria) and Section 5.4.1 (Concomitant Tafamadis Use):

Revised text:

Section 4.1 (Inclusion Criteria)

Revised text:

4b, On tafamidis (Note: must be on-label use of commercial tafamidis per ~~the~~ **an** approved **cardiomyopathy** indication and dose in the country of use)

5.4.1. Concomitant Tafamidis Use

Revised text:

Per inclusion criterion #4, at baseline patients are either: 1) tafamidis-naïve or 2) currently on tafamidis (Note: must be on-label use **of commercial tafamidis** per ~~the~~ **an** approved **cardiomyopathy** indication **and dose** in the country **of use** ~~in which the patient is receiving treatment~~; limited to no more than 30% of the study population).

Sections also reflecting this change:

- Synopsis

Purpose: Inclusion Criterion 6, CCI [redacted]

The primary change occurs in Section 4.1, Inclusion Criteria

Revised text:

6. Screening CCI [redacted]

Purpose: Exclusion Criterion 4, The exclusionary threshold for AST/ALT levels at Screening was increased to >2.0 × upper limit of normal (ULN; previously >1.5 × ULN). The exclusionary threshold for total bilirubin at Screening was increased to >2.0 × ULN for all patients (previously >1.5 × ULN for all patients; with patients with Gilbert's syndrome being eligible if total bilirubin was <2×ULN)

The primary change occurs in Section 4.2, Exclusion Criteria

Revised text:

4. Has any of the following laboratory parameter assessments at Screening:
   a. AST or ALT levels ~~>1.5 × ULN~~ >2.0 × ULN,
   b. Total bilirubin >2.0 × ULN ~~>1.5 × ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2 × ULN)~~
   c. International normalized ratio (INR) >1.5 (unless patients were on anticoagulant therapy in which case excluded if INR >3.5)

Purpose: Exclusion Criterion 9, The required diflunisal wash-out period was reduced to at least 30-days prior to dosing (Day 1) (previously was at least 3 months).

The primary change occurs in Section 4.2, Exclusion Criteria

Revised text:

9. Is currently taking diflunisal; if previously on this agent, must have at least a ~~3 month~~ **30-day** wash-out prior to dosing (Day 1).

Purpose: Exclusion Criteria 10 and 11, Added ursodeoxycholic acid to the list of TTR lowering agents to be avoided during the study.

The primary change occurs in Section 4.2, Exclusion Criteria

Revised text:

10. Is currently taking doxycycline, **ursodeoxycholic acid,** or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 30-day wash-out prior to dosing (Day 1).

11. Unwilling to avoid any concurrent treatment with diflunisal, **ursodeoxycholic acid**/tauroursodeoxycholate/doxycycline, or TTR lowering agents (eg, patisiran, inotersen)

Sections also reflecting this change:

- Section 5.4 (Concomitant Medications)

Purpose: Exclusion Criterion 23, Exclusion criteria widened to include a history of allergic reaction to any component of or excipient in the study drug

The primary change occurs in Section 4.2, Exclusion Criteria

23. History of multiple drug allergies; or history of allergic reaction to **any component of or excipient in the study drug** ~~an oligonucleotide or GalNAc~~.

Purpose: Added a clarification that doxycycline use is permitted if taken for short-term treatment of infection; use of doxycycline is otherwise excluded.

The primary change occurs in Section 5.4 (Concomitant Medications)

Revised text (also includes revisions described above relate to ursodeoxycholic acid)

Use of the following medications/treatments are prohibited during study participation (Section 4.2):

- any investigational agent other than study drug
- diflunisal
- **ursodeoxycholic acid**/tauroursodeoxycholate/doxycycline **(Doxycycline is permitted if being taken for short-term treatment of infection Also see exclusion criterion 10)**.

- TTR lowering agents (eg., patisiran, inotersen)
- calcium channel blockers (eg, verapamil, diltiazem) or digitalis; given they are widely recognized to be contraindicated in this patient population

References

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