CLINICAL STUDY PROTOCOL
ALN-TTR02-011
DATED 30 JUNE 2021

Protocol Title:	APOLLO-B: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Short Title:	APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Study Drug:	Patisiran (ALN-TTR02)
EudraCT Number:	2019-001458-24
IND Number:	141240
Protocol Date:	Original protocol, 18 April 2019 Amendment 1: 20 December 2019 Amendment 2: 22 May 2020 Amendment 3: 30 June 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

[redacted]

01 JUL 2021

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTR02-011 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

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

Short Title

APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Study Drug

Patisiran (ALN-TTR02)

Phase

Phase 3

Study Center(s)

The study will be conducted at approximately 85 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality, hospitalizations, and urgent heart failure (HF) visits	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV) events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month double-blind period

Objectives	Endpoints
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV events • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV events (CV hospitalizations and urgent HF visits) over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI) o Cardiac magnetic resonance (CMR) parameters o Technetium scintigraphy parameters o Troponin I levels o Norfolk QoL-DN
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (AEs)

Study Design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study

population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the Investigator. This group will be capped at 30% of total enrollment in the study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 36-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period.

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive intravenous (IV) treatment every 3 weeks with either patisiran or placebo. Prior to receiving randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an infusion related reaction (IRR) with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. Study drug will be administered as an approximately 80-minute IV infusion.

During the open-label extension period, all patients will receive treatment with open-label patisiran.

Study drug administration at a location other than the study center (eg, at home) may be administered as follows:

- Double-blind period: Patients who have received ≥2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.
- Open-label extension period: Patients who have received ≥2 doses of open-label patisiran at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have patisiran administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Patisiran administration will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion, with oversight of the Investigator.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint; this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period. The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score. In situations where an efficacy study visit at Months 6, 9, and/or 12 is unable to be completed at the study center due to the coronavirus disease 2019 (COVID-19) pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the

Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended for that visit as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.

Safety will be assessed throughout the double-blind and open-label extension periods of the study.

Number of Planned Patients

Approximately 300 patients are planned for enrollment in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults age 18 (or age of legal consent, whichever is older) to 85 years of age, inclusive, with ATTR amyloidosis with cardiomyopathy (hereditary or wild-type [wt]) who, at baseline, are either: 1) tafamidis naïve (on tafamidis for ≤30 days and none within 6 months prior to baseline); or 2) currently on tafamidis (for ≥6 months) with disease progression in the opinion of the Investigator.

Study Drug, Dose, and Mode of Administration

Patisiran is a ribonucleic acid (RNA) interference (RNAi) therapeutic consisting of a double-stranded small interfering RNA (siRNA) targeting TTR mRNA formulated in a lipid nanoparticle (LNP). The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG2000-C-DMG) in isotonic phosphate buffered saline.

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs.

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days. Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended patisiran dose is 30 mg.

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described above for double-blind patisiran.

Reference Treatment, Dose, and Mode of Administration

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

Duration of Treatment and Study Participation

The treatment duration in this study is up to 48 months, inclusive of a 12-month, double-blind, treatment period, and a 36-month, open-label, treatment period. The estimated total time on

study for each patient is up to 50.5 months, including up to 45 days of screening, up to 48 months of treatment, and a 28-day safety follow-up period.

Statistical Methods

The planned enrollment for this study is 300 patients. Randomization (1:1) will be stratified by: 1) baseline tafamidis (yes vs no); 2) genotype (hATTR vs wtATTR); and 3) NYHA Class I or II and age < 75 years vs all other.

For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a treatment difference at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment.

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), age (<75 vs ≥75 years), the treatment-by-visit interaction, the treatment-by-baseline tafamidis interaction, the visit-by-baseline tafamidis interaction, and the treatment-by-visit-by-baseline tafamidis interaction as fixed factors. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

For patients who are tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

Safety data will be summarized descriptively.

Figure 1: Study Design

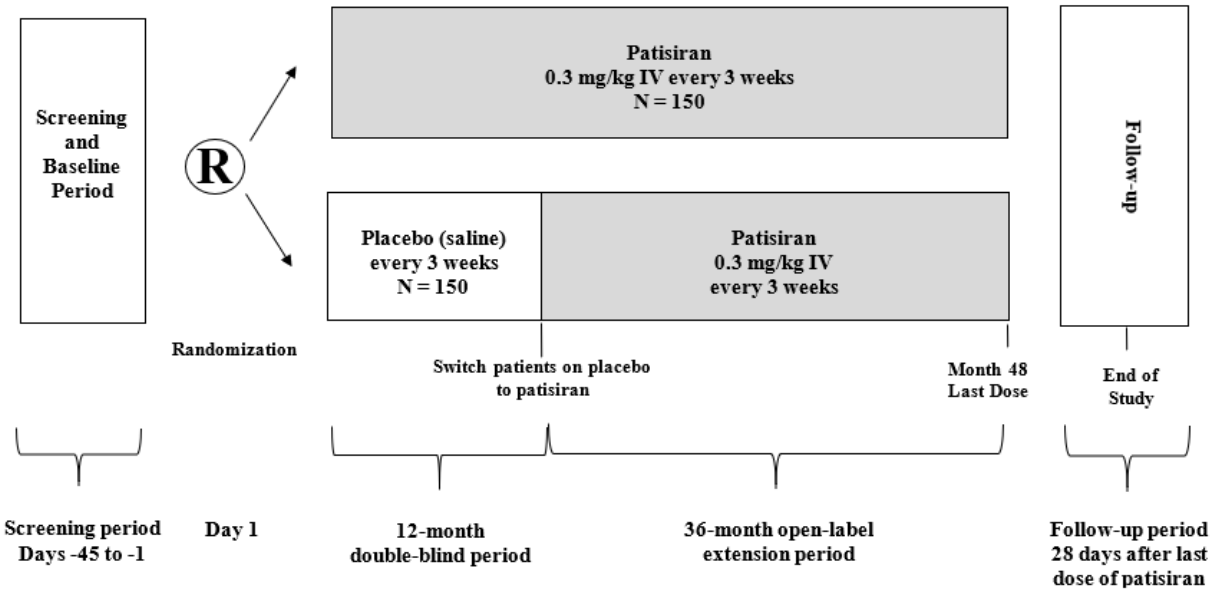

Table 1: Year 1 Schedule of Assessments: Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	For Details see Section	Screen-ing	Baseline			Double-blind Treatment Period																		Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose	D22±3	D43±3	D64±3	D85±3	D106±3	D127±3	D148±3	D169±3	D176-D183[a]	D190±3	D211±3	D232±3	D253±3	D260-D267[a]	D274±3	D295±3	D316±3	D337±3	D358±3	D365-D372[a]		
Study Day ±Visit Window	For Details see Section	Day -45 to Day -1		Day 1																						
Study Week				Week 1		3	6	9	12	15	18	21	24	25-26	27	30	33	36	37-38	39	42	45	48	51	52-53	52-53	NA
Informed Consent	6.1	X																								
Inclusion / Exclusion Criteria	4.1, 4.2	X	X																							
Demographics / Medical History	6.1	X	X																							
PND Score	6.2.7	X																								
Height	6.5.2	X																								
Efficacy Assessments																										
6-MWT	6.2.1	X	X											X[d]					X[d]						X[d]	X[d]	X[d]
KCCQ	6.2.2			X										X					X						X	X	X
mBMI	6.2.4			X									X										X				X
Cardiac Biomarker Samples	6.2.5.1	NT-proBNP	X						X					X					X						X	X	X
ATTR amyloidosis disease stage	6.2.5.2		X																						X	X	X
NYHA Class	6.2.5.3	X												X					X						X		
Echocardiogram	6.2.5.4	X																							X		
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5		X																						X		
Norfolk QoL-DN	6.2.6		X																						X	X	

Table 1: Year 1 Schedule of Assessments: Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	For Details see Section	Screening	Baseline			Double-blind Treatment Period																			Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose																						
		Day -45 to Day -1		Day 1		D22±3	D43±3	D64±3	D85±3	D106±3	D127±3	D148±3	D169±3	D176-D183[a]	D190±3	D211±3	D232±3	D253±3	D260-D267[a]	D274±3	D295±3	D316±3	D337±3	D358±3	D365-D372[a]		
Study Week				Week 1		3	6	9	12	15	18	21	24	25-26	27	30	33	36	37-38	39	42	45	48	51	52-53	52-53	NA
Pharmacodynamic Assessments																											
TTR Protein	6.3		X	X		X			X					X					X				X	X	X	X
Exploratory Biomarkers (plasma, serum)	6.6		X						X					X					X					X		
Safety Assessments																											
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	X		X	X
Weight	6.5.2	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed unless noted as full)	6.5.3	X Full	X						X					X					X						X Full	X Full	X
Single 12-lead ECG (unless otherwise indicated)	6.5.4		X (in triplicate, either visit)						X				X					X						X			X
Serum Chemistry, Liver Function Tests	6.5.5	X		X									X										X		X[e]	X[e]	X
Hematology	6.5.5	X		X									X										X				X
Coagulation	6.5.5	X																									
Vitamin A Levels				X																							
ADA (on dosing days, prior to dosing)	6.5.5.1			X		X			X				X											X			X

Table 1: Year 1 Schedule of Assessments: Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	**For Details see Section**	**Screen-ing**	**Baseline**		**Double-blind Treatment Period**																		**Month 12 Efficacy Visit**	**Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]**	**Pre-tafamidis Drop-in Visit[c]**
		V1	**V2**	**Pre-dose**	**Post-dose**																					
		Day -45 to Day -1		**Day 1**		**D22±3**	**D43±3**	**D64±3**	**D85±3**	**D106±3**	**D127±3**	**D148±3**	**D169±3**	**D176-D183[a]**	**D190±3**	**D211±3**	**D232±3**	**D253±3**	**D260-D267[a]**	**D274±3**	**D295±3**	**D316±3**	**D337±3**	**D358±3**	**D365-D372[a]**		
Study Week				**Week 1**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25-26**	**27**	**30**	**33**	**36**	**37-38**	**39**	**42**	**45**	**48**	**51**	**52-53**	**52-53**	**NA**
FSH (to confirm postmenopausal, if applicable)	Table 5, 6.5.5.2	X																								
Pregnancy Test	Table 5, 6.5.5.2	X		X					X				X					X					X			
Review/Record Hospitalization, Urgent HF Visits, Urgent Care Visits, and Procedures			----------X----------																						
Review/Record AEs, Con Meds	6.5.7, 5.3		----------X----------																						
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																											
Plasma PK	6.4			X	X				X				X					X						X			
Drug Administration																											
Randomization	3.5 Window is 5D prior to Day 1			X																							
Premedication/ Study Drug	5.2.1, 5.2.3			X		X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; COVID-19=coronavirus disease 2019; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; FSH=follicle-stimulating hormone; KCCQ=Kansas City Cardiomyopathy Questionnaire; HF=heart failure; M=month; mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit. In situations where a Month 6 (Day 176-183), Month 9 (Day 260-267), and/or Month 12 (Day 365-372) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.

[b] This Modified Month 12 Efficacy Visit is to be performed at Month 12 for patients who discontinued treatment early (ie, prior to Month 12), and choose to remain in the study. All patients who discontinue from study drug during the double-blind period will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including this Modified Month 12 Efficacy Visit. Such patients will also receive assessments at the Early Treatment Discontinuation Visit (7 to 14 days after their last dose of study drug); and the safety follow-up visit (28 days after the last dose of study drug) (Table 4), as described in Section 4.3.1. In situations where the Modified Month 12 Efficacy Visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing for these efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended, up to Day 417 (as is permitted for the regular Month 12 visit).

[c] See Section 5.3.1; patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period. In all cases, the Pre-tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of double-blind study drug (ie, 7 to 14 days post dose). Thereafter, the patient will continue with all assessments per the Schedule of Assessments, including the Month 12 Efficacy Visit. At the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

[d] As described in Section 6.2.1, to avoid a potential training effect resulting from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be performed within each of the following time periods: Day 2 to Day 214 (includes the scheduled Weeks 25-26 assessment); Day 215 to Day 319 (includes the scheduled Weeks 37-38 assessment); and Day 320 to Day 417 (includes the scheduled Weeks 52-53 assessment). Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit [Table 4]); no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed as scheduled.

[e] Serum creatinine only.

Table 2: Year 2 Schedule of Assessments: Open-label Extension Period (Through Month 24)

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																				
		D379±3	D400±3	D421±3	D442±3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107
Efficacy Assessments																						
6-MWT	6.2.1										X					X						X
KCCQ	6.2.2										X					X						X
mBMI	6.2.4							X										X				
Cardiac Biomarker Samples	6.2.5.1					X					X					X						X
ATTR amyloidosis disease stage	6.2.5.2																					X
NYHA Class	6.2.5.3										X					X						X
Echocardiogram	6.2.5.4										X											X
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5										X[b]											X
Norfolk QoL-DN	6.2.6																					X
Pharmacodynamic Assessments																						
TTR Protein	6.3					X					X					X						X
Exploratory Biomarkers (plasma, serum)	6.6					X					X					X						X
Safety Assessments																						
Vital Signs	6.5.1	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	
Weight	6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed)	6.5.3					X					X					X						X
Single 12-lead ECG	6.5.4					X				X					X						X	
Serum Chemistry, Liver Function Tests	6.5.5							X										X				X[c]
Hematology	6.5.5							X										X				
Pregnancy Test	Table 5, 6.5.5.2			X				X					X					X			X	
Review/Record Hospitalization, Urgent HF Visits, Urgent Care Visits, and Procedures		----------X----------																				
Review/Record AEs, Con Meds	6.5.7, 5.3	----------X----------																				
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Year 2 Schedule of Assessments: Open-label Extension Period (Through Month 24)

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																			
		D379±3	D400±3	D421±3	D442±3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107
Pharmacokinetic Assessments																						
Plasma PK	6.4																					
Drug Administration																						
Premedication, Study Drug	5.2.1, 5.2.3	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; COVID-19=coronavirus disease 2019; CMR=cardiac magnetic resonance; D=day; ECG=electrocardiogram; HF=heart failure; KCCQ=Kansas City Cardiomyopathy Questionnaire; mBMI=modified body mass index; 6-MWT=6-minute walk test; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit. In situations where a Month 18 (Day 554-561), Month 21 (Day 638-645), and/or Month 24 (Day 743-750) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 18, 21, and/or 24 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 18 up to Day 592; Month 21 up to Day 697; Month 24, up to Day 791.

[b] Consecutive CMR scans should not be performed within 5 months of each other. Consecutive technetium scans should not be performed within 5 months of each other.

[c] Serum creatinine only.

Table 3: Year 3 Schedule of Assessments: Open-label Extension Period (Through Month 36)

Study Day ±Visit Window	**For Details see Section**	**Open-label Extension Period**																			
		D757±3	**D778±3**	**D799±3**	**D820±3**	**D841±3**	**D862±3**	**D883±3**	**D904±3**	**D925±3**	**D932-D938[a]**	**D946±3**	**D967±3**	**D988±3**	**D1009±3**	**D1016-D1022[a]**	**D1030±3**	**D1051±3**	**D1072±3**	**D1093±3**	**D1100-D1106[a]**
Study Week		**108**	**111**	**114**	**117**	**120**	**123**	**126**	**129**	**132**	**133-134**	**135**	**138**	**141**	**144**	**145-146**	**147**	**150**	**153**	**156**	**157-158**
Efficacy Assessments																					
6-MWT	6.2.1										X					X					X
KCCQ	6.2.2										X					X					X
mBMI	6.2.4							X										X			X
Cardiac Biomarker Samples	6.2.5.1					X					X					X					X
ATTR amyloidosis disease stage	6.2.5.2																				X
NYHA Class	6.2.5.3										X					X					X
Echocardiogram	6.2.5.4										X										X
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5																				X
Norfolk QoL-DN	6.2.6																				X
Pharmacodynamic Assessments																					
TTR Protein	6.3										X										X
Exploratory Biomarkers (plasma, serum)	6.6										X										X
Safety Assessments																					
Vital Signs	6.5.1	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	
Weight	6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed)	6.5.3										X										X
Single 12-lead ECG	6.5.4										X					X					X
Serum Chemistry, Liver Function Tests	6.5.5							X										X			X[b]
Hematology	6.5.5							X										X			
Pregnancy Test	Table 5, 6.5.5.2			X				X					X					X		X	
Review/Record Hospitalization, Urgent HF Visits, Urgent Care Visits, and Procedures		----------X----------																			
Review/Record AEs, Con Meds	6.5.7, 5.3	----------X----------																			

Table 3: Year 3 Schedule of Assessments: Open-label Extension Period (Through Month 36)

Study Day ±Visit Window	**For Details see Section**	**Open-label Extension Period**																		
		D757±3	**D778±3**	**D799±3**	**D820±3**	**D841±3**	**D862±3**	**D883±3**	**D904±3**	**D925±3**	**D932-D938[a]**	**D946±3**	**D967±3**	**D988±3**	**D1009±3**	**D1016-D1022[a]**	**D1030±3**	**D1051±3**	**D1072±3**	**D1093±3**	**D1100-D1106[a]**
Study Week		**108**	**111**	**114**	**117**	**120**	**123**	**126**	**129**	**132**	**133-134**	**135**	**138**	**141**	**144**	**145-146**	**147**	**150**	**153**	**156**	**157-158**
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																					
Plasma PK	6.4																				
Drug Administration																					
Premedication, Study Drug	5.2.1, 5.2.3	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; COVID-19=coronavirus disease 2019; CMR=cardiac magnetic resonance; D=day; ECG=electrocardiogram; HF=heart failure; KCCQ=Kansas City Cardiomyopathy Questionnaire; mBMI=modified body mass index; 6-MWT=6-minute walk test; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit. In situations where a Week 133-134 (Day 932-938), Week 145-146 (Day 1016-1022), and/or Week 157-158 (Day 1100-1106) study visit is unable to be completed at the study center, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the efficacy assessments for those visits. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Day 932-938 up to Day 977; Day 1016-1022 up to Day 1061; Day 1100-1106 up to Day 1148.

[b] Serum creatinine only.

Table 4: Year 4 Schedule of Assessments: Open-label Extension Period (Through Month 48), Early Treatment Discontinuation Visit, and Follow-up

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																		Early Treatment Disc Visit[b]	Follow-up
																			EOS[a]		
		D1114±3	D1135±3	D1156±3	D1177±3	D1198±3	D1219±3	D1240±3	D1261±3	D1282±3	D1289-D1295[a]	D1303±3	D1324±3	D1345±3	D1366±3	D1387±3	D1408±3	D1429±3	D1450±3	D1457-D1463[a]	7- 14 Days after Last Dose	D1478±10
Study Week		159	162	165	168	171	174	177	180	183	184-185	186	189	192	195	198	201	204	207	208-209	NA	211
Efficacy Assessments																						
6-MWT	6.2.1										X									X	X	
KCCQ	6.2.2										X									X	X	
mBMI	6.2.4										X									X	X	
Cardiac Biomarker Samples	6.2.5.1										X									X	X	
ATTR amyloidosis disease stage	6.2.5.2																			X		
NYHA Class	6.2.5.3										X									X		
Echocardiogram	6.2.5.4										X									X		
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5																			X		
Norfolk QoL-DN	6.2.6																			X		
Pharmacodynamic Assessments																						
TTR Protein	6.3										X									X	X	X
Exploratory Biomarkers (plasma, serum)	6.6										X									X		
Safety Assessments																						
Vital Signs	6.5.1	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X
Weight	6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed)	6.5.3										X									X	X	X
Single 12-lead ECG	6.5.4										X									X	X	

Table 4: Year 4 Schedule of Assessments: Open-label Extension Period (Through Month 48), Early Treatment Discontinuation Visit, and Follow-up

		Open-label Extension Period																			Early Treatment Disc Visit[b]	Follow-up
																				EOS[a]		
Study Day ±Visit Window	**For Details see Section**	**D1114±3**	**D1135±3**	**D1156±3**	**D1177±3**	**D1198±3**	**D1219±3**	**D1240±3**	**D1261±3**	**D1282±3**	**D1289-D1295[a]**	**D1303±3**	**D1324±3**	**D1345±3**	**D1366±3**	**D1387±3**	**D1408±3**	**D1429±3**	**D1450±3**	**D1457-D1463[a]**	**7- 14 Days after Last Dose**	**D1478±10**
Study Week		**159**	**162**	**165**	**168**	**171**	**174**	**177**	**180**	**183**	**184-185**	**186**	**189**	**192**	**195**	**198**	**201**	**204**	**207**	**208-209**	**NA**	**211**
Serum Chemistry, Liver Function Tests	6.5.5										X									X	X	X
Hematology	6.5.5										X									X	X	X
Pregnancy Test	Table 5, 6.5.5.2			X				X					X				X			X	X	
Review/Record Hospitalization, Urgent HF Visits, Urgent Care Visits, and Procedures		----------X----------																				
Review/Record AEs, Con Meds	6.5.7, 5.3	----------X----------																				
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																						
Plasma PK	6.4																				X	
Drug Administration																						
Premedication, Study Drug	5.2.1, 5.2.3	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; COVID-19=coronavirus disease 2019; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; EOS=End of Study (visit); HF=heart failure; KCCQ=Kansas City Cardiomyopathy Questionnaire; mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit. This EOS visit will also be completed by patients who have completed Year 2 of the study and who transition to commercial patisiran (ie, patisiran is commercially available in the patient's country of residence and patisiran is accessible to the patient); these patients do not need to complete efficacy assessments if those assessments were completed within the prior 3 months; consecutive CMR scans should not

be performed within 5 months of each other; consecutive technetium scans should not be performed within 5 months of each other. In situations where a Week 184-185 (Day 1289-1295) and/or Week 208-209 (Day 1457-1463) study visit is unable to be completed at the study center, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the efficacy assessments for those visits. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Day 1289-1295 up to Day 1337; Day 1457-1463 up to Day 1488.

[b] Patients who discontinue early from study drug will be asked to complete the Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug. In addition, patients discontinuing early from study drug during the double-blind period will be encouraged to remain on the study and complete assessments through Month 12 and complete the Modified Month 12 Efficacy Visit (see Table 1); they will also be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug as described in Section 4.3.1.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALN-18328	siRNA targeting TTR
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APOLLO	Patisiran pivotal Phase 3 clinical study ALN-TTR02-004
AST	Aspartate aminotransferase
ATTR	Amyloid transthyretin
BMI	Body mass index
BUN	Blood urea nitrogen
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration at end of infusion
$C_{max,ss}$	Steady-state C_{max}
C_{min}	Minimum pre-infusion concentration
$C_{min,ss}$	Steady-state C_{min}
CMR	Cardiac magnetic resonance
Con Meds	Concomitant medication
COVID-19	Coronavirus disease 2019
$C_{p(30min)}$	30-minute post-infusion concentration
$C_{p,ss(30min)}$	Steady-state $C_{p(30min)}$
CRF	Case report form
CFR	Code of Federal Regulations
CV	Cardiovascular
DLin-MC3-DMA	1,2-Dilinoleyloxy-N,N-dimethylpropylamine
DMC	Data Monitoring Committee
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunoassay
EOS	End of study

Abbreviation	Definition
EU	European Union
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
HF	Heart failure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRS	Interactive Response System
IV	Intravenous(ly)
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire– Overall Summary
LNP	Lipid nanoparticle
LS	Least squares
mBMI	Modified body mass index
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 neurological impairment score +7
mRNA	Messenger ribonucleic acid
6-MWT	6-minute walk test
NA	Not applicable
Norfolk QoL-DN	Norfolk Quality of Life - Diabetic Neuropathy
NSAID	Nonsteroidal anti-inflammatory drug

Abbreviation	Definition
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEG_{2000}-C-DMG	3-N-[(ω-methoxy poly(ethylene glycol)2000) carbamoyl]-1,2-dimyristyloxy-propylamine
PK	Pharmacokinetic
PND	Polyneuropathy disability
PT	Preferred term
RBC	Red blood cell
RBP	Retinol binding protein
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
siRNA	Small interfering RNA
Tc	Technetium
TTR	Transthyretin
ULN	Upper limit of normal
US	United States
V30M	Valine to methionine mutation at position 30
V122I	Valine to isoleucine mutation at position 122
wt	Wild type
wtTTR	Wild type transthyretin

1. INTRODUCTION

1.1. Disease Overview

Transthyretin (TTR)-mediated amyloidosis (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 (ageing) causes, respectively. In ATTR amyloidosis, deposition of TTR in various organs results in progressive, chronically debilitating morbidity and mortality. The most common manifestations of ATTR amyloidosis are polyneuropathy and cardiomyopathy (ie, ATTR amyloidosis with cardiomyopathy).

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]

In hATTR amyloidosis, 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. These misfolded TTR monomers can then self-assemble into oligomers and form amyloid fibrils and plaques in the extracellular space of various tissues [Hou 2007], including the peripheral nervous system, heart, gastrointestinal tract, kidney, central nervous system and eye, leading to cellular injury and organ dysfunction with corresponding clinical manifestations. Since almost all patients are heterozygous for the mutated TTR allele, the amyloid fibrils typically consist of both mutant and wtTTR.

There are over 120 reported TTR genetic mutations associated with hATTR amyloidosis, and almost all patients are heterozygous for the mutated TTR allele.[Ando 2013; Connors 2003] The phenotypic expression varies depending on the predominant site of deposition of the amyloid fibrils with some mutations associated with predominantly polyneuropathy manifestations and others associated with predominantly cardiomyopathy manifestations. However, most patients experience both over the course of their disease.

The most common TTR mutation is the valine to methionine mutation at position 30 (V30M), accounting for approximately 50% of cases worldwide, and occurring primarily in families with heritage from Portugal, Sweden, Japan, and Brazil.[Parman 2016] This genotype is most commonly associated with multisystemic polyneuropathy. The valine to isoleucine at position 122 (V122I) mutation is most commonly associated with cardiomyopathy and occurs primarily in African Americans. In these individuals, the mean age at diagnosis is approximately 65 to 70 years, with symptom onset typically occurring after the age of 65.[Jacobson 2011; Quarta 2015] While there appears to be an association between carrier status and the development of heart failure (HF) and echocardiographic features of cardiac amyloidosis, the exact penetrance of this particular allele is unknown, and estimates vary widely.

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] Patients with this

condition do not have a pathogenic mutation in the TTR gene and the amyloid fibrils consist only of wtTTR protein, which form amyloid deposits typically found in heart tissue.

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 preserved until late stages of the disease.[Castano 2015; Dungu 2012; Mohty 2013; Ruberg 2012] Cardiac infiltration by amyloid can also lead to conduction disturbances and arrhythmias.[Adams 2016; Ando 2013; Benson and Kincaid 2007; Connors 2004] Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, in addition to clinical measurements of ambulation, and quality of life. Progression of disease in this population can be seen over a period of 12 months as demonstrated by differences in 6-minute walk test (6-MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ) – Overall Summary (KCCQ-OS) in the Phase 3 ATTR-ACT study.[Maurer 2018] Based on natural history data, patients typically experience progressive symptoms of HF resulting in hospitalization and with death typically occurring 2.5 to 5 years after diagnosis.[Castano 2015; Damy 2015; Dungu 2012; Hawkins 2015]

1.2. Current Treatments

The treatment of ATTR amyloidosis requires a multidisciplinary approach primarily involving cardiology, neurology, and gastroenterology specialties. While there are treatments for polyneuropathy that are available to hATTR amyloidosis patients, for most regions no treatments are currently available for the cardiomyopathy phenotype for either the hATTR or wtATTR forms. Palliative/symptomatic therapies directed at specific symptoms, including volume control and treatment of cardiac arrhythmias and conduction system disturbances, including cardiac pacemakers where appropriate, have been the mainstay of treatment despite their limited effectiveness.

Given that the liver is the primary source of TTR, orthotopic liver transplantation (OLT) has been used for hATTR amyloidosis patients since the early 1990s. However, OLT is intended to eliminate mutant TTR from circulation, but has no effect on the hepatic production of wtTTR, which continues to be made by the transplanted liver and can continue to deposit in the heart. OLT has also only been shown to be effective in slowing the progression of disease in patients with an early age of onset (<50 years of age) [Okamoto 2009], and especially for those with the V30M mutation and short disease duration before transplant. Consequently, almost two-thirds of patients with hATTR amyloidosis are not transplant-eligible.

Tafamidis, a TTR tetramer stabilizer that acts by binding to the thyroxine-binding site on TTR to reduce its dissociation into misfolded amyloidogenic monomers, is currently approved in a number of markets, but not in the United States (US), for the treatment of patients with hATTR amyloidosis with polyneuropathy.[Coelho 2016] In addition, tafamidis has been approved in some regions, including the European Union (EU) and US, 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] In Japan, tafamidis was approved for use in transthyretin-type cardiac amyloidosis (wt and mutant), in addition to approval for transthyretin-type familial amyloid polyneuropathy. The ATTR-ACT trial demonstrated that tafamidis treatment over

30 months was associated with lower all-cause mortality and cardiovascular (CV)-related hospitalizations compared with placebo treatment.[Maurer 2018] Additionally, tafamidis treatment resulted in a slowing of the decline in functional capacity (6-MWT) and quality of life (KCCQ-OS) compared to placebo. However, consistent with the expected pharmacodynamic (PD) effect of TTR stabilization, the effects of tafamidis on mortality outcomes was not observed until late in treatment, with differentiation between treatment groups occurring only after 18 months of treatment. Furthermore, although improvements with tafamidis relative to placebo were observed in 6-MWT and KCCQ-OS, minimal changes in echocardiographic parameters were observed, and tafamidis-treated patients still progressed during the study.

The results of the ATTR-ACT study 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 a ribonucleic acid (RNA) interference (RNAi) therapeutic, may be required to halt or reverse the debilitating and ultimately fatal course of disease.

1.3. Patisiran Clinical Development

Patisiran is a small interfering RNA (siRNA) specific for TTR, which is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration.[Akinc 2010] The patisiran drug product (ALN-TTR02; patisiran-LNP, hereafter referred to as "patisiran") is designed to significantly suppress liver production of both wt and all mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with ATTR amyloidosis.

Patisiran utilizes the mechanism of RNAi to selectively degrade TTR messenger RNA (mRNA) and thereby reduce the expression of its corresponding protein.[Bumcrot 2006] Patisiran is formulated (via the LNP) to target delivery to hepatocytes in the liver, the primary source of TTR protein in circulation. Following IV infusion, opsonization of the LNP by apolipoprotein E facilitates binding to the low-density lipoprotein receptor on hepatocytes and subsequent endocytosis. Fusion of the ionizable lipid component of the LNP with the endosomal membrane then leads to release of the siRNA into the cytoplasm where it can bind to and activate the RNA-induced silencing complex (RISC). Upon binding and activation of RISC in the cytoplasm within hepatocytes, the siRNA duplex unwinds, and the antisense strand specifically binds to a genetically conserved sequence in the 3' untranslated region of wt and mutant TTR mRNA. The Argonaute-2 endonuclease within the RISC/siRNA enzyme complex catalytically degrades wt and mutant TTR mRNA, resulting in a reduction of wt and mutant TTR protein.

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing patisiran for the treatment of patients with ATTR amyloidosis. Based on results from the pivotal Phase 3 APOLLO study (Section 1.3.1), patisiran is approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults and in the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 and stage 2 polyneuropathy. Ongoing development is intended to establish patisiran for the treatment of ATTR (hereditary and wt) amyloidosis with cardiomyopathy based on exploratory cardiac results from the APOLLO study (Section 1.3.1.1), which provides

preliminary evidence in support of the use of patisiran for the treatment of the cardiomyopathy manifestations of the disease.

The nonclinical pharmacology, pharmacokinetics (PK), and toxicology of patisiran were evaluated in a series of in vitro and in vivo studies that have enabled chronic dosing in clinical studies.

1.3.1. The Phase 3 APOLLO Study

The safety and efficacy of patisiran was shown in a Phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study (ALN-TTR02-004, APOLLO) that met the primary and all secondary endpoints.[Adams 2018] This study demonstrated that, in patients with hATTR amyloidosis who exhibited a broad range of disease severity and TTR genotypes, treatment with patisiran leads to a significant improvement in neuropathy (modified neurological impairment score +7 [mNIS+7]) relative to placebo at 18 months (primary endpoint), as well as significant improvement in quality of life (Norfolk Quality of Life - Diabetic Neuropathy [Norfolk QoL-DN], key secondary endpoint) relative to placebo at 18 months. Significant improvement in neuropathy and quality of life were also observed at Month 9. This study furthermore demonstrated that treatment with patisiran is associated with an improvement in overall health (gait speed, nutritional status, and disability), with improvement in these endpoints seen as early as at Month 9.

In the patisiran group, serum TTR reduction was seen after the first dose and was stably maintained over the duration of the study; the mean TTR percent reduction from baseline was 82.6% and 84.3% at Months 9 and 18, respectively. A correlation (Pearson's r, 0.59; 95% CI, 0.49-0.68) was observed between the degree of TTR reduction from baseline and the change in the mNIS+7 at 18 months.

Patisiran showed an acceptable safety profile in the APOLLO study. Common adverse events (AEs) occurring more frequently with patisiran compared to placebo included peripheral edema (30% versus 22%) and infusion related reactions (IRRs) (19% versus 9%, respectively).

1.3.1.1. Cardiac Results and Cardiac Subpopulation Data from APOLLO

In APOLLO, evidence of potential cardiac amyloid involvement was seen in most patients in the study; 80% had left ventricular wall thickness >13 mm and 79% had abnormal levels of the cardiac biomarker N-terminal prohormone B-type natriuretic peptide (NT-proBNP).[Solomon 2018] As well, 56% of the population met the prespecified criteria for inclusion in a subpopulation of patients with evidence of cardiac amyloid involvement (ie, the cardiac subpopulation, with baseline left ventricular wall thickness ≥13 mm and no history of hypertension or aortic valve disease). In these patients, treatment with patisiran for up to 18 months resulted in improvement relative to placebo in important measures of cardiac structure and function. These included reduction in ventricular wall thickness and decrease (improvement) in global longitudinal strain.[Solomon 2018] In addition, patisiran treatment led to a reduction (improvement) in NT-proBNP and an improvement in functional capacity, as measured by 10-meter walk test assessment of gait speed, relative to the placebo group.

Overall, patisiran had an acceptable safety profile, based on an in-depth analysis of cardiac events in both the overall (modified intent-to-treat) population and the cardiac subpopulation. Importantly, in a post hoc analysis of safety data in the modified intent-to-treat population, rates

of any hospitalization and/or all-cause death were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups respectively, while the rates of cardiac hospitalizations and/or all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups respectively. This approximates a reduction in event rate of approximately 50% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality for patients in the patisiran group compared to those in the placebo group.[Solomon 2018] Similar reductions in the event rates were observed in the cardiac subpopulation in APOLLO (approximately 55% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality; data on file).

The observed cardiac data from the APOLLO study support the therapeutic hypothesis that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis and warrant ongoing development for this indication.

1.3.2. Phase 3, Open-label Extension Study

Study ALN-TTR02-006 is an ongoing multicenter, open-label extension study designed to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis who have completed a prior Phase 2 or 3 parent study with patisiran (ALN-TTR02-003 or ALN-TTR02-004 [APOLLO]). The interim data from this open-label extension study were consistent with, and extended, the acceptable safety profile and clinical efficacy of patisiran observed in the Phase 3 APOLLO study.

No new safety signals have emerged for patients with long-term patisiran treatment.

1.4. Study Design Rationale

This study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of patisiran in adult patients with ATTR amyloidosis with cardiomyopathy. The efficacy of patisiran on functional capacity will be evaluated via change at Month 12 in the 6-MWT (primary endpoint). The study will include patients with wtATTR and hATTR amyloidosis with cardiomyopathy who, at baseline, are either tafamidis naïve or have been on tafamidis for ≥6 months with disease progression, in the opinion of the Investigator.

Confidence in a beneficial treatment effect with patisiran in this patient population with ATTR amyloidosis with cardiomyopathy comes from the Phase 3 APOLLO study of patisiran in patients with hATTR amyloidosis with polyneuropathy. As described in Section 1.3.1 and Section 1.3.1.1, TTR lowering with patisiran demonstrated multiple benefits in a broad range of disease manifestations, including a substantial improvement in neuropathy and quality of life, as well as autonomic symptoms, motor strength, ambulatory ability, disability, and nutritional status.[Adams 2018] Furthermore, in a prespecified subgroup of patients with evidence of cardiac involvement, which was a majority (56%) of the overall study population, a beneficial treatment effect of patisiran compared to placebo was observed for assessments of cardiac structure and function as well as the cardiac biomarker NT-proBNP.[Solomon 2018]

The 6-MWT (primary endpoint assessment) 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 2014] The KCCQ-OS (first secondary endpoint assessment) 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 et al. 2006) Both 6-MWT and KCCQ-OS were shown to rapidly and consistently decline over time in cardiac ATTR amyloidosis patients and, in the 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 primary and key secondary endpoints, respectively.

Assessment of the primary endpoint at Month 12 is supported by placebo-arm data from the ATTR-ACT study showing substantial disease progression (via the 6-MWT) over an equivalent time; as well, data from APOLLO demonstrated a patisiran treatment effect as early as 9 months on multiple manifestations of hATTR amyloidosis (neuropathy, quality of life, NT-proBNP, and functional capacity [ie, gait speed]).[Maurer 2018]

The inclusion of placebo as a control allows for a rigorous analysis of the treatment effect of patisiran. If tafamidis becomes an approved therapy for ATTR amyloidosis with cardiomyopathy in a given region while this study is in progress, patients who are naïve to tafamidis treatment at baseline may commence concomitant on-label tafamidis during the study (ie, tafamidis drop-in) (Section 5.3.1).

1.5. Dose Rationale

The approved and recommended dosage of patisiran for the treatment of the polyneuropathy in patients with hATTR amyloidosis is 0.3 mg/kg administered IV every 3 weeks for patients weighing <100 kg and a fixed dose of 30 mg administered every 3 weeks for patients weighing 100 kg or more. This dosage was selected based on dose-response analyses from three Phase 1 and 2 studies demonstrating dose-dependent TTR reduction, with the maximum reduction achieved at 0.3 mg/kg. This regimen was further confirmed in the pivotal Phase 3 APOLLO study, where this dosage showed significant clinical activity and was well tolerated by patients with hATTR amyloidosis with polyneuropathy, including those in the cardiac subpopulation. The approved dosing regimen used in the treatment of polyneuropathy is being employed in this study since the mechanism of action of patisiran (ie, serum TTR lowering) for treatment of polyneuropathy and cardiomyopathy is the same.

1.6. Benefit-risk Assessment

ATTR amyloidosis with cardiomyopathy is a rare, serious, life-threatening, multisystemic disease characterized by deposition of TTR in various organs. Without treatment, the disease progresses, resulting in chronically debilitating morbidity and mortality, with the most common manifestations being cardiomyopathy and polyneuropathy. Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, ambulation, and quality of life seen over a period of 18 months or less.[Ruberg and Berk 2012]

The benefit-risk profile of patisiran has been established in extensive clinical development; in Phase 1, 2, and 3 clinical studies, patisiran administered IV demonstrated a potent, dose-dependent inhibition of TTR. In the Phase 3 APOLLO study of patisiran, the primary and all secondary endpoints were met.[Adams 2018] Furthermore, exploratory cardiac results from

the APOLLO study suggest that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon 2018] and provide preliminary evidence in support of the use of patisiran for the treatment of patients with ATTR amyloidosis with cardiomyopathy (Section 1.3.1.1).

In APOLLO, as well as in the ongoing Phase 3, open-label extension study (ALN-TTR02-006), an acceptable safety profile with patisiran was demonstrated. Most AEs were mild or moderate in severity. Transient infusion-related reactions (IRRs) were observed, but all IRRs were mild or moderate in severity, none were reported as serious AEs (SAEs). No clinically significant laboratory or hematologic changes were observed. Furthermore, in APOLLO, an acceptable safety profile was also observed in a prespecified subgroup of patients with evidence of cardiac amyloid involvement. [Solomon 2018]

For patisiran, important identified risks include IRRs. To minimize this risk, all patients must receive premedication with a corticosteroid, paracetamol/acetaminophen, and H1 and H2 blockers prior to patisiran administration (Section 5.2.1). The infusion may be interrupted or slowed if an IRR occurs (Sections 5.2.3 and 5.2.4). Important potential risks also include severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients. Patisiran is contraindicated in patients with a history of severe hypersensitivity (eg, anaphylaxis or anaphylactoid reactions) to patisiran or any of the excipients.

Vitamin A deficiency is also considered an important potential risk. Nonclinical and clinical data with patisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in 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 (Section 5.3). 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 patisiran.

Detailed information about the known and expected benefits and risks of patisiran may be found in the current edition of the Investigator's Brochure.

During the study, patients will be monitored, including evaluation of laboratory monitoring for liver function test abnormalities, renal function, and other standard hematology and blood chemistries. As the risk of embryofetal toxicity is currently unknown, females of child-bearing potential participating in the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception as specified in the protocol.

An external, independent Data Monitoring Committee (DMC) will monitor and ensure the safety of trial participants (see Section 3.7).

In conclusion, exploratory cardiac results from the APOLLO study suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon 2018] (Section 1.3.1.1) together with the established benefit-risk profile of patisiran demonstrated in the Phase 3 APOLLO study (and supportive data from the ALN-TTR02-003 and ALN-TTR02-006 studies), support the evaluation of patisiran in a Phase 3 study in adult patients with ATTR amyloidosis (wtATTR and hATTR) cardiomyopathy.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality, hospitalizations, and urgent heart failure (HF) visits	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV) events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month double-blind period
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV events • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV events (CV hospitalizations and urgent HF visits) over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI) o Cardiac magnetic resonance (CMR) parameters o Technetium scintigraphy parameters o Troponin I levels o Norfolk QoL-DN

Objectives	Endpoints
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (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 patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the Investigator. This group will be capped at 30% of total enrollment in the study.

In addition to patients who have never taken tafamidis, patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve for this study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 36-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period (Figure 1).

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive IV treatment every 3 weeks with either patisiran (0.3 mg/kg for patients weighing <100 kg; 30-mg fixed dose for patients weighing ≥100 kg) or placebo. Prior to receiving randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an IRR with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. (Patients randomized to placebo will also receive premedications to maintain the blind.) Study drug will be administered as an approximately 80-minute IV infusion.

During the open-label extension period, all patients will receive treatment with open-label patisiran.

Study drug administration at a location other than the study center (eg, at home) may be administered as follows:

- Double-blind period: Patients who have received ≥2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.
- Open-label extension period: Patients who have received ≥2 doses of open-label patisiran at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have patisiran administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Patisiran administration will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion, with oversight of the Investigator.

Patients may receive patisiran on the study until the end of the open-label extension period or until the first of one of the following occurs: 1) they meet any of the study discontinuation criteria; 2) patisiran is commercially available in the patient's country of residence, and patisiran is accessible to the patient, and the patient has completed Year 2 of the study, including the end of study visit; or 3) the patisiran development program is discontinued.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint (Section 2); this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period at the time points noted in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score.

In situations where an efficacy study visit at Months 6, 9, and/or 12 is unable to be completed at the study center due to the coronavirus disease 2019 (COVID-19) pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended for that visit as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran (Table 1). Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed. For the open-label extension period, the windows for study visits are also extended (Table 2, Table 3, and Table 4).

Safety will be assessed throughout the study, as described in the Schedule of Assessments for the double-blind period (Table 1) and for the open-label extension period (Table 2, Table 3, and Table 4).

3.2. Duration of Treatment

The treatment duration in this study is up to 48 months, inclusive of a 12-month, double-blind, treatment period, and a 36-month, open-label, treatment period.

3.3. Duration of Study Participation

The estimated total time on study for each patient is up to 50.5 months, including up to 45 days of screening, up to 48 months of treatment (see Section 3.2), and a 28-day safety follow-up period.

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:

- the patient has completed the end of study (EOS) visit, or
- the patient has completed the follow-up visit 28 days after the last dose of patisiran.

Patients who have transitioned to commercial patisiran (see Section 3.1 and Table 4) should have completed the end of study visit and are therefore considered to have reached the end of the study.

3.4. Number of Planned Patients

The planned enrollment for this study is 300 patients with wtATTR and hATTR amyloidosis with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR.

3.5. Method of Assigning Patients to Treatment Groups

Using the interactive response system (IRS), patients will be randomized 1:1 to the patisiran or placebo arm. Randomization will be stratified by:

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

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 IRS. The Investigator or his/her designee will contact the IRS to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

3.6. Blinding

During the double-blind period of the study, all personnel will be blinded to the study treatment, except the pharmacist and designated pharmacy/healthcare personnel who will set-up, dispense, and prepare the infusion. Patisiran confers a slightly opalescent color relative to the clear saline (placebo) infusate; therefore, all infusion bags and lines will be covered with amber bags and line

covers by the unblinded personnel to prevent visualization by the blinded study personnel and patient, as described in detail in the Pharmacy Manual.

After the pharmacist (or designated pharmacy/healthcare personnel) has prepared the infusion, separate blinded personnel will monitor the patient during and after the infusion. All patients will be blinded to treatment and will receive an IV infusion once every 3 weeks using identical volumes for patisiran and placebo.

Study personnel performing assessments related to the primary and secondary endpoints will be different from the Investigator and other personnel managing the patient, and all of these study personnel will be blinded to any clinical laboratory results that could potentially unblind them (eg, TTR levels). In addition, the study personnel performing assessments related to the primary and secondary efficacy endpoints will not reference the results of any previous assessments.

Study personnel involved in a patient's medical care will also refrain from obtaining local laboratory results that could potentially unblind them to the patient's treatment until after the study has been unblinded. Such laboratory results would include TTR (ie, prealbumin), vitamin A, and RBP measurements.

Furthermore, unblinded source documentation containing all descriptions of pharmacy preparations and infusions or distribution of study drug or randomization data will be stored separate from all other study data/records and from other pharmacy staff not participating on the study.

Blinding will be maintained until the last patient completes their Month 12 visit.

3.6.1. Emergency Unblinding

During the double-blind period of the study, 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. 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 IRS instructions for details on emergency unblinding.

3.7. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study through the double-blind period (through Month 12), providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.8. Adjudication Committee

An independent Adjudication Committee will review deaths and non-elective hospitalizations and will attribute a cause (CV versus non-CV) according to the responsible underlying disease process rather than the immediate mechanism. Urgent HF visits will also be adjudicated.

Deaths, hospitalizations, and urgent HF visits will be classified as specified in the Adjudication Committee 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 and Sex

1. Age 18 (or age of legal consent, 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:

   Hereditary ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

   a. TTR pathogenic mutation consistent with hATTR.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at screening).
   c. 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 ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) has been excluded.
   d. If MGUS, confirm TTR protein in tissue with immunohistochemistry (IHC) or mass spectrometry.

   Wild-type ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

   a. Absence of pathogenic TTR mutation.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at screening).
   c. Amyloid deposits in cardiac tissue with TTR precursor identification by IHC, mass spectrometry, **OR** technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc] or ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if MGUS has been excluded.
   d. If MGUS, confirm TTR protein in cardiac tissue with IHC or mass spectrometry.

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; in addition to patients who have never taken tafamidis, those who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.
    b. Currently on tafamidis (for ≥6 months) and has demonstrated disease progression, as determined by the Investigator. (At the time of study entry, tafamidis treatment must be on-label use of commercial tafamidis for the treatment of ATTR amyloidosis with cardiomyopathy at the approved 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. Able to complete ≥150 m on the 6-MWT at screening.
7. Screening NT-proBNP >300 ng/L and <8500 ng/L; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP >600 ng/L and <8500 ng/L.

Informed Consent

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent; and patient agrees to sign the medical records release form for collection of vital status.

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) or leptomeningeal amyloidosis.
2. NYHA Class III **AND** ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3000 ng/L and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2).[Gillmore 2018]
3. NYHA Class IV at the Screening visit.
4. Has a polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires cane or stick to walk, or is wheelchair bound) at the Screening visit.

Laboratory Assessments

5. Has any of the following laboratory parameter assessments at screening:
    a. Aspartate transaminase (AST) or alanine transaminase (ALT) levels >2.0 × the upper limit of normal (ULN).
    b. Total bilirubin >2×ULN.

c. International normalized ratio (INR) >1.5 (unless patient is on anticoagulant therapy, in which case excluded if INR >3.5).

6. Has eGFR <30 mL/min/1.73 m^2 (using the modification of diet in renal disease [MDRD] formula).
7. Has known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.

Prior/Concomitant Therapy

8. Tafamidis naïve patients (at baseline) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
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. Received prior TTR-lowering treatment (including patisiran) or participated in a gene therapy trial for hATTR amyloidosis.
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 6 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 chronic 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 electrocardiogram [ECG] changes).
15. Has non-amyloid disease affecting exercise testing (eg, severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation).
16. Recent or planned orthopedic procedure during the double-blind period (eg, lower extremity or back surgery) that could impact 6-MWT.
17. Unstable congestive heart failure (CHF) (eg, no adjustment of diuretics at time of screening required to achieve optimal treatment of CHF).
18. Had acute coronary syndrome or unstable angina within the past 3 months.
19. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.

20. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
21. Has persistent elevation of systolic (>180 mmHg) and diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.
22. Has untreated hypo- or hyperthyroidism.
23. Prior or planned heart, liver, or other organ transplant.
24. Had a malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
25. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient.
26. Has a history of severe hypersensitivity (eg, anaphylaxis) to any of the excipients in patisiran. Also see exclusion Criterion 11, which excludes all patients with prior TTR-lowering treatment including patisiran.

Contraception, Pregnancy, and Breastfeeding

27. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.
28. Female patient is pregnant or breast-feeding.

Alcohol Use

29. Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (for females, more than 14 units of alcohol per week; for males, more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer]);
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 or their legal guardians 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 electronic case report form (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; which includes required treatment with prohibited medication (as defined in Section 5.3) per Investigator discretion
- 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 6.5.7.7 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 is captured in the final analyses.

If this occurs, 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, Table 2, Table 3, and Table 4), 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 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 6.5.7. 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 from study drug during the 12-month double-blind period, defined as the time the first dose of study drug is administered on Day 1 through completion of the Month 12 Efficacy Visit (primary endpoint assessment), will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including a Modified Month 12 Efficacy Visit (Table 1). They will also be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug (Table 4); see Section 3.3.1.

In situations where the Modified Month 12 Efficacy Visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate

timing of these efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended up to Day 417 (as is permitted for the regular Month 12 visit).

Patients who discontinue patisiran during the open-label extension period will be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, per the Schedule of Assessments (Table 4), 28 days after the last dose of patisiran; see Section 3.3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop the patient's participation in the study-at any time. A patient or legal guardian 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, through the Modified Month 12 Efficacy Visit, and the 28-day follow-up visit, or alternatively may complete any minimal assessments for which the patient or legal guardian consents as described in Section 4.3.1. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 12 visit, every effort should be made to conduct the assessments scheduled to be performed at the Modified Efficacy Visit (Table 1).

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, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and 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.

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 6.5.7.

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 or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian 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 or legal guardian (where possible, 3 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 or legal guardian 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 can search publicly available records (where permitted and allowed by local law) to ascertain survival status. 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 preparation, administration, and storage of study drug (patisiran and placebo) is provided in the Pharmacy Manual.

All patients will be instructed to take the recommended daily allowance of vitamin A while on the study.

5.2.1. Premedication

All patients will receive premedication prior to study drug administration to reduce the risk of IRRs. Each of the following medicinal products should be given on the day of study drug infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent; IV or oral nonsedating H1 blockers are acceptable.)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

Oral premedication equivalents are permitted, but must be administered in the presence of a healthcare professional.

Modifications to lower the corticosteroid dose may be made to the premedication regimen for either of the following 2 reasons:

1. Double-blind and open-label periods: If a patient is having difficulty tolerating the steroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the steroid premedication may be allowed for that patient after consultation with the medical monitor at any time during the study.
2. Double-blind period: For patients who are tolerating their double-blind study drug infusions well with their current corticosteroid premedication regimen (ie, no IRRs during the past 3 or more infusions), corticosteroid dose may be reduced in 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (IV) or equivalent.
    a. Open-label period: At the start of the open-label period, patients must take dexamethasone 10 mg or the equivalent as their corticosteroid premedication. Patients taking more than 10 mg of dexamethasone at the end of the double-blind period should take the higher dose. The corticosteroid dose may then be tapered as described above if the patient is tolerating infusions. However, if a patient's steroid premedication had been decreased in the double-blind period due to their inability to tolerate the premedication regimen as described above, continuation of the reduced dose regimen (as it had been in the double-blind period) may be permitted after consultation with the Medical Monitor.

Infusions during corticosteroid tapering may be performed at the study center or at a location other than the study center (eg, at home), as described in detail in the Pharmacy Manual, at the discretion of the Investigator and after consultation with the Medical Monitor.

Additional or higher doses of 1 or more of the premedications may be administered to reduce the risk of IRRs, if needed. For suggested guidelines for management of IRRs, see Section 5.2.4; further details can be found in the Pharmacy Manual.

5.2.2. Study Drug Description

Patisiran is a RNAi therapeutic consisting of a double-stranded siRNA targeting TTR mRNA formulated in an LNP. The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline. Patisiran Solution for IV infusion contains 2 mg/mL of patisiran.

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

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

5.2.3. Dose and Administration

Detailed instructions for study drug preparation and administration are found in the Pharmacy Manual.

5.2.3.1. Double-blind Study Drug (Patisiran or Placebo)

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days.

The amount (in mg) of double-blind patisiran to be administered should be determined based on the patient's weight (kg). Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended dose is 30 mg.

Weight from the previous visit may be used for calculating dose. Weight must be collected prior to dosing with study drug. Study drug will be administered as an approximately 80-minute IV infusion (approximately 1 mL/minute for the first 15-minutes followed by approximately 3 mL/minute for the remainder of the infusion). The patient’s infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient will be observed for 1 hour following completion of dosing for observation and completion of assessments.

Patients who have received ≥2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.

Missed doses of double-blind study drug

If a patient does not receive a dose of study drug within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit (ie, +4 days after the +3-day dosing window per the Schedule of Assessments [Table 1]), after consultation with the Medical

Monitor. If a dose is administered with a delay, the next dose will resume following the original schedule per the Schedule of Assessments.

A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses 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 in the study.

5.2.3.2. Open-label Extension Period (Patisiran)

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described in Section 5.2.3.1 for double-blind patisiran. As noted in Section 3.6, blinding will be maintained until the last patient completes their Month 12 visit.

During the open-label extension period, patients who have received at least 2 doses of open-label patisiran at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have patisiran administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Patisiran administration will be performed by a healthcare professional trained on the protocol and administration of premedications and patisiran infusion.

All patients will receive premedications prior to open-label patisiran administration to reduce the risk of IRRs (Section 5.2.1).

Missed doses of open-label patisiran

If a patient does not receive a dose of open-label patisiran within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit (ie, +4 days after the +3-day dosing window per the Schedule of Assessments [Table 2, Table 3, and Table 4]), after consultation with the Medical Monitor. If a dose is administered with a delay, the next dose will resume following the original schedule per the Schedule of Assessments.

5.2.4. Suggested Guidelines for Management of Infusion-related Reactions

Criteria for categorizing IRRs are provided in Section 10.3.

- In the event of an IRR, the infusion of study drug may be slowed or stopped and the patient closely monitored until resolution of the reaction. Drugs that may be used to facilitate resolution and permit resumption of study drug administration include but are not limited to: paracetamol/acetaminophen (or equivalent), additional histamine H1/H2 receptor antagonists (eg, ranitidine), nonsteroidal anti-inflammatory drugs (NSAIDs), adrenaline, supplemental oxygen, IV fluids, and/or corticosteroids.
- Following resolution of a mild or moderate IRR that required interruption of the study drug infusion, resumption of administration may occur at the Investigator's discretion at a slower infusion rate for that dose and for subsequent doses of study drug. If the infusion is delayed, the administration of the infusion should be completed no more than 16 hours after study drug is first diluted in saline (including infusion time).

- Study drug administration will not be resumed for any patient following a severe IRR until the case is discussed with the Medical Monitor.
- If after consultation with the Medical Monitor it is agreed that an individual patient's steroid premedication will be increased, then the following steps are **recommended**:
    1. If the IRR occurred while the patient received 10 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and did not resolve with slowing of the infusion rate, then the patient should be increased by multiples of 5 mg IV dexamethasone or equivalent at least 60 minutes before the infusion.
    2. Increased dose of premedication steroids should NOT exceed the combination of 20 mg IV dexamethasone or equivalent on the day of infusion.
    3. If the IRR occurred while the patient received less than 10 mg IV dexamethasone or equivalent, then the patient should return to the prior dose of IV dexamethasone or equivalent that did not result in an IRR.

Patients will be instructed to call the Investigator if they experience symptoms such as fever, chills, myalgia, or nausea/vomiting after discharge from the site.

5.2.5. 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.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of study drug (patisiran and placebo) doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately (5 ±3°C) until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

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 will be provided in the Pharmacy Manual.

5.2.7. 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. Additional details will be available in the Pharmacy Manual.

5.2.8. 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, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.3. Concomitant Medications and Procedures

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

Use of the following medications/treatments are prohibited during study participation:

- Any investigational agent other than study drug.
- Inotersen, doxycycline, ursodeoxycholic acid, tauroursodeoxycholic acid, and diflunisal are also prohibited during the study (see exclusion Criterion 10 in Section 4.2). Doxycycline is permitted if being taken for short-term treatment of infection.

All patients will be asked to take the recommended daily allowance of vitamin A for the duration of their participation in the study while being administered study drug. In countries where relevant, the clinical sites will provide patients with a prescription for vitamin A at a dose consistent with local guidelines.

Standard vitamins and topical medications are permitted. Any concomitant medication or treatment that is required for the patient's welfare may be given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the CRF, as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Concomitant medications include 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 CRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Concomitant Tafamidis Use

Per inclusion Criterion 4, at baseline patients are either: 1) tafamidis naïve or 2) currently on tafamidis for ≥6 months with demonstrated disease progression, as determined by the Investigator. Patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.

For patients on tafamidis at baseline, the reasons for considering the patient to have demonstrated disease progression will be recorded in the eCRF. Patients who are on tafamidis at

baseline are encouraged, if it is medically appropriate in the opinion of the Investigator, to remain on tafamidis for the duration of the double-blind period.

Per exclusion Criterion 8, patients who are tafamidis naïve at baseline, for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period (taking into consideration clinical status, patient preference, and/or commercial availability of tafamidis), should not be enrolled in the trial.

However, if tafamidis is granted approval by a Health Agency for treatment in patients with ATTR amyloidosis with cardiomyopathy in a given region, all enrolled patients in this region will be made aware of its potential benefits and risks at the time of regulatory approval and all patients will be reconsented. In such circumstances, tafamidis is not considered prohibited and the Investigator may, using their medical judgement, commence concomitant on-label tafamidis during the study, if it is felt to be in the best interest of the patient and if it is commercially available in the country.

Patients who are tafamidis naïve at baseline, but begin taking commercial tafamidis (ie, "tafamidis drop-in"), will remain in the study. 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). In all cases, the Pre tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of study drug (ie, 7 to 14 days post study drug dose). Thereafter, the patient will continue with all assessments per the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). In addition, at the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

Initiation of TTR stabilizer therapies other than tafamidis (eg, diflunisal) is not allowed during the double-blind period of this study.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

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 12 weeks after the last dose of study drug in this study.

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.
- 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 12 weeks after the last dose of study drug.

Investigators should advise females of childbearing 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 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 6.5.5.2).

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 (double-blind period) and Table 2, Table 3, and Table 4 (open-label extension period). Additional information on the collection of study assessments will be detailed in the respective reference manuals.

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient or legal guardian before the Screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF. In addition, a medical records release form will be required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries.

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

To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, the Investigator will notify the Sponsor

before screening patients to allow an assessment of the ability of the study center or any new trial participant to comply with the protocol given COVID-19 limitations.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening (once) 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, including completion of ophthalmologic history in the eCRF. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

If a genetic test result that shows the presence or absence of a TTR pathogenic mutation, which would be consistent with either wtATTR or hATTR, is not available at Screening for the assessment of eligibility (Section 4.1, inclusion Criterion 2a), genotyping may be conducted at a central laboratory. Alternatively, a local laboratory may be selected by the study center in consultation with the Medical Monitor.

The study eligibility biopsies and technetium scintigraphy noted in inclusion Criterion 2 are intended to be historical, as part of the patient's clinical care and diagnosis, and are not performed as part of the study.

If a diagnostic result that confirms ATTR amyloidosis is not available at Screening for the assessment of eligibility (inclusion Criterion 2c/d), testing may be conducted at a laboratory or diagnostic center selected by the study center, in consultation with the Medical Monitor, in countries in which this test is not standard of care.

An echocardiogram will be performed at screening Visit 1 and results confirmed centrally to assess study eligibility, as indicated in the Schedule of Assessments (Table 1).

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. Any additional repeat testing may be considered 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, or who fails to complete screening activities due to unforeseen or unavoidable circumstances, may be rescreened once after consultation with the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment. A patient will be re-consented if rescreening occurs outside of the 45-day screening window. In this case, all screening procedures must be repeated.

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

As noted in Table 1, in situations where a Month 6 (Day 176-183), Month 9 (Day 260-267), and/or Month 12 (Day 365-372) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.

For the open-label extension period, as noted in Table 2, in situations where a Month 18 (Day 554-561), Month 21 (Day 638-645), and/or Month 24 (Day 743-750) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 18, 21, and/or 24 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 18 up to Day 592; Month 21 up to Day 697; Month 24, up to Day 791.

Similarly, for Years 3 and 4, in situations where a study visit at which efficacy assessments were to be performed is unable to be completed at the study center, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the efficacy assessments for those visits. After consultation with the Medical Monitor, efficacy assessments may be extended, as described in Table 3 and Table 4.

6.2.1. 6-Minute Walk Test (6-MWT)

The 6-MWT, which will be assessed as the primary endpoint, is an assessment of functional exercise capacity. The 6-MWT will be administered by staff trained in the procedure per the relevant study manual. The staff administering the 6-MWT will be different from the Investigator or designee managing the care of the patient.

The 6-MWT will be performed at each of the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). At screening Visit 1, the 6-MWT will be administered for study eligibility purposes (per inclusion Criterion 6 [Section 4.1]). At screening Visit 1, prior to conducting the 6-MWT, 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.

On Day 1 (baseline), which is a dosing day, the 6-MWT will be performed prior to study drug administration. (No other dosing days have a 6-MWT assessment.)

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 within the permitted visit window.

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.

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

A 1.5-month window will be used to group 6-MWT assessments to the Month 6 (Weeks 25-26), Month 9 (Weeks 37-38), and Month 12 (Weeks 52-53) visits. During the double-blind period, a patient may opt to begin tafamidis treatment or to discontinue study treatment, in which case they would complete a Pre-tafamidis Drop-in Visit (Table 1) or Early Treatment Discontinuation Visit (Table 4), respectively. To avoid the potential training effect from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be collected for the following time periods: Day 2 to Day 214 (for Month 6), Day 215 to Day 319 (for Month 9), and Day 320 to Day 417 (for Month 12).

Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit); no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed per the Schedule of Assessments (Table 1).

6.2.2. 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-OS will be assessed for the first secondary endpoint.

The KCCQ questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4).

6.2.3. Deaths, Hospitalizations, and Urgent Heart Failure Visits

All deaths and hospitalizations will be recorded at Day 1 post dose and throughout the study as specified as part of AEs monitoring (see Section 6.5.7) and per the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). All urgent HF visits will also be recorded in the eCRF.

Reasons for deaths and non-elective hospitalizations will be adjudicated by an independent Adjudication Committee (Section 3.8). Urgent HF visits will also be adjudicated.

6.2.4. Modified Body Mass Index (mBMI)

The nutritional status of patients is evaluated using the mBMI, calculated as the product of body mass index (BMI) (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

Weight, height, and serum albumin (collected as part of the serum chemistry panel) will be collected pre-dose at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). The site will not perform the calculation for mBMI.

6.2.5. Cardiac Assessments

Manifestations of cardiac amyloid involvement will be assessed via cardiac biomarker, NYHA class, echocardiograms, CMR, and technetium scintigraphy imaging, as described.

Qualified personnel will be required to administer cardiac imaging assessments as specified in the respective reference manuals.

6.2.5.1. Cardiac Biomarkers

The cardiac biomarkers NT-proBNP and troponin I will be used to assess cardiac stress and heart failure severity. These biomarkers have been shown to be prognostic of outcomes in HF, including in ATTR amyloidosis.[Damy 2016; Kristen 2017; Merlini 2016] Blood samples will be drawn to measure cardiac biomarker levels at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and will be measured at a central laboratory. At screening Visit 1, only NT-proBNP will be assessed for eligibility purposes.

Details on cardiac biomarker sample collection, processing, and storage will be provided in a Study Laboratory Manual.

6.2.5.2. ATTR Amyloidosis Disease Stage

Based on published data from Gillmore et al, the ATTR amyloidosis disease staging used for this protocol stratifies patients with ATTR amyloidosis with cardiomyopathy (both hATTR and wtATTR) into prognostic categories using the serum biomarkers NT-proBNP and eGFR.[Gillmore 2018] Patients are categorized as follows:

- Stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min/1.73 m^2
- Stage 2 (intermediate risk): all other patients not meeting criteria for Stages 1 or 3
- Stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 ml/min/1.73 m^2

Based on published data, this staging system discriminates between patients with median survival of ~6 years, ~4 years, and ~2 years for Stage 1, Stage 2, and Stage 3, respectively.

6.2.5.3. 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 Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). The score collected at screening will be used to determine eligibility.

6.2.5.4. Echocardiogram

Echocardiographic parameters will be used for assessment of cardiac structure and function. Echocardiograms will be performed at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4), and analyzed at a central cardiac imaging core lab.

Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

6.2.5.5. Technetium Scintigraphy Imaging

At select sites, in a subset of approximately 100 patients, technetium scintigraphy will be collected according to the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4), as an optional exploratory imaging assessment, to assess cardiac amyloid involvement. Based on local practice standards, either ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc], or ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) can be used as the tracer. Technetium scintigraphy images will be interpreted at a central imaging core laboratory. Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

For patients in whom technetium scintigraphy is performed as a study efficacy parameter, the results of the baseline scan must be reviewed by the central reader and confirmed to be consistent with the diagnosis of ATTR amyloidosis prior to randomization.

At select sites where technetium scintigraphy is being performed as an exploratory efficacy assessment, patients may be exempt from the baseline scan if technetium scintigraphy has been performed prior to study entry as part of the patient's clinical care within 6 months prior to the baseline assessment. In such cases, the historical technetium scintigraphy examination performed prior to study entry as part of the patient's clinical care should be collected and transferred to the central imaging core laboratory for interpretation; if the historical scan cannot be transferred to the central reader, or is deemed by the central reader to be of inadequate quality for interpretation, the patient should not participate in this optional efficacy assessment.

6.2.5.6. Cardiac Magnetic Resonance (CMR)

At select sites, in a subset of patients (≤60 patients), CMR will be collected according to the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4), as an optional exploratory imaging assessment to assess cardiac amyloid involvement. CMR imaging with late gadolinium enhancement will only be performed on patients without contraindications (ie, pacemakers, severe renal failure with eGFR <30 mL/min/1.73 m^2, defibrillators, or allergy to gadolinium).

Details for image acquisition and upload for central review can be found in the relevant study manual.

6.2.6. Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN)

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that assesses 5 domains: physical function, large-fiber neuropathy, activities of daily living, symptoms, small-fiber neuropathy, and autonomic neuropathy. The total score ranges from -4 (best possible quality of life) to 136 points (worst possible quality of life).[Vinik 2005; Vinik 2014]

The Norfolk QoL-DN questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4).

6.2.7. Polyneuropathy Disability (PND)

Physician assessment of ambulation via PND score [Coutinho 1980; Yamamoto 2007] will be evaluated only at screening to assess eligibility for the study as specified in the Schedule of Assessments (Table 1). PND scoring is described in Section 10.1.

6.3. Pharmacodynamic Assessments

In this study, serum samples for measurement of TTR levels will be collected for the assessment of PD effects. TTR levels will be determined by a validated enzyme-linked immunoassay (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 Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, blood samples for assessment of TTR protein may be collected by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of plasma concentrations of ALN-18328 (siRNA component of patisiran) and 2 lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) during the double-blind period at the timepoints specified in the Schedule of Assessments (Table 1). To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, these blood samples may be collected at the study center, or by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.

Plasma PK samples will be collected: predose (within 1 hour of planned study drug dosing); at the end of the infusion (+5 minutes); and 30 minutes after the end of the infusion (+15 minutes) at the specified visits.

For patients who discontinue treatment early during the double-blind period, a single PK sample will be taken at any time during the Early Treatment Discontinuation Visit, per the Schedule of Assessment (Table 4).

Actual dates and times of sample collection will be recorded.

Plasma concentrations of the 3 analytes will be determined using validated assay methods. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

PK parameters will be analyzed, whenever possible, as outlined in Section 7.2.7.

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 in addition an independent DMC as described in Section 3.7.

In situations where a study visit is not completed at the study center, offsite (eg, at home) assessments may be completed within the study visit window as follows:

- Routine assessments (ie, vital signs and weight, blood collection, pregnancy testing, physical examinations, and ECGs) may be performed at a location other than the study center (eg, at home) by a trained healthcare professional at all timepoints, where applicable country and local regulations and infrastructure allow. The Investigator or qualified designee will review all ECGs, including those collected by a healthcare professional outside of the study center.
- Collection of relevant safety information: The study physician (or delegate) must, at a minimum, verbally contact the patient within the expected study visit window to assess relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, vital status). This information may also be collected by a home healthcare professional as part of an offsite study visit.
- Blood samples for assessment of ADA may be collected by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and include blood pressure, heart rate, 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 10 minutes. Blood pressure should be taken using the same arm. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary 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 sign assessments, as medically 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 Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and will be recorded in the eCRF.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4); 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.

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.

6.5.4. Electrocardiogram

12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval will be obtained, as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Patients should be supine for at least 5 minutes before each ECG is obtained. The 12-lead ECGs will be performed in triplicate at baseline, with readings approximately 1 minute apart. At all other time points, a single 12-lead ECG will be performed.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn, when possible.

The Investigator or qualified designee will review all ECGs, including those collected by a healthcare professional outside of the study center, to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator. Recordings will be archived in the patient's files.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. 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 laboratory tests and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 5 and will be assessed as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 5, which are performed at the clinic 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.

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 5: 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 and eGFR (using the MDRD formula)	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Coagulation (at Screening)	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.5.5.1)	
Antidrug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.5.2)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; MDRD=modification of diet in renal disease; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid.

6.5.5.1. Immunogenicity

Serum samples will be collected to evaluate the presence of antidrug antibodies (ADA) as outlined in the Schedule of Assessments (Table 1). Details regarding the blood volume, processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

A validated ELISA will be used that specifically detects antibodies to PEG_{2000}-C-DMG, which is a component of patisiran-LNP. Serum samples will first be analyzed with a screening assay. Samples testing positive for ADA in the screening assay will be further evaluated in a confirmatory assay. For the samples that tested positive for ADA in the confirmatory assay, the

ADA titer will then be determined as the reciprocal of the highest dilution of the sample that yielded a positive ADA test result.

6.5.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4).

A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter at the timepoints specified in the Schedule of Assessments. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. 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 6.5.7.7 for follow-up instructions).

In situations where a pregnancy test was missed as per the Schedule of Assessments because of the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center, a pregnancy test must be performed prior to receiving the next dose of study drug.

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

6.5.6. Vital Status Check

A vital status check will be performed at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4).

Due to the inclusion of all-cause mortality in the secondary endpoint analysis, a medical records release form will be required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries. The signing of this medical records release form is in addition to the ICF. 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.

6.5.7. Adverse Events

6.5.7.1. 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 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

An 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

No AEs of clinical interest are defined for this study.

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 AE.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. AEs 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.

6.5.7.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, 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.

All IRRs will be recorded as AEs. All information on IRRs is to be recorded on the applicable eCRF per the CRF completion guidelines.

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 to determine if an ophthalmological assessment is needed. 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.

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

Not applicable. There were no AEs of Clinical Interest identified for this study.

6.5.7.4. 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 6.5.7.1 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 Reference 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.

6.5.7.5. 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 Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.7.6. 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.

6.5.7.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 12 weeks following the last dose of study drug, 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 12 weeks after the last dose of study drug.

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 6.5.7.4.

6.5.7.8. Overdose Reporting

An overdose is defined as any dose 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. In the event of an overdose, the actual dose administered must be recorded as specified in the Pharmacy Manual.

All reports of overdose (with or without an AE) must be reported within 24 hours following the instructions outlined in the Pharmacy Manual for reporting an overdose.

6.5.8. 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.

6.6. Biomarkers and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of patisiran.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Potential exploratory investigations may include RNA or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

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

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

The planned enrollment for this study is 300 patients. For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a mean difference between treatment groups at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment (Section 7.2.10).

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 12-month, double-blind period. More complete plans, including planned analyses for the open-label extension period, will be detailed in the SAP. 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 data summaries to help understand any impact of COVID-19 on efficacy and safety assessments 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 randomized patients who received any amount of study drug, grouped according to the randomized treatment arm.
- Safety Analysis Set: All patients who received any amount of study drug, grouped according to the treatment actually received.

- PK Analysis Set: All patients who received at least 1 complete dose of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- PD Analysis Set: All patients who received at least 1 complete dose 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.

Note that a complete dose of study drug is defined as ≥80% (≥160 mL) of the planned infusion volume (200 mL).

Efficacy endpoints will be analyzed using the Full Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology 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 and overall for the FAS and Safety Analysis Set.

7.2.5. Efficacy Analyses

The overall Type I error rate will be strongly controlled at a 2-sided 0.05 significance level for the primary and secondary endpoints using a fixed sequential testing procedure at the final analysis. The primary endpoint will be compared between treatment arms at the 0.05 significance level. If the test of the primary endpoint is statistically significant, then the secondary endpoints will each be tested in the order specified in the Secondary Endpoints section (see Section 2). If a test of the primary or a secondary endpoint is not statistically significant, the testing of the remaining endpoints in the sequence will stop.

For patients who were tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

7.2.5.1. Primary Endpoint

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), age (<75 vs ≥75 years), the treatment-by-visit interaction, the treatment-by-baseline tafamidis interaction, the visit-by-baseline tafamidis interaction, and the treatment-by-visit-by-baseline tafamidis

interaction as fixed factors. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

Sensitivity analyses will be detailed in the SAP.

7.2.5.2. Secondary Endpoints

Secondary endpoints are described in Section 2.

KCCQ-OS will be analyzed using a similar MMRM model as used for the primary endpoint.

The composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT will be analyzed using a generalized rank-based win ratio method, which makes pairwise comparisons (for all possible patisiran/placebo patient pairs) of the 3 components in the hierarchical order specified above. The point estimate for the win ratio is defined as the total number of better outcomes divided by the total number of worse outcomes in the patisiran group. The detailed algorithm for assessment of this endpoint will be provided in the SAP.

The composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits will be analyzed using a modified Andersen-Gill model stratified by baseline tafamidis (yes vs no), including treatment, genotype (hATTR vs wtATTR), NYHA Class (I/II vs III), and age (<75 vs ≥75 years) as covariates.

Patients who undergo a heart transplantation and/or ventricular assist device placement after randomization will be handled in the same manner as death in the primary analyses of mortality related endpoints.

Deaths and hospitalizations due to COVID-19 will be excluded from the primary analyses of endpoints involving all-cause death and/or all-cause hospitalizations. Analyses of the individual components of the composite endpoints will be detailed in the SAP.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

7.2.5.3. Exploratory Endpoints

Descriptive summaries will be provided for the exploratory endpoints (Section 2), and additional analyses may be conducted. Details will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

The PD endpoint is serum TTR. Summary tables will be provided for observed values, change and percentage change from baseline for each scheduled time point. In addition, the maximum and mean percentage reduction over 12 months will be summarized.

7.2.7. Pharmacokinetic Analysis

7.2.7.1. Pharmacokinetic Analysis

Plasma concentrations of ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG will be obtained using a model-independent method. PK exposure parameters will include: maximum plasma concentration at the end of infusion (C_{max}), 30-minute post-infusion concentration ($C_{p(30min)}$), and

pre-infusion concentration (C_{min}). In addition, the steady-state C_{max} ($C_{max,ss}$), steady-state $C_{p(30min)}$ ($C_{p,ss(30min)}$), and steady-state C_{min} ($C_{min,ss}$) will be calculated as the average of the respective values at Week 24, Week 36, and Month 12.

The PK exposure parameters will be summarized by visit, and the steady-state PK parameters will be summarized.

7.2.7.2. Exposure-Response Analysis

Mean and maximum percent TTR reduction from baseline will be summarized by quartiles of the steady state PK parameters for all 3 analytes. Change from baseline at Month 12 in clinical efficacy parameters may also be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

PK exposure will be summarized by mortality status. In addition, the incidence of AEs and SAEs will be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

7.2.7.3. Population PK, PK/PD, and Disease Progression Modelling Analysis

Population PK, PK/PD, and disease progression modelling analyses may be performed, if appropriate. If performed, the analyses would be conducted according to a pre-specified analysis plan and reported separately.

7.2.8. Safety Analyses

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 examinations. The 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 and Preferred Term. The frequency and percentage of patients experiencing AEs, SAEs, related AEs, and AEs leading to discontinuation will be summarized by System Organ Class (SOC) and PT. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics will be provided for clinical laboratory data, ECG, and vital signs data, summarizing the observed values and change from baseline over time. Laboratory shift tables from baseline at the worst post-baseline values will be presented. 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. Sample Size Re-assessment

Patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period, which could result in a loss of statistical power. An interim assessment may be performed to assess the impact of tafamidis drop-in on the power and the potential need to increase the sample size. The interim assessment, if conducted, would examine the overall tafamidis drop-in rate in a blinded manner (ie, a non-comparative assessment of the drop-in rate); therefore, no impact on the type I error is expected and no multiplicity adjustment will be made. A detailed sample size re-estimation plan will be outlined in a separate document prior to implementation.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the informed consent form (see Section 4.3.2).

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 required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries. 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 6.5.7. 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 serious 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. CRFs 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).

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10. APPENDICES

10.1. Polyneuropathy Disability (PND) Scores

Stage	Description
0	No symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capacity but ability to walk without a stick or crutches
IIIA **IIIB**	Walking with the help of one stick or crutch Walking with the help of two sticks or crutches
IV	Confined to a wheelchair or bedridden

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.

10.3. Categorization of Infusion-Related Reactions

Signs and symptoms of an IRR usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritus/itching,

rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, urticaria (hives, welts, wheals), vomiting.

Categorization of IRRs is as follows:

Categorization	**Description**
Mild	Mild reaction: infusion may be continued; if intervention is indicated it is minimal and additional treatment (other than paracetamol for delayed reactions) is not required.
Moderate	Moderate reaction: requires treatment including more intensive therapy (eg, IV fluids, NSAIDs) in addition to infusion interruption but responds promptly to medication. Treatment is indicated for ≤24 hours.
Severe	More than moderate reaction: not rapidly responsive to medication or to interruption of infusion; and/ or prolonged (treatment is indicated for >24 hours); recurrence of severe symptoms following initial improvement.

ALN-TTR02-011 PROTOCOL AMENDMENT 3
SUMMARY OF CHANGES DATED 30 JUNE 2021

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

1. RATIONALE FOR PROTOCOL AMENDMENT

The primary purpose for this protocol amendment is to extend the open-label extension period from 12 months to 36 months, for a total treatment period during the study of up to 48 months, to collect longer-term safety and efficacy data. Key protocol modifications relating to this change include the following (as detailed in Section 2):

- Addition of Schedule of Assessments for Years 3 and 4.

In addition, other protocol modifications or clarifications include:

- Update to the mixed-effects model repeated measures (MMRM) model specification to allow for potentially different treatment effects between the baseline tafamidis use (yes/no) subgroups.
- Total number of study centers at which the study is being conducted was updated to 85 centers (from 65).
- Update to allow unblinded personnel to administer study drug, while monitoring of the patient during and after the infusion will be performed by blinded personnel.
- Clarification that study personnel involved in a patient's medical care will not obtain local laboratory results that could potentially unblind them to the patient's treatment until after the study has been unblinded.
- Clarification to note that the assessment of reasons for hospitalizations by the Adjudication Committee will be for non-elective hospitalizations.
- Clarification in the definitions of the PK analysis set and PD analysis set to include all patients who received at least 1 complete dose of study drug.
- Clarification of the dosing window for missed doses of study drug.
- Clarification regarding allowable premedication equivalents to intravenous histamine 1 receptor blockers.
- Clarification that cardiac magnetic resonance (CMR) or technetium scans should not be performed within 5 months of another scan.

Minor changes such as corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

2. PROTOCOL AMENDMENT 3 DETAILED SUMMARY OF CHANGES

The primary sections 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: Extended the open-label extension period from 12 months to 36 months, for a total treatment period during the study of up to 48 months, to collect longer term safety and efficacy data. Schedule of Assessments for Years 3 and 4 were added.

The primary change occurs in Table 2, Table 3, and Table 4, Schedules of Assessments

Revised text:

- Added Table 3, Year 3 Schedule of Assessments: Open-label Extension Period (Through Month 36)
- Added Table 4, Year 4 Schedule of Assessments: Open-label Extension Period (Through Month 48), Early Treatment Discontinuation Visit, and Follow-up
- Moved the Early Treatment Discontinuation Visit, End of Study Visit, and Follow-up from Table 2 to Table 4
- Added the following text to Section 3.3.1: **Patients who have transitioned to commercial patisiran (see Section 3.1 and Table 4) should have completed the end of study visit and are therefore considered to have reached the end of the study.**

Sections also reflecting this change:

- Synopsis
- Figure 1, Study Design
- Section 3.1, Summary of Study Design
- Section 6.2, Duration of Treatment
- Section 3.3, Duration of Study Participation
- Section 6.2, Efficacy Assessments

Purpose: Updated the mixed-effects model repeated measures (MMRM) model specification to allow for potentially different treatment effects between the baseline tafamidis use (yes/no) subgroups.

The primary change occurs in Section 7.2.5.1, Primary Endpoint

Revised text:

The model will include the baseline value as a covariate, treatment, visit, ~~the treatment-by-visit interaction,~~ baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), ~~and~~ age (<75 vs ≥75 years)**, the treatment-by-visit interaction, the treatment-by-baseline tafamidis interaction, the visit-by-baseline tafamidis interaction, and the treatment-by-visit-by-baseline tafamidis interaction** as fixed factors~~, and patient as a random effect~~.

Section also reflecting this change:

- Synopsis

Purpose: Total number of study centers at which the study is being conducted was updated to 85 centers (from 65).

The primary change occurs in the Synopsis

Revised text:

The study will be conducted at approximately ~~65~~ **85** clinical study centers worldwide.

Purpose: Allow unblinded personnel to administer study drug, while monitoring of the patient during and after the infusion will be performed by blinded personnel. Clarification that study personnel involved in a patient's medical care will not obtain local laboratory results that could potentially unblind them to the patient's treatment until after the study has been unblinded.

The primary change occurs in Section 3.6, Blinding

Revised text:

After the pharmacist (or designated pharmacy/healthcare personnel) has prepared the infusion, separate blinded personnel will ~~administer study drug and~~ monitor the patient during and after the infusion. All patients will be blinded to treatment and will receive an IV infusion once every 3 weeks using identical volumes for patisiran and placebo.

…

Study personnel involved in a patient's medical care will also refrain from obtaining local laboratory results that could potentially unblind them to the patient's treatment until after the study has been unblinded. Such laboratory results would include TTR (ie, prealbumin), vitamin A, and RBP measurements.

Purpose: Clarification to note that the assessment of reasons for hospitalizations by the Adjudication Committee will be for non-elective hospitalizations.

The primary change occurs in Section 3.8, Adjudication Committee and Section 6.2.3, Death, Hospitalizations, and Urgent Heart Failure Visits

Revised text:

An independent Adjudication Committee will review deaths and **non-elective** hospitalizations and will attribute a cause (CV versus non-CV) according to the responsible underlying disease process rather than the immediate mechanism.

…

Reasons for deaths and **non-elective** hospitalizations will be adjudicated by an independent Adjudication Committee (Section 3.8).

Purpose: Clarification in the definitions of the PK analysis set and PD analysis set to include all patients who received at least 1 complete dose of study drug.

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

Revised text:

- PK Analysis Set: All patients who received ~~any amount~~ **at least 1 complete dose** of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- PD Analysis Set: All patients who received ~~any amount~~ **at least 1 complete dose** 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.

Note that a complete dose of study drug is defined as ≥80% (≥160 mL) of the planned infusion volume (200 mL).

Purpose: Clarification of the dosing window for missed doses of study drug.

The primary change occurs in Section 5.2.3.1, Double-blind Study Drug (Patisiran or Placebo) and Section 5.2.3.2, Open-label Extension Period (Patisiran)

Revised text:

If a patient does not receive a dose of study drug within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit **(ie, +4 days after the +3-day dosing window per the Schedule of Assessments [Table 1]),** after consultation with the Medical Monitor.

…

If a patient does not receive a dose of open-label patisiran within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit **(ie, +4 days after the +3-day dosing window per the Schedule of Assessments [Table 2, Table 3, and Table 4,]),** after consultation with the Medical Monitor.

Purpose: Clarification regarding allowable premedication equivalents to intravenous histamine 1 receptor blockers.

The primary change occurs in Section 5.2.1, Premedication

Revised text:

- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent~~)~~**; IV or oral nonsedating H1 blockers are acceptable.)**

Purpose: Clarification that cardiac magnetic resonance (CMR) or technetium scans should not be performed within 5 months of another scan.

The primary change occurs in Footnote to Table 2, Year 2 Schedule of Assessments

Added text:

[b] Consecutive CMR scans should not be performed within 5 months of each other. Consecutive technetium scans should not be performed within 5 months of each other.

CLINICAL STUDY PROTOCOL
ALN-TTR02-011
DATED 22 MAY 2020

Protocol Title:	APOLLO-B: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Short Title:	APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Study Drug:	Patisiran (ALN-TTR02)
EudraCT Number:	2019-001458-24
IND Number:	141240
Protocol Date:	Original protocol, 18 April 2019 Amendment 1: 20 December 2019 Amendment 2: 22 May 2020
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

[redacted]

28 MAY 2020

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTR02-011 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

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

Short Title

APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Study Drug

Patisiran (ALN-TTR02)

Phase

Phase 3

Study Center(s)

The study will be conducted at approximately 65 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality, hospitalizations, and urgent heart failure (HF) visits	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV) events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month double-blind period

Objectives	Endpoints
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV events • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV events (CV hospitalizations and urgent HF visits) over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI) o Cardiac magnetic resonance (CMR) parameters o Technetium scintigraphy parameters o Troponin I levels o Norfolk QoL-DN
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (AEs)

Study Design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study

population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the Investigator. This group will be capped at 30% of total enrollment in the study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 12-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period.

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive intravenous (IV) treatment every 3 weeks with either patisiran or placebo. Prior to receiving randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an infusion related reaction (IRR) with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. Study drug will be administered as an approximately 80-minute IV infusion.

During the 12-month open-label extension period, all patients will receive treatment with open-label patisiran.

Study drug administration at a location other than the study center (eg, at home) may be administered as follows:

- Double-blind period: Patients who have received ≥2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.
- 12-month open-label extension period: Patients who have received ≥2 doses of open-label patisiran at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have patisiran administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Patisiran administration will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion, with oversight of the Investigator.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint; this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period. The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score. In situations where an efficacy study visit at Months 6, 9, and/or 12 is unable to be completed at the study center due to the Coronavirus disease 2019 (COVID-19) pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the

Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended for that visit as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.

Safety will be assessed throughout the double-blind and open-label extension periods of the study.

Number of Planned Patients

Approximately 300 patients are planned for enrollment in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults age 18 (or age of legal consent, whichever is older) to 85 years of age, inclusive, with ATTR amyloidosis with cardiomyopathy (hereditary or wild-type [wt]) who, at baseline, are either: 1) tafamidis naïve (on tafamidis for ≤30 days and none within 6 months prior to baseline); or 2) currently on tafamidis (for ≥6 months) with disease progression in the opinion of the Investigator.

Study Drug, Dose, and Mode of Administration

Patisiran is a ribonucleic acid (RNA) interference (RNAi) therapeutic consisting of a double-stranded small interfering RNA (siRNA) targeting TTR mRNA formulated in a lipid nanoparticle (LNP). The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG2000-C-DMG) in isotonic phosphate buffered saline.

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs.

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days. Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended patisiran dose is 30 mg.

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described above for double-blind patisiran.

Reference Treatment, Dose, and Mode of Administration

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

Duration of Treatment and Study Participation

The treatment duration in this study is up to 24 months, inclusive of a 12-month, double-blind, treatment period, and a 12-month, open-label, treatment period. The estimated total time on

study for each patient is up to 26.5 months, including up to 45 days of screening, up to 24 months of treatment, and a 28-day safety follow-up period.

Statistical Methods

The planned enrollment for this study is 300 patients. Randomization (1:1) will be stratified by: 1) baseline tafamidis (yes vs no); 2) genotype (hATTR vs wtATTR); and 3) NYHA Class I or II and age < 75 years vs all other.

For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a treatment difference at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment.

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, the treatment-by-visit interaction, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), and age (<75 vs ≥75 years) as fixed factors, and patient as a random effect. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

For patients who are tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

Safety data will be summarized descriptively.

Figure 1: Study Design

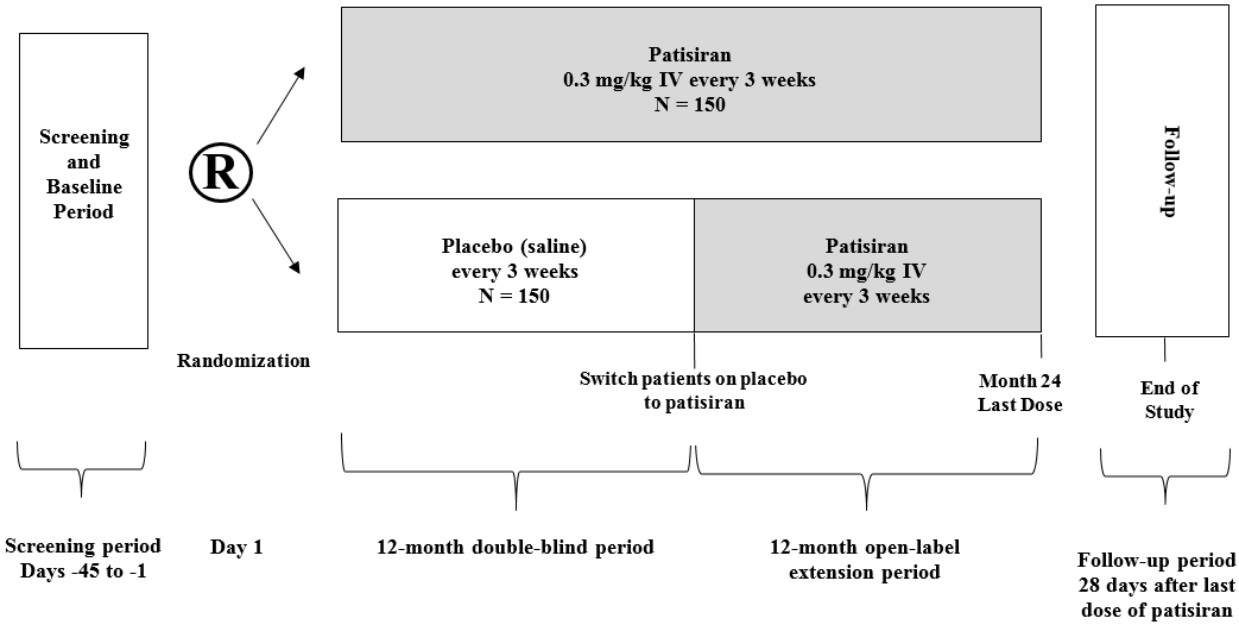

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

		Screen-ing	Baseline			Double-blind Treatment Period																		Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose																					
Study Day ±Visit Window	**For Details see Section**	**Day -45 to Day -1**		**Day 1**		**D22±3**	**D43±3**	**D64±3**	**D85±3**	**D106±3**	**D127±3**	**D148±3**	**D169±3**	**D176-D183[a]**	**D190±3**	**D211±3**	**D232±3**	**D253±3**	**D260-D267[a]**	**D274±3**	**D295±3**	**D316±3**	**D337±3**	**D358±3**	**D365-D372[a]**		
Study Week				**Week 1**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25-26**	**27**	**30**	**33**	**36**	**37-38**	**39**	**42**	**45**	**48**	**51**	**52-53**	**52-53**	**NA**
Informed Consent	6.1	X																								
Inclusion / Exclusion Criteria	4.1, 4.2	X	X																							
Demographics / Medical History	6.1	X	X																							
PND Score	6.2.7	X																								
Height	6.5.2	X																								
Efficacy Assessments																										
6-MWT	6.2.1	X	X											X[d]					X[d]						X[d]	X[d]	X[d]
KCCQ	6.2.2			X										X					X						X	X	X
mBMI	6.2.4			X									X										X				X
Cardiac Biomarker Samples	6.2.5.1	NT-proBNP	X						X					X					X						X	X	X
ATTR amyloidosis disease stage	6.2.5.2		X																						X	X	X
NYHA Class	6.2.5.3	X												X					X						X		
Echocardiogram	6.2.5.4	X																							X		
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5		X																						X		
Norfolk QoL-DN	6.2.6		X																						X	X	

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	For Details see Section	Screen-ing	Baseline			Double-blind Treatment Period																			Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose																						
		Day -45 to Day -1		Day 1		D22±3	D43±3	D64±3	D85±3	D106±3	D127±3	D148±3	D169±3	D176-D183[a]	D190±3	D211±3	D232±3	D253±3	D260-D267[a]	D274±3	D295±3	D316±3	D337±3	D358±3	D365-D372[a]		
Study Week				Week 1		3	6	9	12	15	18	21	24	25-26	27	30	33	36	37-38	39	42	45	48	51	52-53	52-53	NA
Pharmacodynamic Assessments																											
TTR Protein	6.3		X	X		X			X					X					X				X	X	X	X
Exploratory Biomarkers (plasma, serum)	6.6		X						X					X					X					X		
Safety Assessments																											
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	X		X	X
Weight	6.5.2	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed unless noted as full)	6.5.3	X Full	X						X					X					X						X Full	X Full	X
Single 12-lead ECG (unless otherwise indicated)	6.5.4		X (in triplicate, either visit)						X				X					X						X			X
Serum Chemistry, Liver Function Tests	6.5.5	X		X									X										X		X[e]	X[e]	X
Hematology	6.5.5	X		X									X										X				X
Coagulation	6.5.5	X																									
Vitamin A Levels				X																							
ADA (on dosing days, prior to dosing)	6.5.5.1			X		X			X				X											X			X

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	For Details see Section	Screening	Baseline			Double-blind Treatment Period																			Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose	D22±3	D43±3	D64±3	D85±3	D106±3	D127±3	D148±3	D169±3	D176-D183[a]	D190±3	D211±3	D232±3	D253±3	D260-D267[a]	D274±3	D295±3	D316±3	D337±3	D358±3	D365-D372[a]		
Study Day ±Visit Window		Day -45 to Day -1		Day 1																							
Study Week				Week 1		3	6	9	12	15	18	21	24	25-26	27	30	33	36	37-38	39	42	45	48	51	52-53	52-53	NA
FSH (to confirm postmenopausal, if applicable)	Table 3, 6.5.5.2	X																									
Pregnancy Test	Table 3, 6.5.5.2	X		X					X				X					X					X				
Review/Record Hospitalization, Urgent HF Visits, Urgent Care Visits, and Procedures			----------X----------																								
Review/Record AEs, Con Meds	6.5.7, 5.3		----------X----------																								
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																											
Plasma PK	6.4			X	X				X				X					X					X				
Drug Administration																											
Randomization	3.5 Window is 5D prior to Day 1			X																							
Premedication/ Study Drug	5.2.1, 5.2.3			X		X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; COVID-19=Coronavirus disease 2019; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; FSH=follicle-stimulating hormone; KCCQ=Kansas City Cardiomyopathy Questionnaire; HF=heart failure; M=month; mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit. In situations where a Month 6 (Day 176-183), Month 9 (Day 260-267), and/or Month 12 (Day 365-372) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.

[b] This Modified Month 12 Efficacy Visit is to be performed at Month 12 for patients who discontinued treatment early (ie, prior to Month 12), and choose to remain in the study. All patients who discontinue from study drug during the double-blind period will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including this Modified Month 12 Efficacy Visit. Such patients will also receive assessments at the Early Treatment Discontinuation Visit (7 to 14 days after their last dose of study drug); and the safety follow-up visit (28 days after the last dose of study drug) (Table 2), as described in Section 4.3.1. In situations where the Modified Month 12 Efficacy Visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing for these efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended, up to Day 417 (as is permitted for the regular Month 12 visit).

[c] See Section 5.3.1; patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period. In all cases, the Pre-tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of double-blind study drug (ie, 7 to 14 days post dose). Thereafter, the patient will continue with all assessments per the Schedule of Assessments, including the Month 12 Efficacy Visit. At the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

[d] As described in Section 6.2.1, to avoid a potential training effect resulting from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be performed within each of the following time periods: Day 2 to Day 214 (includes the scheduled Weeks 25-26 assessment); Day 215 to Day 319 (includes the scheduled Weeks 37-38 assessment); and Day 320 to Day 417 (includes the scheduled Weeks 52-53 assessment). Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit [Table 2]); no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed as scheduled.

[e] Serum creatinine only.

Table 2: Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																					Early Treatment Disc Visit[b]	Follow-up
																						EOS		
		D379±3	D400±3	D421±3	D442+3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]	7- 14 Days after Last Dose	D764±10
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107	NA	109
Efficacy Assessments																								
6-MWT	6.2.1										X					X						X	X	
KCCQ	6.2.2										X					X						X	X	
mBMI	6.2.4							X										X					X	
Cardiac Biomarker Samples	6.2.5.1					X					X					X						X	X	
ATTR amyloidosis disease stage	6.2.5.2																					X		
NYHA Class	6.2.5.3										X					X						X		
Echocardiogram	6.2.5.4										X											X		
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5										X											X		
Norfolk QoL-DN	6.2.6																					X		
Pharmacodynamic Assessments																								
TTR Protein	6.3					X					X					X						X	X	X
Exploratory Biomarkers (plasma, serum)	6.6					X					X					X						X		
Safety Assessments																								
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
Weight	6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed)	6.5.3					X					X					X						X	X	X
Single 12-lead ECG	6.5.4					X				X					X						X		X	

Table 2: Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																					Early Treatment Disc Visit[b]	Follow-up
																						EOS		
		D379±3	D400±3	D421±3	D442+3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]	7- 14 Days after Last Dose	D764±10
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107	NA	109
Serum Chemistry, Liver Function Tests	6.5.5							X										X				X[c]	X	X
Hematology	6.5.5							X										X					X	X
Pregnancy Test	Table 3, 6.5.5.2			X				X					X					X			X	X	X	
Review/Record Hospitalization, Urgent HF Visits, Urgent Care Visits, and Procedures		----------X----------																						
Review/Record AEs, Con Meds	6.5.7, 5.3	----------X----------																						
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																								
Plasma PK	6.4																						X	
Drug Administration																								
Premedication, Study Drug	5.2.1, 5.2.3	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; COVID-19=Coronavirus disease 2019; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; EOS=End of Study (visit); HF=heart failure; KCCQ=Kansas City Cardiomyopathy Questionnaire; mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit. In situations where a Month 18 (Day 554-561), Month 21 (Day 638-645), and/or Month 24 (Day 743-750) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible

to determine the appropriate timing of the Month 18, 21, and/or 24 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 18 up to Day 592; Month 21 up to Day 697; Month 24, up to Day 774.

[b] Patients who discontinue early from study drug will be asked to complete the Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug. In addition, patients discontinuing early from study drug during the double-blind period will be encouraged to remain on the study and complete assessments through Month 12 and complete the Modified Month 12 Efficacy Visit (see Table 1); they will also be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug as described in Section 4.3.1.

[c] Serum creatinine only.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALN-18328	siRNA targeting TTR
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APOLLO	Patisiran pivotal Phase 3 clinical study ALN-TTR02-004
AST	Aspartate aminotransferase
ATTR	Amyloid transthyretin
BMI	Body mass index
BUN	Blood urea nitrogen
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration at end of infusion
$C_{max,ss}$	Steady-state C_{max}
C_{min}	Minimum pre-infusion concentration
$C_{min,ss}$	Steady-state C_{min}
CMR	Cardiac magnetic resonance
Con Meds	Concomitant medication
COVID-19	Coronavirus disease 2019
$C_{p(30min)}$	30-minute post-infusion concentration
$C_{p,ss(30min)}$	Steady-state $C_{p(30min)}$
CRF	Case report form
CFR	Code of Federal Regulations
CV	Cardiovascular
DLin-MC3-DMA	1,2-Dilinoleyloxy-N,N-dimethylpropylamine
DMC	Data Monitoring Committee
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunoassay
EOS	End of study

Abbreviation	Definition
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
HF	Heart failure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRS	Interactive Response System
IV	Intravenous(ly)
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire– Overall Summary
LNP	Lipid nanoparticle
LS	Least squares
mBMI	Modified body mass index
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 neurological impairment score +7
mRNA	Messenger ribonucleic acid
6-MWT	6-minute walk test
NA	Not applicable
Norfolk QoL-DN	Norfolk Quality of Life - Diabetic Neuropathy
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone B-type natriuretic peptide

Abbreviation	Definition
NYHA	New York Heart Association
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEG_{2000}-C-DMG	3-N-[(ω-methoxy poly(ethylene glycol)2000) carbamoyl]-1,2-dimyristyloxy-propylamine
PK	Pharmacokinetic
PND	Polyneuropathy disability
PT	Preferred term
RBC	Red blood cell
RBP	Retinol binding protein
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
siRNA	Small interfering RNA
Tc	Technetium
TTR	Transthyretin
ULN	Upper limit of normal
US	United States
V30M	Valine to methionine mutation at position 30
V122I	Valine to isoleucine mutation at position 122
wt	Wild type
wtTTR	Wild type transthyretin

1. INTRODUCTION

1.1. Disease Overview

Transthyretin (TTR)-mediated amyloidosis (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 (ageing) causes, respectively. In ATTR amyloidosis, deposition of TTR in various organs results in progressive, chronically debilitating morbidity and mortality. The most common manifestations of ATTR amyloidosis are polyneuropathy and cardiomyopathy (ie, ATTR amyloidosis with cardiomyopathy).

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]

In hATTR amyloidosis, 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. These misfolded TTR monomers can then self-assemble into oligomers and form amyloid fibrils and plaques in the extracellular space of various tissues [Hou 2007], including the peripheral nervous system, heart, gastrointestinal tract, kidney, central nervous system and eye, leading to cellular injury and organ dysfunction with corresponding clinical manifestations. Since almost all patients are heterozygous for the mutated TTR allele, the amyloid fibrils typically consist of both mutant and wtTTR.

There are over 120 reported TTR genetic mutations associated with hATTR amyloidosis, and almost all patients are heterozygous for the mutated TTR allele.[Ando 2013; Connors 2003] The phenotypic expression varies depending on the predominant site of deposition of the amyloid fibrils with some mutations associated with predominantly polyneuropathy manifestations and others associated with predominantly cardiomyopathy manifestations. However, most patients experience both over the course of their disease.

The most common TTR mutation is the valine to methionine mutation at position 30 (V30M), accounting for approximately 50% of cases worldwide, and occurring primarily in families with heritage from Portugal, Sweden, Japan, and Brazil.[Parman 2016] This genotype is most commonly associated with multisystemic polyneuropathy. The valine to isoleucine at position 122 (V122I) mutation is most commonly associated with cardiomyopathy and occurs primarily in African Americans. In these individuals, the mean age at diagnosis is approximately 65 to 70 years, with symptom onset typically occurring after the age of 65.[Jacobson 2011; Quarta 2015] While there appears to be an association between carrier status and the development of heart failure (HF) and echocardiographic features of cardiac amyloidosis, the exact penetrance of this particular allele is unknown, and estimates vary widely.

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] Patients with this

condition do not have a pathogenic mutation in the TTR gene and the amyloid fibrils consist only of wtTTR protein, which form amyloid deposits typically found in heart tissue.

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 preserved until late stages of the disease.[Castano 2015; Dungu 2012; Mohty 2013; Ruberg 2012] Cardiac infiltration by amyloid can also lead to conduction disturbances and arrhythmias.[Adams 2016; Ando 2013; Benson and Kincaid 2007; Connors 2004] Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, in addition to clinical measurements of ambulation, and quality of life. Progression of disease in this population can be seen over a period of 12 months as demonstrated by differences in 6-minute walk test (6-MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ) – Overall Summary (KCCQ-OS) in the Phase 3 ATTR-ACT study.[Maurer 2018] Based on natural history data, patients typically experience progressive symptoms of HF resulting in hospitalization and with death typically occurring 2.5 to 5 years after diagnosis.[Castano 2015; Damy 2015; Dungu 2012; Hawkins 2015]

1.2. Current Treatments

The treatment of ATTR amyloidosis requires a multidisciplinary approach primarily involving cardiology, neurology, and gastroenterology specialties. While there are treatments for polyneuropathy that are available to hATTR amyloidosis patients, for most regions no treatments are currently available for the cardiomyopathy phenotype for either the hATTR or wtATTR forms. Palliative/symptomatic therapies directed at specific symptoms, including volume control and treatment of cardiac arrhythmias and conduction system disturbances, including cardiac pacemakers where appropriate, have been the mainstay of treatment despite their limited effectiveness.

Given that the liver is the primary source of TTR, orthotopic liver transplantation (OLT) has been used for hATTR amyloidosis patients since the early 1990s. However, OLT is intended to eliminate mutant TTR from circulation, but has no effect on the hepatic production of wtTTR, which continues to be made by the transplanted liver and can continue to deposit in the heart. OLT has also only been shown to be effective in slowing the progression of disease in patients with an early age of onset (<50 years of age) [Okamoto 2009], and especially for those with the V30M mutation and short disease duration before transplant. Consequently, almost two-thirds of patients with hATTR amyloidosis are not transplant-eligible.

Tafamidis, a TTR tetramer stabilizer that acts by binding to the thyroxine-binding site on TTR to reduce its dissociation into misfolded amyloidogenic monomers, is currently approved in Europe, Japan, Mexico, and select countries in South America, but not in the United States (US), for the treatment of patients with hATTR amyloidosis with polyneuropathy.[Coelho 2016] Recently, tafamidis was evaluated in the Phase 3 ATTR-ACT trial in patients with ATTR amyloidosis with cardiomyopathy (including hereditary and wt).[Maurer 2018] This study demonstrated that tafamidis treatment over 30 months was associated with lower all-cause mortality and cardiovascular (CV)-related hospitalizations compared with placebo treatment. Additionally, tafamidis treatment resulted in a slowing of the decline in functional capacity

(6-MWT) and quality of life (KCCQ-OS) compared to placebo. However, consistent with the expected pharmacodynamic (PD) effect of TTR stabilization, the effects of tafamidis on mortality outcomes was not observed until late in treatment, with differentiation between treatment groups occurring only after 18 months of treatment. Furthermore, although improvements with tafamidis relative to placebo were observed in 6-MWT and KCCQ-OS, minimal changes in echocardiographic parameters were observed, and tafamidis-treated patients still progressed during the study.

As of early 2019, tafamidis was not approved in the US for patients with ATTR amyloidosis (neither polyneuropathy nor cardiomyopathy phenotypes); however, it is anticipated that tafamidis may become available for patients with the cardiomyopathy phenotype in the US and in other regions, based on the ATTR-ACT study results. In Japan, tafamidis was approved in 2019 for use in transthyretin-type cardiac amyloidosis (wt and mutant), in addition to approval for transthyretin-type familial amyloid polyneuropathy.

The results of the ATTR-ACT study 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 a ribonucleic acid (RNA) interference (RNAi) therapeutic, may be required to halt or reverse the debilitating and ultimately fatal course of disease.

1.3. Patisiran Clinical Development

Patisiran is a small interfering RNA (siRNA) specific for TTR, which is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration.[Akinc 2010] The patisiran drug product (ALN-TTR02; patisiran-LNP, hereafter referred to as "patisiran") is designed to significantly suppress liver production of both wt and all mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with ATTR amyloidosis.

Patisiran utilizes the mechanism of RNAi to selectively degrade TTR messenger RNA (mRNA) and thereby reduce the expression of its corresponding protein.[Bumcrot 2006] Patisiran is formulated (via the LNP) to target delivery to hepatocytes in the liver, the primary source of TTR protein in circulation. Following IV infusion, opsonization of the LNP by apolipoprotein E facilitates binding to the low-density lipoprotein receptor on hepatocytes and subsequent endocytosis. Fusion of the ionizable lipid component of the LNP with the endosomal membrane then leads to release of the siRNA into the cytoplasm where it can bind to and activate the RNA-induced silencing complex (RISC). Upon binding and activation of RISC in the cytoplasm within hepatocytes, the siRNA duplex unwinds, and the antisense strand specifically binds to a genetically conserved sequence in the 3' untranslated region of wt and mutant TTR mRNA. The Argonaute-2 endonuclease within the RISC/siRNA enzyme complex catalytically degrades wt and mutant TTR mRNA, resulting in a reduction of wt and mutant TTR protein.

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing patisiran for the treatment of patients with ATTR amyloidosis. Based on results from the pivotal Phase 3 APOLLO study (Section 1.3.1), patisiran is approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults and in the European Union for the treatment of hATTR

amyloidosis in adult patients with stage 1 and stage 2 polyneuropathy. Ongoing development is intended to establish patisiran for the treatment of ATTR (hereditary and wt) amyloidosis with cardiomyopathy based on exploratory cardiac results from the APOLLO study (Section 1.3.1.1), which provides preliminary evidence in support of the use of patisiran for the treatment of the cardiomyopathy manifestations of the disease.

The nonclinical pharmacology, pharmacokinetics (PK), and toxicology of patisiran were evaluated in a series of in vitro and in vivo studies that have enabled chronic dosing in clinical studies.

1.3.1. The Phase 3 APOLLO Study

The safety and efficacy of patisiran was shown in a Phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study (ALN-TTR02-004, APOLLO) that met the primary and all secondary endpoints.[Adams 2018] This study demonstrated that, in patients with hATTR amyloidosis who exhibited a broad range of disease severity and TTR genotypes, treatment with patisiran leads to a significant improvement in neuropathy (modified neurological impairment score +7 [mNIS+7]) relative to placebo at 18 months (primary endpoint), as well as significant improvement in quality of life (Norfolk Quality of Life - Diabetic Neuropathy [Norfolk QoL-DN], key secondary endpoint) relative to placebo at 18 months. Significant improvement in neuropathy and quality of life were also observed at Month 9. This study furthermore demonstrated that treatment with patisiran is associated with an improvement in overall health (gait speed, nutritional status, and disability), with improvement in these endpoints seen as early as at Month 9.

In the patisiran group, serum TTR reduction was seen after the first dose and was stably maintained over the duration of the study; the mean TTR percent reduction from baseline was 82.6% and 84.3% at Months 9 and 18, respectively. A correlation (Pearson's r, 0.59; 95% CI, 0.49-0.68) was observed between the degree of TTR reduction from baseline and the change in the mNIS+7 at 18 months.

Patisiran showed an acceptable safety profile in the APOLLO study. Common adverse events (AEs) occurring more frequently with patisiran compared to placebo included peripheral edema (30% versus 22%) and infusion related reactions (IRRs) (19% versus 9%, respectively).

1.3.1.1. Cardiac Results and Cardiac Subpopulation Data from APOLLO

In APOLLO, evidence of potential cardiac amyloid involvement was seen in most patients in the study; 80% had left ventricular wall thickness >13 mm and 79% had abnormal levels of the cardiac biomarker N-terminal prohormone B-type natriuretic peptide (NT-proBNP).[Solomon 2018] As well, 56% of the population met the prespecified criteria for inclusion in a subpopulation of patients with evidence of cardiac amyloid involvement (ie, the cardiac subpopulation, with baseline left ventricular wall thickness ≥13 mm and no history of hypertension or aortic valve disease). In these patients, treatment with patisiran for up to 18 months resulted in improvement relative to placebo in important measures of cardiac structure and function. These included reduction in ventricular wall thickness and decrease (improvement) in global longitudinal strain.[Solomon 2018] In addition, patisiran treatment led to a reduction (improvement) in NT-proBNP and an improvement in functional capacity, as measured by 10-meter walk test assessment of gait speed, relative to the placebo group.

Overall, patisiran had an acceptable safety profile, based on an in-depth analysis of cardiac events in both the overall (modified intent-to-treat) population and the cardiac subpopulation. Importantly, in a post hoc analysis of safety data in the modified intent-to-treat population, rates of any hospitalization and/or all-cause death were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups respectively, while the rates of cardiac hospitalizations and/or all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups respectively. This approximates a reduction in event rate of approximately 50% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality for patients in the patisiran group compared to those in the placebo group.[Solomon 2018] Similar reductions in the event rates were observed in the cardiac subpopulation in APOLLO (approximately 55% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality; data on file).

The observed cardiac data from the APOLLO study support the therapeutic hypothesis that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis and warrant ongoing development for this indication.

1.3.2. Phase 3, Open-label Extension Study

Study ALN-TTR02-006 is an ongoing multicenter, open-label extension study designed to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis who have completed a prior Phase 2 or 3 parent study with patisiran (ALN-TTR02-003 or ALN-TTR02-004 [APOLLO]). The interim data from this open-label extension study were consistent with, and extended, the acceptable safety profile and clinical efficacy of patisiran observed in the Phase 3 APOLLO study.

No new safety signals have emerged for patients with long-term patisiran treatment.

1.4. Study Design Rationale

This study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of patisiran in adult patients with ATTR amyloidosis with cardiomyopathy. The efficacy of patisiran on functional capacity will be evaluated via change at Month 12 in the 6-MWT (primary endpoint). The study will include patients with wtATTR and hATTR amyloidosis with cardiomyopathy who, at baseline, are either tafamidis naïve or have been on tafamidis for ≥6 months with disease progression, in the opinion of the Investigator.

Confidence in a beneficial treatment effect with patisiran in this patient population with ATTR amyloidosis with cardiomyopathy comes from the Phase 3 APOLLO study of patisiran in patients with hATTR amyloidosis with polyneuropathy. As described in Section 1.3.1 and Section 1.3.1.1, TTR lowering with patisiran demonstrated multiple benefits in a broad range of disease manifestations, including a substantial improvement in neuropathy and quality of life, as well as autonomic symptoms, motor strength, ambulatory ability, disability, and nutritional status.[Adams 2018] Furthermore, in a prespecified subgroup of patients with evidence of cardiac involvement, which was a majority (56%) of the overall study population, a beneficial treatment effect of patisiran compared to placebo was observed for assessments of cardiac structure and function as well as the cardiac biomarker NT-proBNP.[Solomon 2018]

The 6-MWT (primary endpoint assessment) 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 2014] The KCCQ-OS (first secondary endpoint assessment) 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 et al. 2006) Both 6-MWT and KCCQ-OS were shown to rapidly and consistently decline over time in cardiac ATTR amyloidosis patients and, in the 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 primary and key secondary endpoints, respectively.

Assessment of the primary endpoint at Month 12 is supported by placebo-arm data from the ATTR-ACT study showing substantial disease progression (via the 6-MWT) over an equivalent time; as well, data from APOLLO demonstrated a patisiran treatment effect as early as 9 months on multiple manifestations of hATTR amyloidosis (neuropathy, quality of life, NT-proBNP, and functional capacity [ie, gait speed]).[Maurer 2018]

The inclusion of placebo as a control allows for a rigorous analysis of the treatment effect of patisiran. If tafamidis becomes an approved therapy for ATTR amyloidosis with cardiomyopathy in a given region while this study is in progress, patients who are naïve to tafamidis treatment at baseline may commence concomitant on-label tafamidis during the study (ie, tafamidis drop-in) (Section 5.3.1).

1.5. Dose Rationale

The approved and recommended dosage of patisiran for the treatment of the polyneuropathy in patients with hATTR amyloidosis is 0.3 mg/kg administered IV every 3 weeks for patients weighing <100 kg and a fixed dose of 30 mg administered every 3 weeks for patients weighing 100 kg or more. This dosage was selected based on dose-response analyses from three Phase 1 and 2 studies demonstrating dose-dependent TTR reduction, with the maximum reduction achieved at 0.3 mg/kg. This regimen was further confirmed in the pivotal Phase 3 APOLLO study, where this dosage showed significant clinical activity and was well tolerated by patients with hATTR amyloidosis with polyneuropathy, including those in the cardiac subpopulation. The approved dosing regimen used in the treatment of polyneuropathy is being employed in this study since the mechanism of action of patisiran (ie, serum TTR lowering) for treatment of polyneuropathy and cardiomyopathy is the same.

1.6. Benefit-risk Assessment

ATTR amyloidosis with cardiomyopathy is a rare, serious, life-threatening, multisystemic disease characterized by deposition of TTR in various organs. Without treatment, the disease progresses, resulting in chronically debilitating morbidity and mortality, with the most common manifestations being cardiomyopathy and polyneuropathy. Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, ambulation, and quality of life seen over a period of 18 months or less.[Ruberg and Berk 2012]

The benefit-risk profile of patisiran has been established in extensive clinical development; in Phase 1, 2, and 3 clinical studies, patisiran administered IV demonstrated a potent, dose-dependent inhibition of TTR. In the Phase 3 APOLLO study of patisiran, the primary and all secondary endpoints were met.[Adams 2018] Furthermore, exploratory cardiac results from the APOLLO study suggest that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon 2018] and provide preliminary evidence in support of the use of patisiran for the treatment of patients with ATTR amyloidosis with cardiomyopathy (Section 1.3.1.1).

In APOLLO, as well as in the ongoing Phase 3, open-label extension study (ALN-TTR02-006), an acceptable safety profile with patisiran was demonstrated. Most AEs were mild or moderate in severity. Transient infusion-related reactions (IRRs) were observed, but all IRRs were mild or moderate in severity, none were reported as serious AEs (SAEs). No clinically significant laboratory or hematologic changes were observed. Furthermore, in APOLLO, an acceptable safety profile was also observed in a prespecified subgroup of patients with evidence of cardiac amyloid involvement. [Solomon 2018]

For patisiran, important identified risks include IRRs. To minimize this risk, all patients must receive premedication with a corticosteroid, paracetamol/acetaminophen, and H1 and H2 blockers prior to patisiran administration (Section 5.2.1). The infusion may be interrupted or slowed if an IRR occurs (Sections 5.2.3 and 5.2.4). Important potential risks also include severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients. Patisiran is contraindicated in patients with a history of severe hypersensitivity (eg, anaphylaxis or anaphylactoid reactions) to patisiran or any of the excipients.

Vitamin A deficiency is also considered an important potential risk. Nonclinical and clinical data with patisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in 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 (Section 5.3). 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 patisiran.

Detailed information about the known and expected benefits and risks of patisiran may be found in the current edition of the Investigator's Brochure.

During the study, patients will be monitored, including evaluation of laboratory monitoring for liver function test abnormalities, renal function, and other standard hematology and blood chemistries. As the risk of embryofetal toxicity is currently unknown, females of child-bearing potential participating in the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception as specified in the protocol.

An external, independent Data Monitoring Committee (DMC) will monitor and ensure the safety of trial participants (see Section 3.7).

In conclusion, exploratory cardiac results from the APOLLO study suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon

2018] (Section 1.3.1.1) together with the established benefit-risk profile of patisiran demonstrated in the Phase 3 APOLLO study (and supportive data from the ALN-TTR02-003 and ALN-TTR02-006 studies), support the evaluation of patisiran in a Phase 3 study in adult patients with ATTR amyloidosis (wtATTR and hATTR) cardiomyopathy.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality, hospitalizations, and urgent heart failure (HF) visits	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV) events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month double-blind period
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV events • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV events (CV hospitalizations and urgent HF visits) over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI)

Objectives	Endpoints
	○ Cardiac magnetic resonance (CMR) parameters ○ Technetium scintigraphy parameters ○ Troponin I levels ○ Norfolk QoL-DN
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (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 patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the Investigator. This group will be capped at 30% of total enrollment in the study.

In addition to patients who have never taken tafamidis, patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve for this study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 12-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period (Figure 1).

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive IV treatment every 3 weeks with either patisiran (0.3 mg/kg for patients weighing <100 kg; 30-mg fixed dose for patients weighing ≥100 kg) or placebo. Prior to receiving

randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an IRR with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. (Patients randomized to placebo will also receive premedications to maintain the blind.) Study drug will be administered as an approximately 80-minute IV infusion.

During the 12-month open-label extension period, all patients will receive treatment with open-label patisiran.

Study drug administration at a location other than the study center (eg, at home) may be administered as follows:

- Double-blind period: Patients who have received ≥2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.
- 12-month open-label extension period: Patients who have received ≥2 doses of open-label patisiran at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have patisiran administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Patisiran administration will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion, with oversight of the Investigator.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint (Section 2); this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period at the time points noted in the Schedule of Assessments (Table 1 and Table 2). The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score.

In situations where an efficacy study visit at Months 6, 9, and/or 12 is unable to be completed at the study center due to the Coronavirus disease 2019 (COVID-19) pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended for that visit as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran (Table 1). Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed. For the open-label extension period, the windows for study visits are also extended (Table 2).

Safety will be assessed throughout the study, as described in the Schedule of Assessments for the double-blind period (Table 1) and for the open-label extension period (Table 2).

3.2. Duration of Treatment

The treatment duration in this study is up to 24 months, inclusive of a 12-month, double-blind, treatment period, and a 12-month, open-label, treatment period.

3.3. Duration of Study Participation

The estimated total time on study for each patient is up to 26.5 months, including up to 45 days of screening, up to 24 months of treatment (see Section 3.2), and a 28-day safety follow-up period.

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:

- the patient has completed the end of study (EOS; Month 24) visit, or
- the patient has completed the follow-up visit 28 days after the last dose of patisiran.

3.4. Number of Planned Patients

The planned enrollment for this study is 300 patients with wtATTR and hATTR amyloidosis with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR.

3.5. Method of Assigning Patients to Treatment Groups

Using the interactive response system (IRS), patients will be randomized 1:1 to the patisiran or placebo arm. Randomization will be stratified by:

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

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 IRS. The Investigator or his/her designee will contact the IRS to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

3.6. Blinding

During the double-blind period of the study, all personnel will be blinded to the study treatment, except the pharmacist and designated pharmacy/healthcare personnel who will set-up, dispense, and prepare the infusion. Patisiran confers a slightly opalescent color relative to the clear saline (placebo) infusate; therefore, all infusion bags and lines will be covered with amber bags and line covers by the unblinded personnel to prevent visualization by the blinded study personnel and patient, as described in detail in the Pharmacy Manual.

After the pharmacist (or designated pharmacy/healthcare personnel) has prepared the infusion, separate blinded personnel will administer study drug and monitor the patient during and after

the infusion. All patients will be blinded to treatment and will receive an IV infusion once every 3 weeks using identical volumes for patisiran and placebo.

Study personnel performing assessments related to the primary and secondary endpoints will be different from the Investigator and other personnel managing the patient, and all of these study personnel will be blinded to any clinical laboratory results that could potentially unblind them (eg, TTR levels). In addition, the study personnel performing assessments related to the primary and secondary efficacy endpoints will not reference the results of any previous assessments.

Furthermore, unblinded source documentation containing all descriptions of pharmacy preparations and infusions or distribution of study drug or randomization data will be stored separate from all other study data/records and from other pharmacy staff not participating on the study.

Blinding will be maintained until the last patient completes their Month 12 visit.

3.6.1. Emergency Unblinding

During the double-blind period of the study, 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. 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 IRS instructions for details on emergency unblinding.

3.7. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study through the double-blind period (through Month 12), providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.8. Adjudication Committee

An independent Adjudication Committee will review deaths and hospitalizations and will attribute a cause (CV versus non-CV) according to the responsible underlying disease process rather than the immediate mechanism. Urgent HF visits will also be adjudicated. Deaths, hospitalizations, and urgent HF visits will be classified as specified in the Adjudication Committee 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 and Sex

1. Age 18 (or age of legal consent, 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:

   Hereditary ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

   a. TTR pathogenic mutation consistent with hATTR.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at screening).
   c. 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 ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) has been excluded.
   d. If MGUS, confirm TTR protein in tissue with immunohistochemistry (IHC) or mass spectrometry.

   Wild-type ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

   a. Absence of pathogenic TTR mutation.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at screening).
   c. Amyloid deposits in cardiac tissue with TTR precursor identification by IHC, mass spectrometry, **OR** technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc] or ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if MGUS has been excluded.
   d. If MGUS, confirm TTR protein in cardiac tissue with IHC or mass spectrometry.

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; in addition to patients who have never taken tafamidis, those who have been on tafamidis for ≤30 days total and have not received any tafamidis in the

6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.

b. Currently on tafamidis (for ≥6 months) and has demonstrated disease progression, as determined by the Investigator. (At the time of study entry, tafamidis treatment must be on-label use of commercial tafamidis for the treatment of ATTR amyloidosis with cardiomyopathy at the approved 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. Able to complete ≥150 m on the 6-MWT at screening.
7. Screening NT-proBNP >300 ng/L and <8500 ng/L; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP >600 ng/L and <8500 ng/L.

Informed Consent

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent; and patient agrees to sign the medical records release form for collection of vital status.

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) or leptomeningeal amyloidosis.
2. NYHA Class III **AND** ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3000 ng/L and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2).[Gillmore 2018]
3. NYHA Class IV at the Screening visit.
4. Has a polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires cane or stick to walk, or is wheelchair bound) at the Screening visit.

Laboratory Assessments

5. Has any of the following laboratory parameter assessments at screening:
   a. Aspartate transaminase (AST) or alanine transaminase (ALT) levels >2.0 × the upper limit of normal (ULN).
   b. Total bilirubin >2×ULN.
   c. International normalized ratio (INR) >1.5 (unless patient is on anticoagulant therapy, in which case excluded if INR >3.5).
6. Has eGFR <30 mL/min/1.73 m^2 (using the modification of diet in renal disease [MDRD] formula).
7. Has known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.

Prior/Concomitant Therapy

8. Tafamidis naïve patients (at baseline) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
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. Received prior TTR-lowering treatment (including patisiran) or participated in a gene therapy trial for hATTR amyloidosis.
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 6 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 chronic 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 electrocardiogram [ECG] changes).
15. Has non-amyloid disease affecting exercise testing (eg, severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation).
16. Recent or planned orthopedic procedure during the double-blind period (eg, lower extremity or back surgery) that could impact 6-MWT.
17. Unstable congestive heart failure (CHF) (eg, no adjustment of diuretics at time of screening required to achieve optimal treatment of CHF).
18. Had acute coronary syndrome or unstable angina within the past 3 months.
19. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.
20. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
21. Has persistent elevation of systolic (>180 mmHg) and diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.
22. Has untreated hypo- or hyperthyroidism.
23. Prior or planned heart, liver, or other organ transplant.

24. Had a malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
25. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient.
26. Has a history of severe hypersensitivity (eg, anaphylaxis) to any of the excipients in patisiran. Also see exclusion Criterion 11, which excludes all patients with prior TTR-lowering treatment including patisiran.

Contraception, Pregnancy, and Breastfeeding

27. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.
28. Female patient is pregnant or breast-feeding.

Alcohol Use

29. Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (for females, more than 14 units of alcohol per week; for males, more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer]);
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 or their legal guardians 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 electronic case report form (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; which includes required treatment with prohibited medication (as defined in Section 5.3) per Investigator discretion
- 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 6.5.7.7 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 is captured in the final analyses.

If this occurs, 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 and Table 2), 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 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 6.5.7. 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 from study drug during the 12-month double-blind period, defined as the time the first dose of study drug is administered on Day 1 through completion of the Month 12 Efficacy Visit (primary endpoint assessment), will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including a Modified Month 12 Efficacy Visit (Table 1). They will also be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug (Table 2); see Section 3.3.1.

In situations where the Modified Month 12 Efficacy Visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of these efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended up to Day 417 (as is permitted for the regular Month 12 visit).

Patients who discontinue patisiran during the open-label extension period will be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, per the Schedule of Assessments (Table 2), 28 days after the last dose of patisiran; see Section 3.3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop the patient's participation in the study-at any time. A patient or legal guardian 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, through the Modified Month 12 Efficacy Visit, and the 28-day follow-up visit, or alternatively may complete any minimal assessments for which the patient or legal guardian consents as described in Section 4.3.1. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 12 visit, every effort should be made to conduct the assessments scheduled to be performed at the Modified Efficacy Visit (Table 1).

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, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and 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.

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 6.5.7.

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 or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian 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 or legal guardian (where possible, 3 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 or legal guardian 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 can search publicly available records (where permitted and allowed by local law) to ascertain survival status. 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 preparation, administration, and storage of study drug (patisiran and placebo) is provided in the Pharmacy Manual.

All patients will be instructed to take the recommended daily allowance of vitamin A while on the study.

5.2.1. Premedication

All patients will receive premedication prior to study drug administration to reduce the risk of IRRs. Each of the following medicinal products should be given on the day of study drug infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

Oral premedication equivalents are permitted, but must be administered in the presence of a healthcare professional.

Modifications to lower the corticosteroid dose may be made to the premedication regimen for either of the following 2 reasons:

1. Double-blind and open-label periods: If a patient is having difficulty tolerating the steroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the steroid premedication may be allowed for that patient after consultation with the medical monitor at any time during the study.
2. Double-blind period: For patients who are tolerating their double-blind study drug infusions well with their current corticosteroid premedication regimen (ie, no IRRs during the past 3 or more infusions), corticosteroid dose may be reduced in 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (IV) or equivalent.
    a. Open-label period: At the start of the open-label period, patients must take dexamethasone 10 mg or the equivalent as their corticosteroid premedication. Patients taking more than 10 mg of dexamethasone at the end of the double-blind period should take the higher dose. The corticosteroid dose may then be tapered as described above if the patient is tolerating infusions. However, if a patient's steroid premedication had been decreased in the double-blind period due to their inability to tolerate the premedication regimen as described above, continuation of the reduced dose regimen (as it had been in the double-blind period) may be permitted after consultation with the Medical Monitor.

Infusions during corticosteroid tapering may be performed at the study center or at a location other than the study center (eg, at home), as described in detail in the Pharmacy Manual, at the discretion of the Investigator and after consultation with the Medical Monitor.

Additional or higher doses of 1 or more of the premedications may be administered to reduce the risk of IRRs, if needed. For suggested guidelines for management of IRRs, see Section 5.2.4; further details can be found in the Pharmacy Manual.

5.2.2. Study Drug Description

Patisiran is a RNAi therapeutic consisting of a double-stranded siRNA targeting TTR mRNA formulated in an LNP. The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline. Patisiran Solution for IV infusion contains 2 mg/mL of patisiran.

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

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

5.2.3. Dose and Administration

Detailed instructions for study drug preparation and administration are found in the Pharmacy Manual.

5.2.3.1. Double-bind Study Drug (Patisiran or Placebo)

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days.

The amount (in mg) of double-blind patisiran to be administered should be determined based on the patient's weight (kg). Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended dose is 30 mg.

Weight from the previous visit may be used for calculating dose. Weight must be collected prior to dosing with study drug. Study drug will be administered as an approximately 80-minute IV infusion (approximately 1 mL/minute for the first 15-minutes followed by approximately 3 mL/minute for the remainder of the infusion). The patient's infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient will be observed for 1 hour following completion of dosing for observation and completion of assessments.

Patients who have received ≥2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.

Missed doses of double-blind study drug

If a patient does not receive a dose of study drug within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit, after consultation with the Medical Monitor. If a dose is administered with a delay, the next dose will resume following the original schedule per the Schedule of Assessments.

A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses 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 in the study.

5.2.3.2. Open-label Extension Period (Patisiran)

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described in Section 5.2.3.1 for double-blind patisiran. As noted in Section 3.6, blinding will be maintained until the last patient completes their Month 12 visit.

During the open-label extension period, patients who have received at least 2 doses of open-label patisiran at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have patisiran administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Patisiran administration will be performed by a healthcare professional trained on the protocol and administration of premedications and patisiran infusion.

All patients will receive premedications prior to open-label patisiran administration to reduce the risk of IRRs (Section 5.2.1).

Missed doses of open-label patisiran

If a patient does not receive a dose of open-label patisiran within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit, after consultation with the Medical Monitor. If a dose is administered with a delay, the next dose will resume following the original schedule per the Schedule of Assessments.

5.2.4. Suggested Guidelines for Management of Infusion-related Reactions

Criteria for categorizing IRRs are provided in Section 10.3.

- In the event of an IRR, the infusion of study drug may be slowed or stopped and the patient closely monitored until resolution of the reaction. Drugs that may be used to facilitate resolution and permit resumption of study drug administration include but are not limited to: paracetamol/acetaminophen (or equivalent), additional histamine H1/H2 receptor antagonists (eg, ranitidine), nonsteroidal anti-inflammatory drugs (NSAIDs), adrenaline, supplemental oxygen, IV fluids, and/or corticosteroids.
- Following resolution of a mild or moderate IRR that required interruption of the study drug infusion, resumption of administration may occur at the Investigator's discretion at a slower infusion rate for that dose and for subsequent doses of study drug. If the infusion is delayed, the administration of the infusion should be completed no more than 16 hours after study drug is first diluted in saline (including infusion time).
- Study drug administration will not be resumed for any patient following a severe IRR until the case is discussed with the Medical Monitor.
- If after consultation with the Medical Monitor it is agreed that an individual patient's steroid premedication will be increased, then the following steps are **recommended**:
    1. If the IRR occurred while the patient received 10 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and did not resolve with slowing of the infusion rate, then the patient should be increased by multiples of 5 mg IV dexamethasone or equivalent at least 60 minutes before the infusion.

2. Increased dose of premedication steroids should NOT exceed the combination of 20 mg IV dexamethasone or equivalent on the day of infusion.
3. If the IRR occurred while the patient received less than 10 mg IV dexamethasone or equivalent, then the patient should return to the prior dose of IV dexamethasone or equivalent that did not result in an IRR.

Patients will be instructed to call the Investigator if they experience symptoms such as fever, chills, myalgia, or nausea/vomiting after discharge from the site.

5.2.5. 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.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of study drug (patisiran and placebo) doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately (5 ±3°C) until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

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 will be provided in the Pharmacy Manual.

5.2.7. 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. Additional details will be available in the Pharmacy Manual.

5.2.8. 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, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.3. Concomitant Medications and Procedures

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

Use of the following medications/treatments are prohibited during study participation:

- Any investigational agent other than study drug.
- Inotersen, doxycycline, ursodeoxycholic acid, tauroursodeoxycholic acid, and diflunisal are also prohibited during the study (see exclusion Criterion 10 in Section 4.2). Doxycycline is permitted if being taken for short-term treatment of infection.

All patients will be asked to take the recommended daily allowance of vitamin A for the duration of their participation in the study while being administered study drug. In countries where relevant, the clinical sites will provide patients with a prescription for vitamin A at a dose consistent with local guidelines.

Standard vitamins and topical medications are permitted. Any concomitant medication or treatment that is required for the patient's welfare may be given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the CRF, as specified in the Schedule of Assessments (Table 1 and Table 2). Concomitant medications include 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 CRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Concomitant Tafamidis Use

Per inclusion Criterion 4, at baseline patients are either: 1) tafamidis naïve or 2) currently on tafamidis for ≥6 months with demonstrated disease progression, as determined by the Investigator. Patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.

For patients on tafamidis at baseline, the reasons for considering the patient to have demonstrated disease progression will be recorded in the eCRF. Patients who are on tafamidis at baseline are encouraged, if it is medically appropriate in the opinion of the Investigator, to remain on tafamidis for the duration of the double-blind period.

Per exclusion Criterion 8, patients who are tafamidis naïve at baseline, for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period (taking into consideration clinical status, patient preference, and/or commercial availability of tafamidis), should not be enrolled in the trial.

However, if tafamidis is granted approval by a Health Agency for treatment in patients with ATTR amyloidosis with cardiomyopathy in a given region, all enrolled patients in this region will be made aware of its potential benefits and risks at the time of regulatory approval and all patients will be reconsented. In such circumstances, tafamidis is not considered prohibited and

the Investigator may, using their medical judgement, commence concomitant on-label tafamidis during the study, if it is felt to be in the best interest of the patient and if it is commercially available in the country.

Patients who are tafamidis naïve at baseline, but begin taking commercial tafamidis (ie, "tafamidis drop-in"), will remain in the study. 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). In all cases, the Pre tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of study drug (ie, 7 to 14 days post study drug dose). Thereafter, the patient will continue with all assessments per the Schedule of Assessments (Table 1 and Table 2). In addition, at the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

Initiation of TTR stabilizer therapies other than tafamidis (eg, diflunisal) is not allowed during the double-blind period of this study.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

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 12 weeks after the last dose of study drug in this study.

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.
- 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 12 weeks after the last dose of study drug.

Investigators should advise females of childbearing 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 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 6.5.5.2).

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 (double-blind period) and Table 2 (open-label extension period). Additional information on the collection of study assessments will be detailed in the respective reference manuals.

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient or legal guardian before the Screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF. In addition, a medical records release form will be required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries.

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

To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, the Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the study center or any new trial participant to comply with the protocol given COVID-19 limitations.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening (once) 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, including completion of ophthalmologic history in the eCRF. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

If a genetic test result that shows the presence or absence of a TTR pathogenic mutation, which would be consistent with either wtATTR or hATTR, is not available at Screening for the assessment of eligibility (Section 4.1, inclusion Criterion 2a), genotyping may be conducted at a

central laboratory. Alternatively, a local laboratory may be selected by the study center in consultation with the Medical Monitor.

The study eligibility biopsies and technetium scintigraphy noted in inclusion Criterion 2 are intended to be historical, as part of the patient's clinical care and diagnosis, and are not performed as part of the study.

If a diagnostic result that confirms ATTR amyloidosis is not available at Screening for the assessment of eligibility (inclusion Criterion 2c/d), testing may be conducted at a laboratory or diagnostic center selected by the study center, in consultation with the Medical Monitor, in countries in which this test is not standard of care.

An echocardiogram will be performed at screening Visit 1 and results confirmed centrally to assess study eligibility, as indicated in the Schedule of Assessments (Table 1).

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. Any additional repeat testing may be considered 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, or who fails to complete screening activities due to unforeseen or unavoidable circumstances, may be rescreened once after consultation with the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment. A patient will be re-consented if rescreening occurs outside of the 45-day screening window. In this case, all screening procedures must be repeated.

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

As noted in Table 1, in situations where a Month 6 (Day 176-183), Month 9 (Day 260-267), and/or Month 12 (Day 365-372) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.

For the open-label extension period, as noted in Table 2, in situations where a Month 18 (Day 554-561), Month 21 (Day 638-645), and/or Month 24 (Day 743-750) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the

study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 18, 21, and/or 24 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 18 up to Day 592; Month 21 up to Day 697; Month 24, up to Day 774.

6.2.1. 6-Minute Walk Test (6-MWT)

The 6-MWT, which will be assessed as the primary endpoint, is an assessment of functional exercise capacity. The 6-MWT will be administered by staff trained in the procedure per the relevant study manual. The staff administering the 6-MWT will be different from the Investigator or designee managing the care of the patient.

The 6-MWT will be performed at each of the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). At screening Visit 1, the 6-MWT will be administered for study eligibility purposes (per inclusion Criterion 6 [Section 4.1]). At screening Visit 1, prior to conducting the 6-MWT, 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.

On Day 1 (baseline), which is a dosing day, the 6-MWT will be performed prior to study drug administration. (No other dosing days have a 6-MWT assessment.)

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 within the permitted visit window.

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.

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

A 1.5-month window will be used to group 6-MWT assessments to the Month 6 (Weeks 25-26), Month 9 (Weeks 37-38), and Month 12 (Weeks 52-53) visits. During the double-blind period, a patient may opt to begin tafamidis treatment or to discontinue study treatment, in which case they would complete a Pre-tafamidis Drop-in Visit (Table 1) or Early Treatment Discontinuation Visit (Table 2), respectively. To avoid the potential training effect from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be collected for the following time periods: Day 2 to Day 214 (for Month 6), Day 215 to Day 319 (for Month 9), and Day 320 to Day 417 (for Month 12).

Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit); no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed per the Schedule of Assessments (Table 1).

6.2.2. 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-OS will be assessed for the first secondary endpoint.

The KCCQ questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

6.2.3. Deaths, Hospitalizations, and Urgent Heart Failure Visits

All deaths and hospitalizations will be recorded at Day 1 post dose and throughout the study as specified as part of AEs monitoring (see Section 6.5.7) and per the Schedule of Assessments (Table 1 and Table 2). All urgent HF visits will also be recorded in the eCRF.

Reasons for deaths and hospitalizations will be adjudicated by an independent Adjudication Committee (Section 3.8). Urgent HF visits will also be adjudicated.

6.2.4. Modified Body Mass Index (mBMI)

The nutritional status of patients is evaluated using the mBMI, calculated as the product of body mass index (BMI) (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

Weight, height, and serum albumin (collected as part of the serum chemistry panel) will be collected pre-dose at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). The site will not perform the calculation for mBMI.

6.2.5. Cardiac Assessments

Manifestations of cardiac amyloid involvement will be assessed via cardiac biomarker, NYHA class, echocardiograms, CMR, and technetium scintigraphy imaging, as described.

Qualified personnel will be required to administer cardiac imaging assessments as specified in the respective reference manuals.

6.2.5.1. Cardiac Biomarkers

The cardiac biomarkers NT-proBNP and troponin I will be used to assess cardiac stress and heart failure severity. These biomarkers have been shown to be prognostic of outcomes in HF, including in ATTR amyloidosis.[Damy 2016; Kristen 2017; Merlini 2016] Blood samples will be drawn to measure cardiac biomarker levels at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2) and will be measured at a central laboratory. At screening Visit 1, only NT-proBNP will be assessed for eligibility purposes.

Details on cardiac biomarker sample collection, processing, and storage will be provided in a Study Laboratory Manual.

6.2.5.2. ATTR Amyloidosis Disease Stage

Based on published data from Gillmore et al, the ATTR amyloidosis disease staging used for this protocol stratifies patients with ATTR amyloidosis with cardiomyopathy (both hATTR and wtATTR) into prognostic categories using the serum biomarkers NT-proBNP and eGFR.[Gillmore 2018] Patients are categorized as follows:

- Stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min/1.73 m^2
- Stage 2 (intermediate risk): all other patients not meeting criteria for Stages 1 or 3
- Stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 ml/min/1.73 m^2

Based on published data, this staging system discriminates between patients with median survival of ~6 years, ~4 years, and ~2 years for Stage 1, Stage 2, and Stage 3, respectively.

6.2.5.3. 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 Schedule of Assessments (Table 1 and Table 2). The score collected at screening will be used to determine eligibility.

6.2.5.4. Echocardiogram

Echocardiographic parameters will be used for assessment of cardiac structure and function. Echocardiograms will be performed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2), and analyzed at a central cardiac imaging core lab.

Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

6.2.5.5. Technetium Scintigraphy Imaging

At select sites, in a subset of approximately 100 patients, technetium scintigraphy will be collected according to the Schedule of Assessments (Table 1 and Table 2), as an optional exploratory imaging assessment, to assess cardiac amyloid involvement. Based on local practice standards, either ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc], or ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) can be used as the tracer. Technetium scintigraphy images will be interpreted at a central imaging core laboratory. Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

For patients in whom technetium scintigraphy is performed as a study efficacy parameter, the results of the baseline scan must be reviewed by the central reader and confirmed to be consistent with the diagnosis of ATTR amyloidosis prior to randomization.

At select sites where technetium scintigraphy is being performed as an exploratory efficacy assessment, patients may be exempt from the baseline scan if technetium scintigraphy has been performed prior to study entry as part of the patient's clinical care within 6 months prior to the baseline assessment. In such cases, the historical technetium scintigraphy examination performed prior to study entry as part of the patient's clinical care should be collected and transferred to the central imaging core laboratory for interpretation; if the historical scan cannot

be transferred to the central reader, or is deemed by the central reader to be of inadequate quality for interpretation, the patient should not participate in this optional efficacy assessment.

6.2.5.6. Cardiac Magnetic Resonance (CMR)

At select sites, in a subset of patients (≤60 patients), CMR will be collected according to the Schedule of Assessments (Table 1 and Table 2), as an optional exploratory imaging assessment to assess cardiac amyloid involvement. CMR imaging with late gadolinium enhancement will only be performed on patients without contraindications (ie, pacemakers, severe renal failure with eGFR <30 mL/min/1.73 m^2, defibrillators, or allergy to gadolinium).

Details for image acquisition and upload for central review can be found in the relevant study manual.

6.2.6. Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN)

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that assesses 5 domains: physical function, large-fiber neuropathy, activities of daily living, symptoms, small-fiber neuropathy, and autonomic neuropathy. The total score ranges from -4 (best possible quality of life) to 136 points (worst possible quality of life).[Vinik 2005; Vinik 2014]

The Norfolk QoL-DN questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

6.2.7. Polyneuropathy Disability (PND)

Physician assessment of ambulation via PND score [Coutinho 1980; Yamamoto 2007] will be evaluated only at screening to assess eligibility for the study as specified in the Schedule of Assessments (Table 1). PND scoring is described in Section 10.1.

6.3. Pharmacodynamic Assessments

In this study, serum samples for measurement of TTR levels will be collected for the assessment of PD effects. TTR levels will be determined by a validated enzyme-linked immunoassay (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 Schedule of Assessments (Table 1 and Table 2). To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, blood samples for assessment of TTR protein may be collected by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of plasma concentrations of ALN-18328 (siRNA component of patisiran) and 2 lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) during the double-blind period at the timepoints specified in the Schedule of Assessments (Table 1). To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel

and other restrictions related to the COVID-19 pandemic, these blood samples may be collected at the study center, or by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.

Plasma PK samples will be collected: predose (within 1 hour of planned study drug dosing); at the end of the infusion (+5 minutes); and 30 minutes after the end of the infusion (+15 minutes) at the specified visits.

For patients who discontinue treatment early during the double-blind period, a single PK sample will be taken at any time during the Early Treatment Discontinuation Visit, per the Schedule of Assessment (Table 2).

Actual dates and times of sample collection will be recorded.

Plasma concentrations of the 3 analytes will be determined using validated assay methods. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

PK parameters will be analyzed, whenever possible, as outlined in Section 7.2.7.

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 in addition an independent DMC as described in Section 3.7.

In situations where a study visit is not completed at the study center, offsite (eg, at home) assessments may be completed within the study visit window as follows:

- Routine assessments (ie, vital signs and weight, blood collection, pregnancy testing, physical examinations, and ECGs) may be performed at a location other than the study center (eg, at home) by a trained healthcare professional at all timepoints, where applicable country and local regulations and infrastructure allow. The Investigator or qualified designee will review all ECGs, including those collected by a healthcare professional outside of the study center.
- Collection of relevant safety information: The study physician (or delegate) must, at a minimum, verbally contact the patient within the expected study visit window to assess relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, vital status). This information may also be collected by a home healthcare professional as part of an offsite study visit.
- Blood samples for assessment of ADA may be collected by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, 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 10 minutes. Blood pressure should be taken using the same arm. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary 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 sign assessments, as medically 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 Schedule 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 Schedule 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.

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.

6.5.4. Electrocardiogram

12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval will be obtained, as specified in the Schedule of Assessments (Table 1 and Table 2). Patients should be supine for at least 5 minutes before each ECG is obtained. The 12-lead ECGs will be performed in triplicate at baseline, with readings approximately 1 minute apart. At all other time points, a single 12-lead ECG will be performed.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn, when possible.

The Investigator or qualified designee will review all ECGs, including those collected by a healthcare professional outside of the study center, to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These

assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator. Recordings will be archived in the patient's files.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. 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 laboratory tests and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 3 and will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 3, which are performed at the clinic 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.

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 3: 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 and eGFR (using the MDRD formula)	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Coagulation (at Screening)	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.5.5.1)	
Antidrug antibodies	

Pregnancy Testing/FSH Screening (see Section 6.5.5.2)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; MDRD=modification of diet in renal disease; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid.

6.5.5.1. Immunogenicity

Serum samples will be collected to evaluate the presence of antidrug antibodies (ADA) as outlined in the Schedule of Assessments (Table 1). Details regarding the blood volume, processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

A validated ELISA will be used that specifically detects antibodies to PEG_{2000}-C-DMG, which is a component of patisiran-LNP. Serum samples will first be analyzed with a screening assay. Samples testing positive for ADA in the screening assay will be further evaluated in a confirmatory assay. For the samples that tested positive for ADA in the confirmatory assay, the ADA titer will then be determined as the reciprocal of the highest dilution of the sample that yielded a positive ADA test result.

6.5.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. 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 6.5.7.7 for follow-up instructions).

In situations where a pregnancy test was missed as per the Schedule of Assessments because of the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center, a pregnancy test must be performed prior to receiving the next dose of study drug.

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

6.5.6. Vital Status Check

A vital status check will be performed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

Due to the inclusion of all-cause mortality in the secondary endpoint analysis, a medical records release form will be required of all patients for the purpose of obtaining vital status information

from the patient's physician or from death registries. The signing of this medical records release form is in addition to the ICF. 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.

6.5.7. Adverse Events

6.5.7.1. 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 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

An 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

No AEs of clinical interest are defined for this study.

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 AE.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. AEs 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.

6.5.7.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, 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.

All IRRs will be recorded as AEs. All information on IRRs is to be recorded on the applicable eCRF per the CRF completion guidelines.

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 to determine if an ophthalmological assessment is needed. 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.

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

Not applicable. There were no AEs of Clinical Interest identified for this study.

6.5.7.4. 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 6.5.7.1 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 Reference 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.

6.5.7.5. 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 Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.7.6. 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.

6.5.7.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 12 weeks following the last dose of study drug, 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 12 weeks after the last dose of study drug.

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 6.5.7.4.

6.5.7.8. Overdose Reporting

An overdose is defined as any dose 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. In the event of an overdose, the actual dose administered must be recorded as specified in the Pharmacy Manual.

All reports of overdose (with or without an AE) must be reported within 24 hours following the instructions outlined in the Pharmacy Manual for reporting an overdose.

6.5.8. 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.

6.6. Biomarkers and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the

well-described heterogeneous manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of patisiran.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2). Potential exploratory investigations may include RNA or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

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

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

The planned enrollment for this study is 300 patients. For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a mean difference between treatment groups at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment (Section 7.2.10).

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 12-month, double-blind period. More complete plans, including planned analyses for the open-label extension period, will be detailed in the SAP. 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 data summaries to help understand any impact of COVID-19 on efficacy and safety assessments 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 randomized patients who received any amount of study drug, grouped according to the randomized treatment arm.
- Safety Analysis Set: All patients who received any amount of study drug, grouped according to the treatment actually received.
- PK Analysis Set: All patients who received any amount of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- 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.

Efficacy endpoints will be analyzed using the Full Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology 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 and overall for the FAS and Safety Analysis Set.

7.2.5. Efficacy Analyses

The overall Type I error rate will be strongly controlled at a 2-sided 0.05 significance level for the primary and secondary endpoints using a fixed sequential testing procedure at the final analysis. The primary endpoint will be compared between treatment arms at the 0.05 significance level. If the test of the primary endpoint is statistically significant, then the secondary endpoints will each be tested in the order specified in the Secondary Endpoints section

(see Section 2). If a test of the primary or a secondary endpoint is not statistically significant, the testing of the remaining endpoints in the sequence will stop.

For patients who were tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

7.2.5.1. Primary Endpoint

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, the treatment-by-visit interaction, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), and age (<75 vs ≥75 years) as fixed factors, and patient as a random effect. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

Sensitivity analyses will be detailed in the SAP.

7.2.5.2. Secondary Endpoints

Secondary endpoints are described in Section 2.

KCCQ-OS will be analyzed using a similar MMRM model as used for the primary endpoint.

The composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT will be analyzed using a generalized rank-based win ratio method, which makes pairwise comparisons (for all possible patisiran/placebo patient pairs) of the 3 components in the hierarchical order specified above. The point estimate for the win ratio is defined as the total number of better outcomes divided by the total number of worse outcomes in the patisiran group. The detailed algorithm for assessment of this endpoint will be provided in the SAP.

The composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits will be analyzed using an Andersen-Gill model stratified by baseline tafamidis (yes vs no), including treatment, genotype (hATTR vs wtATTR), NYHA Class (I/II vs III), and age (<75 vs ≥75 years) as covariates.

Patients who undergo a heart transplantation and/or ventricular assist device placement after randomization will be handled in the same manner as death in the primary analyses of mortality related endpoints.

Deaths and hospitalizations due to COVID-19 will be excluded from the primary analyses of endpoints involving all-cause death and/or all-cause hospitalizations. Analyses of the individual components of the composite endpoints will be detailed in the SAP.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

7.2.5.3. Exploratory Endpoints

Descriptive summaries will be provided for the exploratory endpoints (Section 2), and additional analyses may be conducted. Details will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

The PD endpoint is serum TTR. Summary tables will be provided for observed values, change and percentage change from baseline for each scheduled time point. In addition, the maximum and mean percentage reduction over 12 months will be summarized.

7.2.7. Pharmacokinetic Analysis

7.2.7.1. Pharmacokinetic Analysis

Plasma concentrations of ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG will be obtained using a model-independent method. PK exposure parameters will include: maximum plasma concentration at the end of infusion (C_{max}), 30-minute post-infusion concentration ($C_{p(30min)}$), and pre-infusion concentration (C_{min}). In addition, the steady-state C_{max} ($C_{max,ss}$), steady-state $C_{p(30min)}$ ($C_{p,ss(30min)}$), and steady-state C_{min} ($C_{min,ss}$) will be calculated as the average of the respective values at Week 24, Week 36, and Month 12.

The PK exposure parameters will be summarized by visit, and the steady-state PK parameters will be summarized.

7.2.7.2. Exposure-Response Analysis

Mean and maximum percent TTR reduction from baseline will be summarized by quartiles of the steady state PK parameters for all 3 analytes. Change from baseline at Month 12 in clinical efficacy parameters may also be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

PK exposure will be summarized by mortality status. In addition, the incidence of AEs and SAEs will be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

7.2.7.3. Population PK, PK/PD, and Disease Progression Modelling Analysis

Population PK, PK/PD, and disease progression modelling analyses may be performed, if appropriate. If performed, the analyses would be conducted according to a pre-specified analysis plan and reported separately.

7.2.8. Safety Analyses

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 examinations. The 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 and Preferred Term. The frequency and percentage of patients experiencing AEs, SAEs, related AEs, and AEs leading to discontinuation will be summarized by System Organ Class (SOC) and PT. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics will be provided for clinical laboratory data, ECG, and vital signs data, summarizing the observed values and change from baseline over time. Laboratory shift tables from baseline at the worst post-baseline values will be presented. 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. Sample Size Re-assessment

Patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period, which could result in a loss of statistical power. An interim assessment may be performed to assess the impact of tafamidis drop-in on the power and the potential need to increase the sample size. The interim assessment, if conducted, would examine the overall tafamidis drop-in rate in a blinded manner (ie, a non-comparative assessment of the drop-in rate); therefore, no impact on the type I error is expected and no multiplicity adjustment will be made. A detailed sample size re-estimation plan will be outlined in a separate document prior to implementation.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the informed consent form (see Section 4.3.2).

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 required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries. 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 6.5.7. 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 serious 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. CRFs 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

10.1. Polyneuropathy Disability (PND) Scores

Stage	Description
0	No symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capacity but ability to walk without a stick or crutches
IIIA **IIIB**	Walking with the help of one stick or crutch Walking with the help of two sticks or crutches
IV	Confined to a wheelchair or bedridden

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.

10.3. Categorization of Infusion-Related Reactions

Signs and symptoms of an IRR usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritus/itching,

rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, urticaria (hives, welts, wheals), vomiting.

Categorization of IRRs is as follows:

Categorization	**Description**
Mild	Mild reaction: infusion may be continued; if intervention is indicated it is minimal and additional treatment (other than paracetamol for delayed reactions) is not required.
Moderate	Moderate reaction: requires treatment including more intensive therapy (eg, IV fluids, NSAIDs) in addition to infusion interruption but responds promptly to medication. Treatment is indicated for ≤24 hours.
Severe	More than moderate reaction: not rapidly responsive to medication or to interruption of infusion; and/ or prolonged (treatment is indicated for >24 hours); recurrence of severe symptoms following initial improvement.

ALN-TTR02-011 PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES DATED 22 MAY 2020

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

1. RATIONALE FOR PROTOCOL AMENDMENT

The primary purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to Investigators in a Dear Investigator Letter dated 07 April 2020 to ensure the safety of study participants while minimizing risks to study integrity amid the Coronavirus disease 2019 (COVID-19) pandemic. These changes, which were adopted immediately by the Investigator site, are in line with guidances published by the European Medicines Agency and the US Food and Drug Administration on the conduct of clinical trials during the COVID-19 pandemic [EMA 2020; FDA 2020] and are outlined in Section 1.1 and a detailed summary of the protocol changes is provided in Section 2.1.

This protocol amendment also incorporates changes to the study endpoints, inclusion and exclusion criteria, and clarifications regarding doxycycline use and efficacy assessment procedures. These changes are summarized in Section 2.1 and a detailed summary of changes is provided in Section 2.2; the changes will not be implemented until appropriate Health Authority and Ethics Committee (EC) and/or Institutional Review Board (IRB) approval.

1.1. 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, and a detailed summary of the USMs is provided in Section 2.1.

- **Expanded Study Drug Dosing Outside the Study Center (eg, at Home)**

  Administration of study drug outside the study center (eg, at home or offsite) by a health care professional is permitted at all timepoints (in both the double-blind and open-label periods) provided the patient has tolerated at least 2 doses of study drug administered at the study center. Previously, dosing outside the study center was only permitted during the open-label extension period, and only after tolerating at least 3 consecutive doses.

  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. Based on the overall safety profile of patisiran, the frequency of infusion related reactions (IRRs) decreases over time and IRRs do not increase in severity. When IRRs have occurred, most have been mild or moderate in severity, have not required any treatment, and have not resulted in interruption during the infusion or change in administration. When infusions have been interrupted due

to an IRR, these have primarily been reported in patients during the first 2 infusions. Thus, for patients who tolerate infusions, these data support offsite study drug administration (eg, at home) following 2 doses administered at the study center. Offsite dosing of study drug will be performed by a health care professional, with oversight of the Investigator, allowing for ongoing appropriate monitoring of the patient.

- **Corticosteroid Tapering**

  Corticosteroid tapering may be performed at the study center or at a location other than the study center (eg, at home) (previously was only permitted at the study center), after consultation with the Medical Monitor. In addition, corticosteroid tapering is now permitted during the double-blind period for patients who are tolerating their infusions well. (Previously, tapering for patients who are tolerating their study drug infusions well was only permitted during the open-label period.)

  This change was implemented to allow for reduction of steroids, where it is deemed in the best interest of the patient by the investigator, in the context of expanded offsite dosing (eg, at home) necessitated by the COVID-19 pandemic as outlined above. Patisiran dosing, and thus steroid tapering, will be performed by a health care professional, with oversight of the investigator, allowing for appropriate monitoring of the patient. Support for this approach comes from a review of data from patisiran studies (ALN-TTR02-003, ALN-TTR02-004, and ALN-TTR02-006) where IRRs were infrequent and mild among patients who had tapered corticosteroids and that corticosteroid tapering was not associated with an increase in the rate of IRRs.

- **Premedication Equivalents may be Administered Orally**

  Clarified that oral premedication equivalents are permitted, but must be administered in the presence of a healthcare professional.

- **Extended Efficacy Assessment Visits Window**

  The window for efficacy assessment visits at the study center was extended in situations where those visits are unable to be completed due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug. This change allows 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.

  Thus, in the situations described above, where a Month 6 (Day 176-183), Month 9 (Day 260-267), and/or Month 12 (Day 365-372) study visit is unable to be completed or patients are unable to receive their scheduled doses of study drug, after consultation with the Medical Monitor, efficacy assessments may be extended as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed. For the

open-label extension period, the windows for study visits are also extended (see Section 2.1).

- **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 pandemic 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.

- **Eliciting Adverse Events**

  Added that, in situations where a study visit is unable to be completed at the study center, the study physician (or delegate) must, at a minimum, verbally contact the patient within the expected study visit window to assess relevant safety information (eg, adverse events [AEs], concomitant medications, hospitalizations/procedures, vital status). This information may also be collected by a home healthcare professional as part of an offsite study visit.

- **Routine Assessments**

  Added that, in situations where a study visit is not completed at the study center, offsite (eg, at home) assessments may be completed within the study visit window as follows:

  – Routine assessments (ie, vital signs and weight, blood collection, pregnancy testing, physical examinations, and ECGs) may be performed at a location other than the study center (eg, at home) by a trained healthcare professional at all timepoints, where applicable country and local regulations and infrastructure allow.

  – Blood samples for assessment of transthyretin (TTR) protein, pharmacokinetics (PK), and anti-drug antibodies (ADA) may be collected by a trained healthcare professional at a location other than the study center (eg, at home).

- **Timing of Physical Examinations**

  Reduced the frequency of physical examinations and aligned the timing with onsite efficacy assessment visits to reduce potential exposure to COVID-19.

- **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.

- **Study Administration Text**

  Text was updated to provide clarification of Investigator responsibilities regarding communication of new study information to patients and Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

1.2. Changes Not Related to Urgent Safety Measures

Several additional changes are being implemented, which are outlined below, and a detailed summary is provided in Section 2.1.

- **Composite Clinical Endpoints**

  The adjudicated composite clinical endpoints (2 secondary endpoints and the first exploratory endpoint) were revised to include urgent heart failure (HF) visits. The corresponding objectives were similarly revised.

  Specifically, the secondary and exploratory endpoints that include "all-cause mortality and frequency of CV-related hospitalizations" were changed to include "all-cause mortality and CV events", where "CV events" are defined in Section 2 as CV hospitalizations plus urgent HF visits. To be included, an urgent HF visit must satisfy 2017 criteria developed by the Standardized Data Collection for Cardiovascular Trials Initiative and the US Food and Drug Administration.[Hicks 2018]

  Similarly, the composite endpoint that includes "all-cause mortality and frequency of all-cause hospitalizations" will be revised to include "all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits".

  The change is being made because the management of HF is likely to shift from the hospital to the outpatient setting due to the COVID-19 pandemic. Inclusion of urgent HF visits will also account for regional variations in practice standards, which may be further exacerbated by the impact of COVID-19.

  In addition, deaths and hospitalizations due to COVID-19 will be excluded from these composite endpoints. The effects of the COVID-19 pandemic on global health are unprecedented, and the pandemic is expected to have a confounding effect on deaths and hospitalization events in the study.

The following inclusion and exclusion criteria were modified based on feedback from Investigators that some criteria are unnecessarily strict and exclude suitable patients in the target population of ATTR amyloidosis with cardiomyopathy. In addition, clarification is provided for some criteria.

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

  Clarified that the use of on-label, commercial tafamidis treatment at study entry must be for the treatment of ATTR amyloidosis with cardiomyopathy, at the approved dose in the country of use. This clarification of the inclusion criterion text is consistent with text elsewhere in the protocol (in Section 5.3.1) and reflects the original intent of the sponsor.

- **Inclusion Criterion 7, NT-proBNP**

  The inclusion criterion for NT-proBNP was changed to a lower threshold of >300 ng/L (previously was >600 ng/L); the upper threshold (<8500 ng/L) remains unchanged. In addition, the criterion added that patients with permanent or persistent atrial fibrillation must have a screening NT-proBNP of >600 ng/L and <8500 ng/L.

The lower limit for NT-proBNP was decreased from 600 to 300 ng/L to better represent the real-world population of patients with ATTR amyloidosis with cardiomyopathy and to include patients who are likely to benefit from treatment. There is no clinically meaningful difference between 300 and 600 ng/L as the lower limit for patients who are not in atrial fibrillation. The threshold of >600 ng/L for patients with atrial fibrillation accounts for the known, additional secretion of NT-proBNP from the fibrillating atrial myocardium.

- **Exclusion Criterion 5b, Total Bilirubin**

  Revised exclusion criterion for total bilirubin to >2×ULN for all patients (previously was >ULN, with patients with Gilbert's syndrome being eligible if total bilirubin was <2×ULN).

  The target population of patients with ATTR amyloidosis with cardiomyopathy is prone to hepatic congestion from HF. The change in the criterion is to avoid excluding patients in the target population who have mild elevations in bilirubin, and to better reflect the real-world population of patients with ATTR amyloidosis with cardiomyopathy. Furthermore, raising the exclusion threshold for total bilirubin is not expected to affect the risk of hepatic adverse effects. In the patisiran clinical development program, the frequency of hepatic adverse events has been low and consistent with that observed in the placebo-controlled experience. No significant changes in liver function tests have been reported in patients treated for up to 5 years. Based on the overall safety profile to date, there have been no hepatic safety concerns. Refer to the Investigator's Brochure, Section 5.4.6.2 (Hepatic Safety) for more information.

- **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 6 months), as this was determined to be a reasonable amount of time to avoid any confounding effects from diflunisal on the baseline assessments.

In addition, the following changes have also been implemented for this study:

- **Doxycycline Use**

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

- **Clarification for efficacy assessments**

  Added a clarification that the study personnel performing assessments related to the primary and secondary efficacy endpoints will not reference the results of any previous assessments (previously, the protocol indicated that the assessor would be blinded to the results).

  For the primary endpoint measure (6-minute walk test), the protocol specifies that the same assessor be used for all assessments, which is critical for consistency across visits for a given patient. Since the assessor may remember a patient's prior test, it is not possible for the assessor to be blinded to previous results. However, the

clarification of instructing the assessor not to refer to the prior results when conducting an assessment will limit bias in the assessment.

- **Screening Assessments**

  Added a clarification that TTR genotyping may be conducted at a central laboratory; or a local laboratory may be selected by the study center in consultation with the Medical Monitor. If a diagnostic result to confirm ATTR amyloidosis is not available at Screening for the assessment of eligibility per inclusion criterion 2c/d, 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.

2. 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.

2.1. Urgent Safety Measure COVID-19-related Changes to be Adopted Immediately

Purpose: Study drug administration at a location other than the study center (eg, at home) was expanded.

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

Revised text:

Study drug will be administered ~~in the clinic~~ as an approximately 80-minute IV infusion.

During the 12-month open-label extension period, all patients will receive treatment with open-label patisiran. ~~Furthermore, patients who have received ≥3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion.~~

Study drug administration at a location other than the study center (eg, at home) may be administered as follows:

- **Double-blind period: Patients who have received ≥2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.**
- **12-month open-label extension period:** ~~Furthermore, P~~**p**atients who have received ~~≥3 consecutive~~ **2** doses of **open-label** patisiran ~~on this study~~ at the **study center** with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at **a location other than the study center (eg, at** home**)**, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion.

Sections also reflecting this change:

- Synopsis

- Section 5.2.3.1
- Section 5.2.3.2

Purpose: Added permitted tapering of corticosteroid dose outside of the clinic (ie, at home). Also added corticosteroid tapering in the double-blind period for patients who are tolerating their double-blind study drug infusions well with their current corticosteroid premedication regimen.

The primary change occurs in Section 5.2.1, Premedication

Revised text:

Modifications to lower the corticosteroid dose may be made to the premedication regimen for either of the following 2 reasons:

1. **Double-blind and open-label periods:** If a patient is having difficulty tolerating the steroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the steroid premedication may be allowed for that patient after consultation with the medical monitor at any time during the study ~~(double-blind and open-label periods)~~.
2. **Double-blind period:** ~~In the open-label extension period only, f~~**F**or patients who are tolerating their **double-blind study** drug infusions well with their current corticosteroid premedication regimen (ie, no IRRs during the past 3 or more infusions), corticosteroid dose may be reduced in 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (IV) or equivalent.
    a. **Open-label period: At the start of the open-label period, patients must take dexamethasone 10 mg or the equivalent as their corticosteroid premedication. Patients taking more than 10 mg of dexamethasone at the end of the double-blind period should take the higher dose. The corticosteroid dose may then be tapered as described above if the patient is tolerating infusions. However, if a patient's steroid premedication had been decreased in the double-blind period due to their inability to tolerate the premedication regimen as described above, continuation of the reduced dose regimen (as it had been in the double-blind period) may be permitted after consultation with the Medical Monitor.**

Infusions during corticosteroid tapering ~~(and the 2 infusions after the new and stable lower corticosteroid dose is established) should~~ **may** be performed ~~in the clinic~~ **at the study center or at a location other than the study center (eg, at home)**, as described in detail in the Pharmacy Manual, **at the discretion of the Investigator and after consultation with the Medical Monitor.**

Purpose: Clarified that oral premedication equivalents are permitted.

The primary change occurs in Section 5.2.1, Premedication

Revised text:

~~For premedications not available or not tolerated intravenously, equivalents may be administered orally.~~ **Oral premedication equivalents are permitted, but must be administered in the presence of a healthcare professional.**

Purpose: Widened the window for completion of efficacy assessments at study visits.

The primary change occurs in Section 6.2, Efficacy Assessments

Added text:

As noted in Table 1, in situations where a Month 6 (Day 176-183), Month 9 (Day 260-267), and/or Month 12 (Day 365-372) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center, efficacy assessments should be completed as close as possible to the time point per the current Schedule of Assessments, but may be extended as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.

For the open-label extension period, as noted in Table 2, in situations where a Month 18 (Day 554-561), Month 21 (Day 638-645), and/or Month 24 (Day 743-750) study visit is unable to be completed at the study center due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the site, efficacy assessments should be completed as close as possible to the time point per the current Schedule of Assessments, but may be extended as follows: Month 18 up to Day 592; Month 21 up to Day 697; Month 24, up to Day 774.

Sections also reflecting this change:

- Synopsis
- Table 1 (Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments))
- Table 2 (Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up)
- Section 3.1
- Section 4.3.1
- Section 6.2.1

Purpose: Added that the Investigator will notify the Sponsor before screening patients.

The primary change occurs in Section 6.1, Screening Assessments

Added text:

To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, 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 limitations.

Purpose: Added that patients who failed screening due to situations related to the COVID-19 pandemic may be allowed to rescreen after consultation with the Medical Monitor.

The primary change occurs in Section 6.1.2, Rescreening

Added text:

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

Purpose: In situations where a study visit is not completed at the study center, offsite (eg, at home) assessments may be completed within the study visit window as follows:

- *Routine assessments outside of the clinic (eg, at home) by a trained healthcare professional at all timepoints, where applicable country and local regulations and infrastructure allow.*
- *Verbal contact with the patient by the Investigator or designee within the study visit window to assess relevant safety information (including, but not limited to, adverse events (AEs), concomitant medications, hospitalizations/procedures) if a study visit is not able to be completed at the site or offsite by an HCP.*
- *Blood sample collection for assessment of ADA by a trained healthcare professional at a location other than the study center (eg, at home).*

The primary change occurs in Section 6.5, Safety Assessments

Added text:

In situations where a study visit is not completed at the study center, offsite (eg, at home) assessments may be completed within the study visit window as follows:

- **Routine assessments (ie, vital signs and weight, blood collection, pregnancy testing, physical examinations, and ECGs) may be performed at a location other than the study center (eg, at home) by a trained healthcare professional at all timepoints, where applicable country and local regulations and infrastructure allow. The Investigator or qualified designee will review all ECGs, including those collected by a healthcare professional outside of the study center.**
- **Collection of relevant safety information: The study physician (or delegate) must, at a minimum, verbally contact the patient within the expected study visit window to assess relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, vital status). This information may also be collected by a home healthcare professional as part of an offsite study visit.**
- **Blood samples for assessment of ADA may be collected by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.**

Sections also reflecting this change:

- Section 4.3.3
- Section 6.5.4
- Section 6.5.5.2

Purpose: Reduced the frequency of physical examinations and changed the timing to align with efficacy assessment visits to reduce potential exposure to COVID-19.

The primary change occurs in Table 1 and Table 2, Schedules of Assessments:

Revised text:

- Table 1:
  - Symptom-directed physical examinations were removed from Weeks 3, 6, 9, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48.
  - Symptom-directed physical examinations were added to Weeks 25/26, 37/38.
  - A full physical examination was moved from Week 51 to Week 52/53.

- Table 2:
    - Symptom-directed physical examinations were removed from Weeks 54, 57, 60, 63, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105.
    - Symptom-directed physical examinations were added to Weeks 78/80, 91/92, 106/107.

Purpose: Blood sample collection for assessment of TTR protein and for assessment of PK are being allowed at a location other than the study center (eg, at home), by a trained healthcare professional.

The primary changes occur in Section 6.3, Pharmacokinetic Assessments, and Section 6.4, Pharmacodynamic Assessments

Revised text:

For this assessment, blood samples will be collected prior to dosing according to the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). **To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, blood samples for assessment of TTR protein may be collected by a trained healthcare professional at a location other than the study center (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.**

…

Blood samples will be collected for assessment of plasma concentrations of ALN-18328 (siRNA component of patisiran) and 2 lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) during the double-blind period at the timepoints specified in the Schedule of Assessments (Table 1). **To ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic, these blood samples may be collected at the site, or by a trained healthcare professional at a location other than the site (eg, at home) at time points coinciding with the dosing visits closest to the intended sampling time points.**

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 6.5.8, 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

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

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.

…

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)**.

2.2. Changes Not Related to Urgent Safety Measures to be Implemented After Regulatory Authority and Ethics Committee Approval

Purpose: The composite clinical endpoints (2 secondary endpoints and the first exploratory endpoints) were revised to include urgent HF visits; the corresponding objectives were also revised.

The primary change occurs in Section 2, Objectives and Endpoints

Revised text:

Objectives

- Patient mortality ~~and~~**,** hospitalizations**, and urgent heart failure (HF) visits**

- All-cause mortality and CV ~~related hospitalizations~~ **events**

Endpoints

- Composite endpoint of all-cause mortality, frequency of cardiovascular (CV) ~~related hospitalizations~~ **events (CV hospitalizations and urgent HF visits)** and change from baseline in 6-MWT over the 12-month double-blind period
- Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations **and urgent heart failure (HF) visits** over the 12-month double-blind period
- Composite endpoint of all-cause mortality and frequency of (CV) ~~related hospitalizations~~ **events (CV hospitalizations and urgent HF visits)** over the 12-month double-blind period

Sections also reflecting this change:

- Synopsis
- Section 3.8, Adjudication Committee
- Section 7.2.5.2, Secondary Endpoints

Purpose: Deaths and hospitalizations due to COVID-19 will be excluded from the primary analyses of endpoints involving all-cause death and/or all-cause hospitalizations.

The primary change occurs in Section 7.2.5.2, Secondary Endpoints

Added text:

Deaths and hospitalizations due to COVID-19 will be excluded from the primary analyses of endpoints involving all-cause death and/or all-cause hospitalizations. Analyses of the individual components of the composite endpoints will be detailed in the SAP.

Purpose: Eligibility requirements have been broadened for inclusion Criterion 7 and exclusion Criterion 5b, and exclusion Criterion 9.

The primary change occurs in Section 4, Selection and Withdrawal of Patients

Revised text:

4.1 Inclusion Criteria

…

7. Screening NT-proBNP >~~600~~**300** ng/L and <8500 ng/L**; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP >600 ng/L and <8500 ng/L**.

…

4.2. Exclusion Criteria

5. Has any of the following laboratory parameter assessments at screening:

a. Aspartate transaminase (AST) or alanine transaminase (ALT) levels >2.0 × the upper limit of normal (ULN).

b. Total bilirubin >**2**×ULN. ~~Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if total bilirubin <2 × ULN.~~

…

9. Is currently taking diflunisal; if previously on this agent, must have at least a ~~6 month~~**30-day** wash-out prior to dosing (Day 1).

Purpose: Added clarification for inclusion Criterion 4b.

The primary change occurs in Section 4.1, Inclusion Criteria

Revised text:

4. Patient meets one of the following criteria:

a. Tafamidis naïve; in addition to patients who have never taken tafamidis, those who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.

b. Currently on tafamidis (for ≥6 months) and has demonstrated disease progression, as determined by the Investigator. (At the time of study entry, tafamidis treatment must be on-label use of commercial tafamidis **for the treatment of ATTR amyloidosis with cardiomyopathy at the approved dose in the country of use**.)

Purpose: Added clarification that use of doxycycline is permitted for short-term treatment of infection.

The primary change occurs in Section 5.3, Concomitant Medications and Procedures

Revised text:

Inotersen, doxycycline, ursodeoxycholic acid, tauroursodeoxycholic acid, and diflunisal are also prohibited during the study **(see exclusion Criterion 10 in Section 4.2). Doxycycline is permitted if being taken for short-term treatment of infection**.

Purpose: Added clarification that study personnel performing assessments related to the primary and secondary efficacy endpoints will not reference the results of any previous assessments.

The primary change occurs in Section 3.6, Blinding

Revised text:

In addition, the study personnel performing assessments related to the primary and secondary efficacy endpoints will ~~also be blinded to~~ **will not reference** the results of any previous assessments.

Purpose: Added clarification that TTR genotyping may be conducted at a central laboratory; or a local laboratory selected in consultation with the Medical Monitor. Added that diagnostic testing for inclusion criterion 2c/d 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.

The primary change occurs in Section 6.1, Screening Assessments

Revised text:

If a genetic test result that shows the presence or absence of a TTR pathogenic mutation, which would be consistent with either wtATTR or hATTR, is not available at Screening for the assessment of eligibility (Section 4.1, inclusion **C**~~c~~riterion 2a), genotyping may be conducted at a **central** laboratory**. Alternatively, a local laboratory may be** selected by the ~~site~~ **study center** in consultation with the Medical Monitor.

The study eligibility biopsies and technetium scintigraphy noted in inclusion Criterion 2 are intended to be historical, as part of the patient's clinical care and diagnosis, and are not performed as part of the study.

If a diagnostic result that confirms ATTR amyloidosis is not available at Screening for the assessment of eligibility (inclusion Criterion 2c/d), 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.

3. REFERENCES

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, Version 2 (27/03/2020; updated 27/03/2020; updated 28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards (03/2020; updated on 16/04/2020). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic

Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137(9):961-72.

CLINICAL STUDY PROTOCOL
ALN-TTR02-011
DATED 20 DECEMBER 2019

Protocol Title:	APOLLO-B: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Short Title:	APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Study Drug:	Patisiran (ALN-TTR02)
EudraCT Number:	2019-001458-24
IND Number:	141240
Protocol Date:	Original protocol, 18 April 2019 Amendment 1: 20 December 2019
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

[redacted]

20 Dec 2019

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTR02-011 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

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

Short Title

APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Study Drug

Patisiran (ALN-TTR02)

Phase

Phase 3

Study Center(s)

The study will be conducted at approximately 65 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality and hospitalizations	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV)-related hospitalizations and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations over the 12-month double-blind period

Objectives	Endpoints
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV-related hospitalizations • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV-related hospitalizations over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI) o Cardiac magnetic resonance (CMR) parameters o Technetium scintigraphy parameters o Troponin I levels o Norfolk QoL-DN
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (AEs)

Study Design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study

population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the investigator. This group will be capped at 30% of total enrollment in the study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 12-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period.

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive intravenous (IV) treatment every 3 weeks with either patisiran or placebo. Prior to receiving randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an infusion related reaction (IRR) with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. Study drug will be administered in the clinic as an approximately 80-minute IV infusion.

During the 12-month open-label extension period, all patients will receive treatment with open-label patisiran. Furthermore, patients who have received ≥3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home during the open-label extension period, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint; this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period. The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score.

Safety will be assessed throughout the double-blind and open-label extension periods of the study.

Number of Planned Patients

Approximately 300 patients are planned for enrollment in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults age 18 (or age of legal consent, whichever is older) to 85 years of age, inclusive, with ATTR amyloidosis with cardiomyopathy (hereditary or wild-type [wt]) who, at baseline, are either: 1) tafamidis naïve (on tafamidis for ≤30 days and none within 6 months prior to baseline); or 2) currently on tafamidis (for ≥6 months) with disease progression in the opinion of the investigator.

Study Drug, Dose, and Mode of Administration

Patisiran is a ribonucleic acid (RNA) interference (RNAi) therapeutic consisting of a double-stranded small interfering RNA (siRNA) targeting TTR mRNA formulated in a lipid

nanoparticle (LNP). The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG2000-C-DMG) in isotonic phosphate buffered saline.

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs.

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days. Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended patisiran dose is 30 mg.

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described above for double-blind patisiran.

Reference Treatment, Dose, and Mode of Administration

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

Duration of Treatment and Study Participation

The treatment duration in this study is up to 24 months, inclusive of a 12-month, double-blind, treatment period, and a 12-month, open-label, treatment period. The estimated total time on study for each patient is up to 26.5 months, including up to 45 days of screening, up to 24 months of treatment, and a 28-day safety follow-up period.

Statistical Methods

The planned enrollment for this study is 300 patients. Randomization (1:1) will be stratified by: 1) baseline tafamidis (yes vs no); 2) genotype (hATTR vs wtATTR); and 3) NYHA Class I or II and age < 75 years vs all other.

For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a treatment difference at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment.

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, the treatment-by-visit interaction, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), and age (<75 vs ≥75 years) as fixed factors, and patient as a random

effect. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

For patients who are tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

Safety data will be summarized descriptively.

Figure 1: Study Design

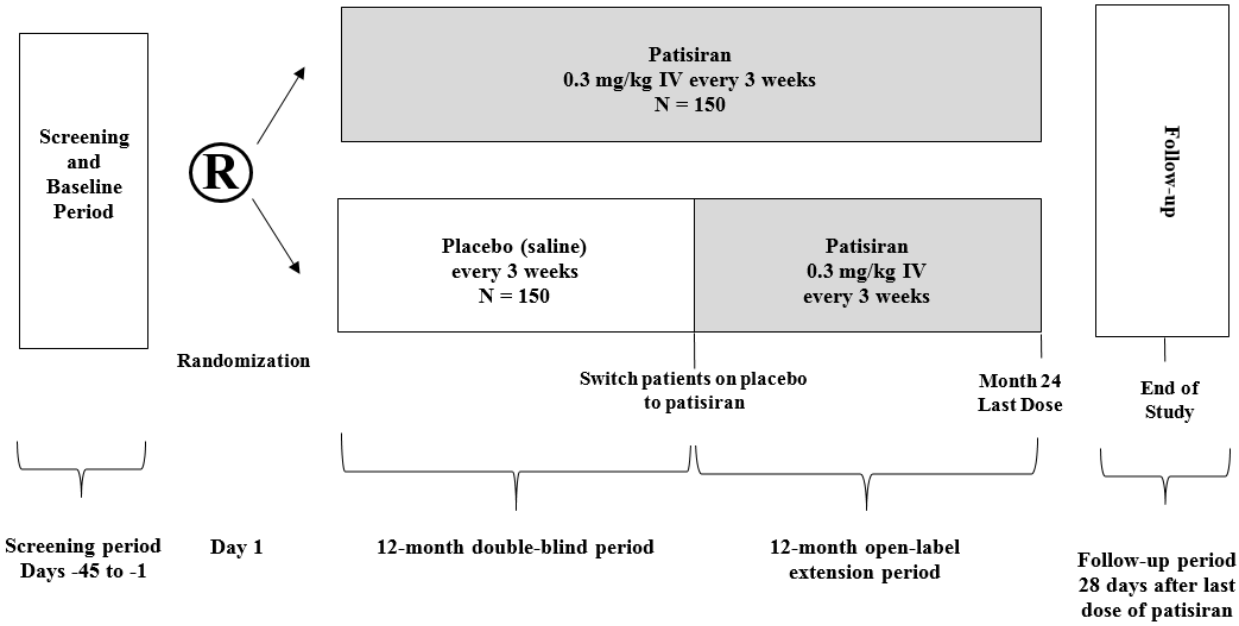

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

		Screen-ing	Baseline			Double-blind Treatment Period																		Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose																					
Study Day ±Visit Window	**For Details see Section**	**Day -45 to Day -1**		**Day 1**		**D22±3**	**D43±3**	**D64±3**	**D85±3**	**D106±3**	**D127±3**	**D148±3**	**D169±3**	**D176-D183[a]**	**D190±3**	**D211±3**	**D232±3**	**D253±3**	**D260-D267[a]**	**D274±3**	**D295±3**	**D316±3**	**D337±3**	**D358±3**	**D365-D372[a]**		
Study Week				**Week 1**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25-26**	**27**	**30**	**33**	**36**	**37-38**	**39**	**42**	**45**	**48**	**51**	**52-53**	**52-53**	**NA[b]**
Informed Consent	6.1	X																								
Inclusion / Exclusion Criteria	4.1, 4.2	X	X																							
Demographics / Medical History	6.1	X	X																							
PND Score	6.2.7	X																								
Height	6.5.2	X																								
Efficacy Assessments																										
6-MWT	6.2.1	X	X											X[d]					X[d]						X[d]	X[d]	X[d]
KCCQ	6.2.2			X										X					X						X	X	X
mBMI	6.2.4			X									X										X				X
Cardiac Biomarker Samples	6.2.5.1	NT-proBNP	X						X					X					X						X	X	X
ATTR amyloidosis disease stage	6.2.5.2		X																						X	X	X
NYHA Class	6.2.5.3	X												X					X						X		
Echocardiogram	6.2.5.4	X																							X		
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5		X																						X		
Norfolk QoL-DN	6.2.6		X																						X	X	

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	For Details see Section	Screening	Baseline			Double-blind Treatment Period																			Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose	D22±3	D43±3	D64±3	D85±3	D106±3	D127±3	D148±3	D169±3	D176-D183[a]	D190±3	D211±3	D232±3	D253±3	D260-D267[a]	D274±3	D295±3	D316±3	D337±3	D358±3	D365-D372[a]		
Study Week				Week 1		3	6	9	12	15	18	21	24	25-26	27	30	33	36	37-38	39	42	45	48	51	52-53	52-53	NA[b]
Day 1		Day -45 to Day -1																									
Pharmacodynamic Assessments																											
TTR Protein	6.3		X	X		X			X					X					X					X	X	X	X
Exploratory Biomarkers (plasma, serum)	6.6		X						X					X					X						X		
Safety Assessments																											
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	X		X	X
Weight	6.5.2	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed unless noted as full)	6.5.3	X Full	X			X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X Full		X Full	X
Single 12-lead ECG (unless otherwise indicated)	6.5.4		X (in triplicate, either visit)						X				X					X						X			X
Serum Chemistry, Liver Function Tests	6.5.5	X		X									X										X		X[e]	X[e]	X
Hematology	6.5.5	X		X									X										X				X
Coagulation	6.5.5	X																									
Vitamin A Levels				X																							
ADA (on dosing days, prior to dosing)	6.5.5.1			X		X			X				X											X			X

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

		Screen-ing	Baseline		Double-blind Treatment Period																			Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose																					
Study Day ±Visit Window	**For Details see Section**	**Day -45 to Day -1**		**Day 1**		**D22±3**	**D43±3**	**D64±3**	**D85±3**	**D106±3**	**D127±3**	**D148±3**	**D169±3**	**D176-D183[a]**	**D190±3**	**D211±3**	**D232±3**	**D253±3**	**D260-D267[a]**	**D274±3**	**D295±3**	**D316±3**	**D337±3**	**D358±3**	**D365-D372[a]**		
Study Week				**Week 1**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25-26**	**27**	**30**	**33**	**36**	**37-38**	**39**	**42**	**45**	**48**	**51**	**52-53**	**52-53**	**NA[b]**
FSH (to confirm postmenopausal, if applicable)	Table 3, 6.5.5.2	X																								
Pregnancy Test	Table 3, 6.5.5.2	X		X					X				X					X					X			
Review/Record Hospitalization, Urgent Care Visits, and Procedures			----------X----------																							
Review/Record AEs, Con Meds	6.5.7, 5.3		----------X----------																							
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																											
Plasma PK	6.4			X	X				X				X					X						X			
Drug Administration																											
Randomization	3.5 Window : 5D prior to Day 1			X																							
Premedication/ Study Drug	5.2.1, 5.2.3			X		X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; FSH=follicle-stimulating hormone; KCCQ=Kansas City Cardiomyopathy Questionnaire; M=month;

mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit.

[b] This Modified Month 12 Efficacy Visit is to be performed at Month 12 for patients who discontinued treatment early (ie, prior to Month 12), and choose to remain in the study. All patients who discontinue from study drug during the double-blind period will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including this Modified Month 12 Efficacy Visit. Such patients will also receive assessments at the Early Treatment Discontinuation Visit (7 to 14 days after their last dose of study drug); and the safety follow-up visit (28 days after the last dose of study drug) (Table 2), as described in Section 4.3.1.

[c] See Section 5.3.1; patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period. In all cases, the Pre-tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of double-blind study drug (ie, 7 to 14 days post dose). Thereafter, the patient will continue with all assessments per the Schedule of Assessments, including the Month 12 Efficacy Visit. At the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

[d] As described in Section 6.2.1, to avoid a potential training effect resulting from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be performed within each of the following time periods: Day 2 to Day 214 (includes the scheduled Weeks 25-26 assessment); Day 215 to Day 319 (includes the scheduled Weeks 37-38 assessment); and Day 320 to Day 372 (includes the scheduled Weeks 52-53 assessment). Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit [Table 2]); no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed as scheduled.

[e] Serum creatinine only.

Table 2: Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																					Early Treatment Disc Visit[b]	Follow-up
																						EOS		
		D379±3	D400±3	D421±3	D442+3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]	7- 14 Days after Last Dose	D764±10
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107	NA	109
Efficacy Assessments																								
6-MWT	6.2.1										X					X						X	X	
KCCQ	6.2.2										X					X						X	X	
mBMI	6.2.4							X										X					X	
Cardiac Biomarker Samples	6.2.5.1					X					X					X						X	X	
ATTR amyloidosis disease stage	6.2.5.2																					X		
NYHA Class	6.2.5.3										X					X						X		
Echocardiogram	6.2.5.4										X											X		
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5										X											X		
Norfolk QoL-DN	6.2.6																					X		
Pharmacodynamic Assessments																								
TTR Protein	6.3					X					X					X						X	X	X
Exploratory Biomarkers (plasma, serum)	6.6					X					X					X						X		
Safety Assessments																								
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
Weight	6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed)	6.5.3	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X		X	X
Single 12-lead ECG	6.5.4					X				X					X						X		X	

Table 2: Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																					Early Treatment Disc Visit[b]	Follow-up
																						EOS		
		D379±3	D400±3	D421±3	D442+3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]	7- 14 Days after Last Dose	D764±10
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107	NA	109
Serum Chemistry, Liver Function Tests	6.5.5							X										X				X [c]	X	X
Hematology	6.5.5							X										X					X	X
Pregnancy Test	Table 3, 6.5.5.2			X				X					X					X			X	X	X	
Review/Record Hospitalization, Urgent Care Visits, and Procedures		----------X----------																						
Review/Record AEs, Con Meds	6.5.7, 5.3	----------X----------																						
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																								
Plasma PK	6.4																						X	
Drug Administration																								
Premedication, Study Drug	5.2.1, 5.2.3	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; EOS=End of Study (visit); KCCQ=Kansas City Cardiomyopathy Questionnaire; mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit.

[b] Patients who discontinue early from study drug will be asked to complete the Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug. In addition, patients discontinuing early from study drug during the double-blind period will be encouraged to remain on the

study and complete assessments through Month 12 and complete the Modified Month 12 Efficacy Visit (see Table 1); they will also be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug as described in Section 4.3.1.

[c] Serum creatinine only.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALN-18328	siRNA targeting TTR
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APOLLO	Patisiran pivotal Phase 3 clinical study ALN-TTR02-004
AST	Aspartate aminotransferase
ATTR	Amyloid transthyretin
BMI	Body mass index
BUN	Blood urea nitrogen
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration at end of infusion
$C_{max,ss}$	Steady-state C_{max}
C_{min}	Minimum pre-infusion concentration
$C_{min,ss}$	Steady-state C_{min}
CMR	Cardiac magnetic resonance
Con Meds	Concomitant medication
$C_{p(30min)}$	30-minute post-infusion concentration
$C_{p,ss(30min)}$	Steady-state $C_{p(30min)}$
CRF	Case report form
CFR	Code of Federal Regulations
CV	Cardiovascular
DLin-MC3-DMA	1,2-Dilinoleyloxy-N,N-dimethylpropylamine
DMC	Data Monitoring Committee
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunoassay
EOS	End of study
FAS	Full analysis set

Abbreviation	Definition
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
HF	Heart failure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRS	Interactive Response System
IV	Intravenous(ly)
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire– Overall Summary
LNP	Lipid nanoparticle
LS	Least squares
mBMI	Modified body mass index
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 neurological impairment score +7
mRNA	Messenger ribonucleic acid
6-MWT	6-minute walk test
NA	Not applicable
Norfolk QoL-DN	Norfolk Quality of Life - Diabetic Neuropathy
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association

Abbreviation	Definition
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEG_{2000}-C-DMG	3-N-[(ω-methoxy poly(ethylene glycol)2000) carbamoyl]-1,2-dimyristyloxy-propylamine
PK	Pharmacokinetic
PND	Polyneuropathy disability
PT	Preferred term
RBC	Red blood cell
RBP	Retinol binding protein
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
siRNA	Small interfering RNA
Tc	Technetium
TTR	Transthyretin
ULN	Upper limit of normal
US	United States
V30M	Valine to methionine mutation at position 30
V122I	Valine to isoleucine mutation at position 122
wt	Wild type
wtTTR	Wild type transthyretin

1. INTRODUCTION

1.1. Disease Overview

Transthyretin (TTR)-mediated amyloidosis (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 (ageing) causes, respectively. In ATTR amyloidosis, deposition of TTR in various organs results in progressive, chronically debilitating morbidity and mortality. The most common manifestations of ATTR amyloidosis are polyneuropathy and cardiomyopathy (ie, ATTR amyloidosis with cardiomyopathy).

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]

In hATTR amyloidosis, 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. These misfolded TTR monomers can then self-assemble into oligomers and form amyloid fibrils and plaques in the extracellular space of various tissues [Hou 2007], including the peripheral nervous system, heart, gastrointestinal tract, kidney, central nervous system and eye, leading to cellular injury and organ dysfunction with corresponding clinical manifestations. Since almost all patients are heterozygous for the mutated TTR allele, the amyloid fibrils typically consist of both mutant and wtTTR.

There are over 120 reported TTR genetic mutations associated with hATTR amyloidosis, and almost all patients are heterozygous for the mutated TTR allele.[Ando 2013; Connors 2003] The phenotypic expression varies depending on the predominant site of deposition of the amyloid fibrils with some mutations associated with predominantly polyneuropathy manifestations and others associated with predominantly cardiomyopathy manifestations. However, most patients experience both over the course of their disease.

The most common TTR mutation is the valine to methionine mutation at position 30 (V30M), accounting for approximately 50% of cases worldwide, and occurring primarily in families with heritage from Portugal, Sweden, Japan, and Brazil.[Parman 2016] This genotype is most commonly associated with multisystemic polyneuropathy. The valine to isoleucine at position 122 (V122I) mutation is most commonly associated with cardiomyopathy and occurs primarily in African Americans. In these individuals, the mean age at diagnosis is approximately 65 to 70 years, with symptom onset typically occurring after the age of 65.[Jacobson 2011; Quarta 2015] While there appears to be an association between carrier status and the development of heart failure (HF) and echocardiographic features of cardiac amyloidosis, the exact penetrance of this particular allele is unknown, and estimates vary widely.

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] Patients with this

condition do not have a pathogenic mutation in the TTR gene and the amyloid fibrils consist only of wtTTR protein, which form amyloid deposits typically found in heart tissue.

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 preserved until late stages of the disease.[Castano 2015; Dungu 2012; Mohty 2013; Ruberg 2012] Cardiac infiltration by amyloid can also lead to conduction disturbances and arrhythmias.[Adams 2016; Ando 2013; Benson and Kincaid 2007; Connors 2004] Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, in addition to clinical measurements of ambulation, and quality of life. Progression of disease in this population can be seen over a period of 12 months as demonstrated by differences in 6-minute walk test (6-MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ) – Overall Summary (KCCQ-OS) in the Phase 3 ATTR-ACT study.[Maurer 2018] Based on natural history data, patients typically experience progressive symptoms of HF resulting in hospitalization and with death typically occurring 2.5 to 5 years after diagnosis.[Castano 2015; Damy 2015; Dungu 2012; Hawkins 2015]

1.2. Current Treatments

The treatment of ATTR amyloidosis requires a multidisciplinary approach primarily involving cardiology, neurology, and gastroenterology specialties. While there are treatments for polyneuropathy that are available to hATTR amyloidosis patients, for most regions no treatments are currently available for the cardiomyopathy phenotype for either the hATTR or wtATTR forms. Palliative/symptomatic therapies directed at specific symptoms, including volume control and treatment of cardiac arrhythmias and conduction system disturbances, including cardiac pacemakers where appropriate, have been the mainstay of treatment despite their limited effectiveness.

Given that the liver is the primary source of TTR, orthotopic liver transplantation (OLT) has been used for hATTR amyloidosis patients since the early 1990s. However, OLT is intended to eliminate mutant TTR from circulation, but has no effect on the hepatic production of wtTTR, which continues to be made by the transplanted liver and can continue to deposit in the heart. OLT has also only been shown to be effective in slowing the progression of disease in patients with an early age of onset (<50 years of age) [Okamoto 2009], and especially for those with the V30M mutation and short disease duration before transplant. Consequently, almost two-thirds of patients with hATTR amyloidosis are not transplant-eligible.

Tafamidis, a TTR tetramer stabilizer that acts by binding to the thyroxine-binding site on TTR to reduce its dissociation into misfolded amyloidogenic monomers, is currently approved in Europe, Japan, Mexico, and select countries in South America, but not in the United States (US), for the treatment of patients with hATTR amyloidosis with polyneuropathy.[Coelho 2016] Recently, tafamidis was evaluated in the Phase 3 ATTR-ACT trial in patients with ATTR amyloidosis with cardiomyopathy (including hereditary and wt).[Maurer 2018] This study demonstrated that tafamidis treatment over 30 months was associated with lower all-cause mortality and cardiovascular (CV)-related hospitalizations compared with placebo treatment. Additionally, tafamidis treatment resulted in a slowing of the decline in functional capacity

(6-MWT) and quality of life (KCCQ-OS) compared to placebo. However, consistent with the expected pharmacodynamic (PD) effect of TTR stabilization, the effects of tafamidis on mortality outcomes was not observed until late in treatment, with differentiation between treatment groups occurring only after 18 months of treatment. Furthermore, although improvements with tafamidis relative to placebo were observed in 6-MWT and KCCQ-OS, minimal changes in echocardiographic parameters were observed, and tafamidis-treated patients still progressed during the study.

As of early 2019, tafamidis was not approved in the US for patients with ATTR amyloidosis (neither polyneuropathy nor cardiomyopathy phenotypes); however, it is anticipated that tafamidis may become available for patients with the cardiomyopathy phenotype in the US and in other regions, based on the ATTR-ACT study results. In Japan, tafamidis was approved in 2019 for use in transthyretin-type cardiac amyloidosis (wt and mutant), in addition to approval for transthyretin-type familial amyloid polyneuropathy.

The results of the ATTR-ACT study 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 a ribonucleic acid (RNA) interference (RNAi) therapeutic, may be required to halt or reverse the debilitating and ultimately fatal course of disease.

1.3. Patisiran Clinical Development

Patisiran is a small interfering RNA (siRNA) specific for TTR, which is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration.[Akinc 2010] The patisiran drug product (ALN-TTR02; patisiran-LNP, hereafter referred to as "patisiran") is designed to significantly suppress liver production of both wt and all mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with ATTR amyloidosis.

Patisiran utilizes the mechanism of RNAi to selectively degrade TTR messenger RNA (mRNA) and thereby reduce the expression of its corresponding protein.[Bumcrot 2006] Patisiran is formulated (via the LNP) to target delivery to hepatocytes in the liver, the primary source of TTR protein in circulation. Following IV infusion, opsonization of the LNP by apolipoprotein E facilitates binding to the low-density lipoprotein receptor on hepatocytes and subsequent endocytosis. Fusion of the ionizable lipid component of the LNP with the endosomal membrane then leads to release of the siRNA into the cytoplasm where it can bind to and activate the RNA-induced silencing complex (RISC). Upon binding and activation of RISC in the cytoplasm within hepatocytes, the siRNA duplex unwinds, and the antisense strand specifically binds to a genetically conserved sequence in the 3' untranslated region of wt and mutant TTR mRNA. The Argonaute-2 endonuclease within the RISC/siRNA enzyme complex catalytically degrades wt and mutant TTR mRNA, resulting in a reduction of wt and mutant TTR protein.

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing patisiran for the treatment of patients with ATTR amyloidosis. Based on results from the pivotal Phase 3 APOLLO study (Section 1.3.1), patisiran is approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults and in the European Union for the treatment of hATTR

amyloidosis in adult patients with stage 1 and stage 2 polyneuropathy. Ongoing development is intended to establish patisiran for the treatment of ATTR (hereditary and wt) amyloidosis with cardiomyopathy based on exploratory cardiac results from the APOLLO study (Section 1.3.1.1), which provides preliminary evidence in support of the use of patisiran for the treatment of the cardiomyopathy manifestations of the disease.

The nonclinical pharmacology, pharmacokinetics (PK), and toxicology of patisiran were evaluated in a series of in vitro and in vivo studies that have enabled chronic dosing in clinical studies.

1.3.1. The Phase 3 APOLLO Study

The safety and efficacy of patisiran was shown in a Phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study (ALN-TTR02-004, APOLLO) that met the primary and all secondary endpoints.[Adams 2018] This study demonstrated that, in patients with hATTR amyloidosis who exhibited a broad range of disease severity and TTR genotypes, treatment with patisiran leads to a significant improvement in neuropathy (modified neurological impairment score +7 [mNIS+7]) relative to placebo at 18 months (primary endpoint), as well as significant improvement in quality of life (Norfolk Quality of Life - Diabetic Neuropathy [Norfolk QoL-DN], key secondary endpoint) relative to placebo at 18 months. Significant improvement in neuropathy and quality of life were also observed at Month 9. This study furthermore demonstrated that treatment with patisiran is associated with an improvement in overall health (gait speed, nutritional status, and disability), with improvement in these endpoints seen as early as at Month 9.

In the patisiran group, serum TTR reduction was seen after the first dose and was stably maintained over the duration of the study; the mean TTR percent reduction from baseline was 82.6% and 84.3% at Months 9 and 18, respectively. A correlation (Pearson's r, 0.59; 95% CI, 0.49-0.68) was observed between the degree of TTR reduction from baseline and the change in the mNIS+7 at 18 months.

Patisiran showed an acceptable safety profile in the APOLLO study. Common adverse events (AEs) occurring more frequently with patisiran compared to placebo included peripheral edema (30% versus 22%) and infusion related reactions (IRRs) (19% versus 9%, respectively).

1.3.1.1. Cardiac Results and Cardiac Subpopulation Data from APOLLO

In APOLLO, evidence of potential cardiac amyloid involvement was seen in most patients in the study; 80% had left ventricular wall thickness >13 mm and 79% had abnormal levels of the cardiac biomarker N-terminal prohormone B-type natriuretic peptide (NT-proBNP).[Solomon 2018] As well, 56% of the population met the prespecified criteria for inclusion in a subpopulation of patients with evidence of cardiac amyloid involvement (ie, the cardiac subpopulation, with baseline left ventricular wall thickness ≥13 mm and no history of hypertension or aortic valve disease). In these patients, treatment with patisiran for up to 18 months resulted in improvement relative to placebo in important measures of cardiac structure and function. These included reduction in ventricular wall thickness and decrease (improvement) in global longitudinal strain.[Solomon 2018] In addition, patisiran treatment led to a reduction (improvement) in NT-proBNP and an improvement in functional capacity, as measured by 10-meter walk test assessment of gait speed, relative to the placebo group.

Overall, patisiran had an acceptable safety profile, based on an in-depth analysis of cardiac events in both the overall (modified intent-to-treat) population and the cardiac subpopulation. Importantly, in a post hoc analysis of safety data in the modified intent-to-treat population, rates of any hospitalization and/or all-cause death were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups respectively, while the rates of cardiac hospitalizations and/or all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups respectively. This approximates a reduction in event rate of approximately 50% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality for patients in the patisiran group compared to those in the placebo group.[Solomon 2018] Similar reductions in the event rates were observed in the cardiac subpopulation in APOLLO (approximately 55% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality; data on file).

The observed cardiac data from the APOLLO study support the therapeutic hypothesis that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis and warrant ongoing development for this indication.

1.3.2. Phase 3, Open-label Extension Study

Study ALN-TTR02-006 is an ongoing multicenter, open-label extension study designed to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis who have completed a prior Phase 2 or 3 parent study with patisiran (ALN-TTR02-003 or ALN-TTR02-004 [APOLLO]). The interim data from this open-label extension study were consistent with, and extended, the acceptable safety profile and clinical efficacy of patisiran observed in the Phase 3 APOLLO study.

No new safety signals have emerged for patients with long-term patisiran treatment.

1.4. Study Design Rationale

This study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of patisiran in adult patients with ATTR amyloidosis with cardiomyopathy. The efficacy of patisiran on functional capacity will be evaluated via change at Month 12 in the 6-MWT (primary endpoint). The study will include patients with wtATTR and hATTR amyloidosis with cardiomyopathy who, at baseline, are either tafamidis naïve or have been on tafamidis for ≥6 months with disease progression, in the opinion of the investigator.

Confidence in a beneficial treatment effect with patisiran in this patient population with ATTR amyloidosis with cardiomyopathy comes from the Phase 3 APOLLO study of patisiran in patients with hATTR amyloidosis with polyneuropathy. As described in Section 1.3.1 and Section 1.3.1.1, TTR lowering with patisiran demonstrated multiple benefits in a broad range of disease manifestations, including a substantial improvement in neuropathy and quality of life, as well as autonomic symptoms, motor strength, ambulatory ability, disability, and nutritional status.[Adams 2018] Furthermore, in a prespecified subgroup of patients with evidence of cardiac involvement, which was a majority (56%) of the overall study population, a beneficial treatment effect of patisiran compared to placebo was observed for assessments of cardiac structure and function as well as the cardiac biomarker NT-proBNP.[Solomon 2018]

The 6-MWT (primary endpoint assessment) 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 2014] The KCCQ-OS (first secondary endpoint assessment) 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 et al. 2006) Both 6-MWT and KCCQ-OS were shown to rapidly and consistently decline over time in cardiac ATTR amyloidosis patients and, in the 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 primary and key secondary endpoints, respectively.

Assessment of the primary endpoint at Month 12 is supported by placebo-arm data from the ATTR-ACT study showing substantial disease progression (via the 6-MWT) over an equivalent time; as well, data from APOLLO demonstrated a patisiran treatment effect as early as 9 months on multiple manifestations of hATTR amyloidosis (neuropathy, quality of life, NT-proBNP, and functional capacity [ie, gait speed]).[Maurer 2018]

The inclusion of placebo as a control allows for a rigorous analysis of the treatment effect of patisiran. If tafamidis becomes an approved therapy for ATTR amyloidosis with cardiomyopathy in a given region while this study is in progress, patients who are naïve to tafamidis treatment at baseline may commence concomitant on-label tafamidis during the study (ie, tafamidis drop-in) (Section 5.3.1).

1.5. Dose Rationale

The approved and recommended dosage of patisiran for the treatment of the polyneuropathy in patients with hATTR amyloidosis is 0.3 mg/kg administered IV every 3 weeks for patients weighing <100 kg and a fixed dose of 30 mg administered every 3 weeks for patients weighing 100 kg or more. This dosage was selected based on dose-response analyses from three Phase 1 and 2 studies demonstrating dose-dependent TTR reduction, with the maximum reduction achieved at 0.3 mg/kg. This regimen was further confirmed in the pivotal Phase 3 APOLLO study, where this dosage showed significant clinical activity and was well tolerated by patients with hATTR amyloidosis with polyneuropathy, including those in the cardiac subpopulation. The approved dosing regimen used in the treatment of polyneuropathy is being employed in this study since the mechanism of action of patisiran (ie, serum TTR lowering) for treatment of polyneuropathy and cardiomyopathy is the same.

1.6. Benefit-risk Assessment

ATTR amyloidosis with cardiomyopathy is a rare, serious, life-threatening, multisystemic disease characterized by deposition of TTR in various organs. Without treatment, the disease progresses, resulting in chronically debilitating morbidity and mortality, with the most common manifestations being cardiomyopathy and polyneuropathy. Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, ambulation, and quality of life seen over a period of 18 months or less.[Ruberg and Berk 2012]

The benefit-risk profile of patisiran has been established in extensive clinical development; in Phase 1, 2, and 3 clinical studies, patisiran administered IV demonstrated a potent, dose-dependent inhibition of TTR. In the Phase 3 APOLLO study of patisiran, the primary and all secondary endpoints were met.[Adams 2018] Furthermore, exploratory cardiac results from the APOLLO study suggest that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon 2018] and provide preliminary evidence in support of the use of patisiran for the treatment of patients with ATTR amyloidosis with cardiomyopathy (Section 1.3.1.1).

In APOLLO, as well as in the ongoing Phase 3, open-label extension study (ALN-TTR02-006), an acceptable safety profile with patisiran was demonstrated. Most AEs were mild or moderate in severity. Transient infusion-related reactions (IRRs) were observed, but all IRRs were mild or moderate in severity, none were reported as serious AEs (SAEs). No clinically significant laboratory or hematologic changes were observed. Furthermore, in APOLLO, an acceptable safety profile was also observed in a prespecified subgroup of patients with evidence of cardiac amyloid involvement. [Solomon 2018]

For patisiran, important identified risks include IRRs. To minimize this risk, all patients must receive premedication with a corticosteroid, paracetamol/acetaminophen, and H1 and H2 blockers prior to patisiran administration (Section 5.2.1). The infusion may be interrupted or slowed if an IRR occurs (Sections 5.2.3 and 5.2.4). Important potential risks also include severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients. Patisiran is contraindicated in patients with a history of severe hypersensitivity (eg, anaphylaxis or anaphylactoid reactions) to patisiran or any of the excipients.

Vitamin A deficiency is also considered an important potential risk. Nonclinical and clinical data with patisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in 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 (Section 5.3). 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 patisiran.

Detailed information about the known and expected benefits and risks of patisiran may be found in the current edition of the Investigator's Brochure.

During the study, patients will be monitored, including evaluation of laboratory monitoring for liver function test abnormalities, renal function, and other standard hematology and blood chemistries. As the risk of embryofetal toxicity is currently unknown, females of child-bearing potential participating in the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception as specified in the protocol.

An external, independent Data Monitoring Committee (DMC) will monitor and ensure the safety of trial participants (see Section 3.7).

In conclusion, exploratory cardiac results from the APOLLO study suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon

2018] (Section 1.3.1.1) together with the established benefit-risk profile of patisiran demonstrated in the Phase 3 APOLLO study (and supportive data from the ALN-TTR02-003 and ALN-TTR02-006 studies), support the evaluation of patisiran in a Phase 3 study in adult patients with ATTR amyloidosis (wtATTR and hATTR) cardiomyopathy.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality and hospitalizations	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV)-related hospitalizations and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations over the 12-month double-blind period
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV-related hospitalizations • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV-related hospitalizations over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI)

Objectives	Endpoints
	○ Cardiac magnetic resonance (CMR) parameters ○ Technetium scintigraphy parameters ○ Troponin I levels ○ Norfolk QoL-DN
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (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 patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the investigator. This group will be capped at 30% of total enrollment in the study.

In addition to patients who have never taken tafamidis, patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve for this study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 12-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period (Figure 1).

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive IV treatment every 3 weeks with either patisiran (0.3 mg/kg for patients weighing <100 kg; 30-mg fixed dose for patients weighing ≥100 kg) or placebo. Prior to receiving

randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an IRR with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. (Patients randomized to placebo will also receive premedications to maintain the blind.) Study drug will be administered in the clinic as an approximately 80-minute IV infusion.

During the 12-month open-label extension period, all patients will receive treatment with open-label patisiran. Furthermore, patients who have received ≥3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint (Section 2); this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period at the time points noted in the Schedule of Assessments (Table 1 and Table 2). The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score.

Safety will be assessed throughout the study, as described in the Schedule of Assessments for the double-blind period (Table 1) and for the open-label extension period (Table 2).

3.2. Duration of Treatment

The treatment duration in this study is up to 24 months, inclusive of a 12-month, double-blind, treatment period, and a 12-month, open-label, treatment period.

3.3. Duration of Study Participation

The estimated total time on study for each patient is up to 26.5 months, including up to 45 days of screening, up to 24 months of treatment (see Section 3.2), and a 28-day safety follow-up period.

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:

- the patient has completed the end of study (EOS; Month 24) visit, or
- the patient has completed the follow-up visit 28 days after the last dose of patisiran.

3.4. Number of Planned Patients

The planned enrollment for this study is 300 patients with wtATTR and hATTR amyloidosis with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR.

3.5. Method of Assigning Patients to Treatment Groups

Using the interactive response system (IRS), patients will be randomized 1:1 to the patisiran or placebo arm. Randomization will be stratified by:

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

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 IRS. The Investigator or his/her designee will contact the IRS to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

3.6. Blinding

During the double-blind period of the study, all site personnel will be blinded to the study treatment, except the pharmacist and designated pharmacy personnel who will set-up, dispense, and prepare the infusion. Patisiran confers a slightly opalescent color relative to the clear saline (placebo) infusate; therefore, all infusion bags and lines will be covered with amber bags and line covers by the unblinded personnel to prevent visualization by the blinded study personnel and patient, as described in detail in the Pharmacy Manual.

After the pharmacist (and designated pharmacy personnel) has prepared the infusion, separate blinded personnel will administer study drug and monitor the patient during and after the infusion. All patients will be blinded to treatment and will receive an IV infusion once every 3 weeks using identical volumes for patisiran and placebo.

Study personnel performing assessments related to the primary and secondary endpoints will be different from the Investigator and other personnel managing the patient, and all of these study personnel will be blinded to any clinical laboratory results that could potentially unblind them (eg, TTR levels). In addition, the study personnel performing assessments related to the primary and secondary efficacy endpoints will also be blinded to the results of any previous assessments.

Furthermore, unblinded source documentation containing all descriptions of pharmacy preparations and infusions or distribution of study drug or randomization data will be stored separate from all other study data/records and from other pharmacy staff not participating on the study.

Blinding will be maintained until the last patient completes their Month 12 visit.

3.6.1. Emergency Unblinding

During the double-blind period of the study, 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. 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 IRS instructions for details on emergency unblinding.

3.7. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study through the double-blind period (through Month 12), providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.8. Adjudication Committee

An independent Adjudication Committee will review deaths and hospitalizations and will attribute a cause (CV versus non-CV) according to the responsible underlying disease process rather than the immediate mechanism. Deaths and hospitalizations will be classified as specified in the Adjudication Committee 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 and Sex

1. Age 18 (or age of legal consent, 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:

   Hereditary ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

   a. TTR pathogenic mutation consistent with hATTR.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at screening).
   c. 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 ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) has been excluded.
   d. If MGUS, confirm TTR protein in tissue with immunohistochemistry (IHC) or mass spectrometry.

Wild-type ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

a. Absence of pathogenic TTR mutation.
b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at screening).
c. Amyloid deposits in cardiac tissue with TTR precursor identification by IHC, mass spectrometry, **OR** technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc] or ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if MGUS has been excluded.
d. If MGUS, confirm TTR protein in cardiac tissue with IHC or mass spectrometry

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; in addition to patients who have never taken tafamidis, those who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.
   b. Currently on tafamidis (for ≥6 months) and has demonstrated disease progression, as determined by the Investigator. (At the time of study entry, tafamidis treatment must be on-label use of commercial tafamidis.)
5. Patient is clinically stable, with no CV-related hospitalizations within 6 weeks prior to randomization, as assessed by the Investigator.
6. Able to complete ≥150 m on the 6-MWT at screening.
7. Screening NT-proBNP >600 ng/L and <8500 ng/L.

Informed Consent

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent; and patient agrees to sign the medical records release form for collection of vital status.

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) or leptomeningeal amyloidosis.

2. NYHA Class III **AND** ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3000 ng/L and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2).[Gillmore 2018]
3. NYHA Class IV at the Screening visit.
4. Has a polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires cane or stick to walk, or is wheelchair bound) at the Screening visit.

Laboratory Assessments

5. Has any of the following laboratory parameter assessments at screening:
   a. Aspartate transaminase (AST) or alanine transaminase (ALT) levels >2.0 × the upper limit of normal (ULN).
   b. Total bilirubin >ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if total bilirubin <2 × ULN.
   c. International normalized ratio (INR) >1.5 (unless patient is on anticoagulant therapy, in which case excluded if INR >3.5).
6. Has eGFR <30 mL/min/1.73 m^2 (using the modification of diet in renal disease [MDRD] formula).
7. Has known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.

Prior/Concomitant Therapy

8. Tafamidis naïve patients (at baseline) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
9. Is currently taking diflunisal; if previously on this agent, must have at least a 6-month 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. Received prior TTR-lowering treatment (including patisiran) or participated in a gene therapy trial for hATTR amyloidosis.
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 6 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 chronic 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 electrocardiogram [ECG] changes).
15. Has non-amyloid disease affecting exercise testing (eg, severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation).
16. Recent or planned orthopedic procedure during the double-blind period (eg, lower extremity or back surgery) that could impact 6-MWT.
17. Unstable congestive heart failure (CHF) (eg, no adjustment of diuretics at time of screening required to achieve optimal treatment of CHF).
18. Had acute coronary syndrome or unstable angina within the past 3 months.
19. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.
20. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
21. Has persistent elevation of systolic (>180 mmHg) and diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.
22. Has untreated hypo- or hyperthyroidism.
23. Prior or planned heart, liver, or other organ transplant.
24. Had a malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
25. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient.
26. Has a history of severe hypersensitivity (eg, anaphylaxis) to any of the excipients in patisiran. Also see exclusion Criterion 11, which excludes all patients with prior TTR-lowering treatment including patisiran.

Contraception, Pregnancy, and Breastfeeding

27. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.
28. Female patient is pregnant or breast-feeding.

Alcohol Use

29. Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (for females, more than 14 units of alcohol per week; for males, more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer]);
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 or their legal guardians 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 electronic case report form (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; which includes required treatment with prohibited medication (as defined in Section 5.3) per investigator discretion
- 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 6.5.7.7 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 is captured in the final analyses.

If this occurs, 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 and Table 2), 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 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 6.5.7. 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 from study drug during the 12-month double-blind period, defined as the time the first dose of study drug is administered on Day 1 through completion of the Month 12 Efficacy Visit (primary endpoint assessment), will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including a Modified Month 12 Efficacy Visit (Table 1). They will also be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug (Table 2); see Section 3.3.1.

Patients who discontinue patisiran during the open-label extension period will be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, per the Schedule of Assessments (Table 2), 28 days after the last dose of patisiran; see Section 3.3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop the patient's participation in the study-at any time. A patient or legal guardian 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, through the Modified Month 12 Efficacy Visit, and the 28-day follow-up visit, or alternatively may complete any minimal assessments for which the patient or legal guardian consents as described in Section 4.3.1. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 12 visit, every effort should be made to conduct the assessments scheduled to be performed at the Modified Efficacy Visit (Table 1).

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, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and 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.

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 6.5.7.

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 fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian 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 or legal guardian (where possible, 3 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 or legal guardian 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 can search publicly available records (where permitted and allowed by local law) to ascertain survival status. 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 preparation, administration, and storage of study drug (patisiran and placebo) is provided in the Pharmacy Manual.

All patients will be instructed to take the recommended daily allowance of vitamin A while on the study.

5.2.1. Premedication

All patients will receive premedication prior to study drug administration to reduce the risk of IRRs. Each of the following medicinal products should be given on the day of study drug infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

If a patient is having difficulty tolerating the steroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the steroid premedication may be allowed for that patient after consultation with the medical monitor at any time during the study (double-blind and open-label periods).

In the open-label extension period only, for patients who are tolerating their drug infusions well with their current corticosteroid premedication regimen (ie, no IRRs during the past 3 or more infusions), corticosteroid dose may be reduced in 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (IV) or equivalent.

Infusions during corticosteroid tapering (and the 2 infusions after the new and stable lower corticosteroid dose is established) should be performed in the clinic, as described in detail in the Pharmacy Manual.

Additional or higher doses of 1 or more of the premedications may be administered to reduce the risk of IRRs, if needed. For suggested guidelines for management of IRRs, see Section 5.2.4; further details can be found in the Pharmacy Manual.

5.2.2. Study Drug Description

Patisiran is a RNAi therapeutic consisting of a double-stranded siRNA targeting TTR mRNA formulated in an LNP. The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline. Patisiran Solution for IV infusion contains 2 mg/mL of patisiran.

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

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

5.2.3. Dose and Administration

Detailed instructions for study drug preparation and administration are found in the Pharmacy Manual.

5.2.3.1. Double-bind Study Drug (Patisiran or Placebo)

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days.

The amount (in mg) of double-blind patisiran to be administered should be determined based on the patient's weight (kg). Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended dose is 30 mg.

Weight from the previous visit may be used for calculating dose. Weight must be collected prior to dosing with study drug. Study drug will be administered as an approximately 80-minute IV infusion (approximately 1 mL/minute for the first 15-minutes followed by approximately 3 mL/minute for the remainder of the infusion). The patient’s infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments.

Missed doses of double-blind study drug

If a patient does not receive a dose of study drug within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit (with the following infusion taken on schedule, per the Schedule of Assessments), after consultation with the Medical Monitor.

A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study.

5.2.3.2. Open-label Extension Period (Patisiran)

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described in Section 5.2.3.1 for double-blind patisiran.

As noted in Section 3.6, blinding will be maintained until the last patient completes their Month 12 visit.

During the open-label extension period, patients who have received at least 3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and administration of premedications and patisiran infusion.

All patients will receive premedications prior to open-label patisiran administration to reduce the risk of IRRs (Section 5.2.1).

Missed doses of open-label patisiran

If a patient does not receive a dose of open-label patisiran within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit (with the following infusion taken on schedule, per the Schedule of Assessments), after consultation with the Medical Monitor.

5.2.4. Suggested Guidelines for Management of Infusion-related Reactions

Criteria for categorizing IRRs are provided in Section 10.3.

- In the event of an IRR, the infusion of study drug may be slowed or stopped and the patient closely monitored until resolution of the reaction. Drugs that may be used to facilitate resolution and permit resumption of study drug administration include but are not limited to: paracetamol/acetaminophen (or equivalent), additional histamine H1/H2 receptor antagonists (eg, ranitidine), nonsteroidal anti-inflammatory drugs (NSAIDs), adrenaline, supplemental oxygen, IV fluids, and/or corticosteroids.
- Following resolution of a mild or moderate IRR that required interruption of the study drug infusion, resumption of administration may occur at the Investigator's discretion at a slower infusion rate for that dose and for subsequent doses of study drug. If the infusion is delayed, the administration of the infusion should be completed no more than 16 hours after study drug is first diluted in saline (including infusion time).
- Study drug administration will not be resumed for any patient following a severe IRR until the case is discussed with the Medical Monitor.
- If after consultation with the Medical Monitor it is agreed that an individual patient's steroid premedication will be increased, then the following steps are **recommended**:
    1. If the IRR occurred while the patient received 10 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and did not resolve with slowing of the infusion rate,

then the patient should be increased by multiples of 5 mg IV dexamethasone or equivalent at least 60 minutes before the infusion.

2. Increased dose of premedication steroids should NOT exceed the combination of 20 mg IV dexamethasone or equivalent on the day of infusion.
3. If the IRR occurred while the patient received less than 10 mg IV dexamethasone or equivalent, then the patient should return to the prior dose of IV dexamethasone or equivalent that did not result in an IRR.

Patients will be instructed to call the Investigator if they experience symptoms such as fever, chills, myalgia, or nausea/vomiting after discharge from the site.

5.2.5. 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.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of study drug (patisiran and placebo) doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately (5 ±3°C) until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

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 will be provided in the Pharmacy Manual.

5.2.7. 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. Additional details will be available in the Pharmacy Manual.

5.2.8. 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, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.3. Concomitant Medications and Procedures

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

Use of the following medications/treatments are prohibited during study participation:

- Any investigational agent other than study drug.
- Inotersen, doxycycline, ursodeoxycholic acid, tauroursodeoxycholic acid, and diflunisal are also prohibited during the study.

All patients will be asked to take the recommended daily allowance of vitamin A for the duration of their participation in the study while being administered study drug. In countries where relevant, the clinical sites will provide patients with a prescription for vitamin A at a dose consistent with local guidelines.

Standard vitamins and topical medications are permitted. Any concomitant medication or treatment that is required for the patient's welfare may be given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the CRF, as specified in the Schedule of Assessments (Table 1 and Table 2). Concomitant medications include 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 CRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Concomitant Tafamidis Use

Per inclusion Criterion 4, at baseline patients are either: 1) tafamidis naïve or 2) currently on tafamidis for ≥6 months with demonstrated disease progression, as determined by the Investigator. Patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.

For patients on tafamidis at baseline, the reasons for considering the patient to have demonstrated disease progression will be recorded in the eCRF. Patients who are on tafamidis at baseline are encouraged, if it is medically appropriate in the opinion of the investigator, to remain on tafamidis for the duration of the double-blind period.

Per exclusion Criterion 8, patients who are tafamidis naïve at baseline, for whom the investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period (taking into consideration clinical status, patient preference, and/or commercial availability of tafamidis), should not be enrolled in the trial.

However, if tafamidis is granted approval by a Health Agency for treatment in patients with ATTR amyloidosis with cardiomyopathy in a given region, all enrolled patients in this region

will be made aware of its potential benefits and risks at the time of regulatory approval and all patients will be reconsented. In such circumstances, tafamidis is not considered prohibited and the investigator may, using their medical judgement, commence concomitant on-label tafamidis during the study, if it is felt to be in the best interest of the patient and if it is commercially available in the country.

Patients who are tafamidis naïve at baseline, but begin taking commercial tafamidis (ie, "tafamidis drop-in"), will remain in the study. 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). In all cases, the Pre tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of study drug (ie, 7 to 14 days post study drug dose). Thereafter, the patient will continue with all assessments per the Schedule of Assessments (Table 1 and Table 2). In addition, at the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

Initiation of TTR stabilizer therapies other than tafamidis (eg, diflunisal) is not allowed during the double-blind period of this study.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

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 12 weeks after the last dose of study drug in this study.

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.
- 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 12 weeks after the last dose of study drug.

Investigators should advise females of childbearing 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 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 6.5.5.2).

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 (double-blind period) and Table 2 (open-label extension period). Additional information on the collection of study assessments will be detailed in the respective reference manuals.

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient or legal guardian before the Screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF. In addition, a medical records release form will be required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries.

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

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening (once) 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, including completion of ophthalmologic history in the eCRF. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

If a genetic test result that shows the presence or absence of a TTR pathogenic mutation, which would be consistent with either wtATTR or hATTR, is not available at Screening for the assessment of eligibility (Section 4.1, inclusion criterion 2a), genotyping may be conducted at a laboratory selected by the site in consultation with the Medical Monitor.

The study eligibility biopsies and technetium scintigraphy noted in inclusion Criterion 2 are intended to be historical, as part of the patient's clinical care and diagnosis, and are not performed as part of the study.

An echocardiogram will be performed at screening Visit 1 and results confirmed centrally to assess study eligibility, as indicated in the Schedule of Assessments (Table 1).

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. Any additional repeat testing may be considered 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, or who fails to complete screening activities due to unforeseen or unavoidable circumstances, may be rescreened once after consultation with the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment. A patient will be re-consented if rescreening occurs outside of the 45-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

6.2.1. 6-Minute Walk Test (6-MWT)

The 6-MWT, which will be assessed as the primary endpoint, is an assessment of functional exercise capacity. The 6-MWT will be administered by staff trained in the procedure per the relevant study manual. The staff administering the 6-MWT will be different from the Investigator or designee managing the care of the patient.

The 6-MWT will be performed at each of the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). At screening Visit 1, the 6-MWT will be administered for study eligibility purposes (per inclusion Criterion 6 [Section 4.1]). At screening Visit 1, prior to conducting the 6-MWT, 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.

On Day 1 (baseline), which is a dosing day, the 6-MWT will be performed prior to study drug administration. (No other dosing days have a 6-MWT assessment.)

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 within the permitted visit window.

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.

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

A 1.5-month window will be used to group 6-MWT assessments to the Month 6 (Weeks 25-26), Month 9 (Weeks 37-38), and Month 12 (Weeks 52-53) visits. During the double-blind period, a patient may opt to begin tafamidis treatment or to discontinue study treatment, in which case they would complete a Pre-tafamidis Drop-in Visit (Table 1) or Early Treatment Discontinuation Visit (Table 2), respectively. To avoid the potential training effect from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be collected for the following time periods: Day 2 to Day 214 (for Month 6), Day 215 to Day 319 (for Month 9), and Day 320 to Day 372 (for Month 12).

Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit); no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed per the Schedule of Assessments (Table 1).

6.2.2. 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-OS will be assessed for the first secondary endpoint.

The KCCQ questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

6.2.3. Deaths and Hospitalizations

All deaths and hospitalizations will be recorded at Day 1 post dose and throughout the study as specified as part of AEs monitoring (see Section 6.5.7) and per the Schedule of Assessments (Table 1 and Table 2).

Reasons for deaths and hospitalizations will be adjudicated by an independent Adjudication Committee (see Section 3.8).

6.2.4. Modified Body Mass Index (mBMI)

The nutritional status of patients is evaluated using the mBMI, calculated as the product of body mass index (BMI) (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

Weight, height, and serum albumin (collected as part of the serum chemistry panel) will be collected pre-dose at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). The site will not perform the calculation for mBMI.

6.2.5. Cardiac Assessments

Manifestations of cardiac amyloid involvement will be assessed via cardiac biomarker, NYHA class, echocardiograms, CMR, and technetium scintigraphy imaging, as described.

Qualified personnel will be required to administer cardiac imaging assessments as specified in the respective reference manuals.

6.2.5.1. Cardiac Biomarkers

The cardiac biomarkers NT-proBNP and troponin I will be used to assess cardiac stress and heart failure severity. These biomarkers have been shown to be prognostic of outcomes in HF, including in ATTR amyloidosis.[Damy 2016; Kristen 2017; Merlini 2016] Blood samples will be drawn to measure cardiac biomarker levels at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2) and will be measured at a central laboratory. At screening Visit 1, only NT-proBNP will be assessed for eligibility purposes.

Details on cardiac biomarker sample collection, processing, and storage will be provided in a Study Laboratory Manual.

6.2.5.2. ATTR Amyloidosis Disease Stage

Based on published data from Gillmore et al, the ATTR amyloidosis disease staging used for this protocol stratifies patients with ATTR amyloidosis with cardiomyopathy (both hATTR and wtATTR) into prognostic categories using the serum biomarkers NT-proBNP and eGFR.[Gillmore 2018] Patients are categorized as follows:

- Stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min/1.73 m^2
- Stage 2 (intermediate risk): all other patients not meeting criteria for Stages 1 or 3
- Stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 ml/min/1.73 m^2

Based on published data, this staging system discriminates between patients with median survival of ~6 years, ~4 years, and ~2 years for Stage 1, Stage 2, and Stage 3, respectively.

6.2.5.3. 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 Schedule of Assessments (Table 1 and Table 2). The score collected at screening will be used to determine eligibility.

6.2.5.4. Echocardiogram

Echocardiographic parameters will be used for assessment of cardiac structure and function. Echocardiograms will be performed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2), and analyzed at a central cardiac imaging core lab.

Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

6.2.5.5. Technetium Scintigraphy Imaging

At select sites, in a subset of approximately 100 patients, technetium scintigraphy will be collected according to the Schedule of Assessments (Table 1 and Table 2), as an optional exploratory imaging assessment, to assess cardiac amyloid involvement. Based on local practice standards, either ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc], or ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) can be used as the tracer. Technetium scintigraphy images will be interpreted at a central imaging core laboratory. Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

For patients in whom technetium scintigraphy is performed as a study efficacy parameter, the results of the baseline scan must be reviewed by the central reader and confirmed to be consistent with the diagnosis of ATTR amyloidosis prior to randomization.

At select sites where technetium scintigraphy is being performed as an exploratory efficacy assessment, patients may be exempt from the baseline scan if technetium scintigraphy has been performed prior to study entry as part of the patient's clinical care within 6 months prior to the baseline assessment. In such cases, the historical technetium scintigraphy examination performed prior to study entry as part of the patient's clinical care should be collected and transferred to the central imaging core laboratory for interpretation; if the historical scan cannot be transferred to the central reader, or is deemed by the central reader to be of inadequate quality for interpretation, the patient should not participate in this optional efficacy assessment.

6.2.5.6. Cardiac Magnetic Resonance (CMR)

At select sites, in a subset of patients (≤60 patients), CMR will be collected according to the Schedule of Assessments (Table 1 and Table 2), as an optional exploratory imaging assessment to assess cardiac amyloid involvement. CMR imaging with late gadolinium enhancement will only be performed on patients without contraindications (ie, pacemakers, severe renal failure with eGFR <30 mL/min/1.73 m^2, defibrillators, or allergy to gadolinium).

Details for image acquisition and upload for central review can be found in the relevant study manual.

6.2.6. Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN)

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that assesses 5 domains: physical function, large-fiber neuropathy, activities of daily living, symptoms, small-fiber neuropathy, and autonomic neuropathy. The total score ranges from -4 (best possible quality of life) to 136 points (worst possible quality of life).[Vinik 2005; Vinik 2014]

The Norfolk QoL-DN questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

6.2.7. Polyneuropathy Disability (PND)

Physician assessment of ambulation via PND score [Coutinho 1980; Yamamoto 2007] will be evaluated only at screening to assess eligibility for the study as specified in the Schedule of Assessments (Table 1). PND scoring is described in Section 10.1.

6.3. Pharmacodynamic Assessments

In this study, serum samples for measurement of TTR levels will be collected for the assessment of PD effects. TTR levels will be determined by a validated enzyme-linked immunoassay (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 Schedule of Assessments (Table 1 and Table 2).

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of plasma concentrations of ALN-18328 (siRNA component of patisiran) and 2 lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) during the double-blind period at the timepoints specified in the Schedule of Assessments (Table 1). Plasma PK samples will be collected: predose (within 1 hour of planned study drug dosing); at the end of the infusion (+5 minutes); and 30 minutes after the end of the infusion (+15 minutes) at the specified visits.

For patients who discontinue treatment early during the double-blind period, a single PK sample will be taken at any time during the Early Treatment Discontinuation Visit, per the Schedule of Assessment (Table 2).

Actual dates and times of sample collection will be recorded.

Plasma concentrations of the 3 analytes will be determined using validated assay methods. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

PK parameters will be analyzed, whenever possible, as outlined in Section 7.2.7.

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 in addition an independent DMC as described in Section 3.7.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, 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 10 minutes. Blood pressure should be taken using the same arm. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary 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 sign assessments, as medically 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 Schedule 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 Schedule 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.

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.

6.5.4. Electrocardiogram

12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval will be obtained, as specified in the Schedule of Assessments (Table 1 and Table 2). Patients should be supine for at least 5 minutes before each ECG is obtained. The 12-lead ECGs will be performed in triplicate at baseline, with readings approximately 1 minute apart. At all other time points, a single 12-lead ECG will be performed.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn, when possible.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator. Recordings will be archived in the patient's files.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. 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 laboratory tests and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 3 and will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 3, which are performed at the clinic 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.

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 3: 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 and eGFR (using the MDRD formula)	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Coagulation (at Screening)	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.5.5.1)	
Antidrug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.5.2)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; MDRD=modification of diet in renal disease; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid.

6.5.5.1. Immunogenicity

Serum samples will be collected to evaluate the presence of antidrug antibodies (ADA) as outlined in the Schedule of Assessments (Table 1). Details regarding the blood volume, processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

A validated ELISA will be used that specifically detects antibodies to PEG_{2000}-C-DMG, which is a component of patisiran-LNP. Serum samples will first be analyzed with a screening assay. Samples testing positive for ADA in the screening assay will be further evaluated in a confirmatory assay. For the samples that tested positive for ADA in the confirmatory assay, the ADA titer will then be determined as the reciprocal of the highest dilution of the sample that yielded a positive ADA test result.

6.5.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. 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 6.5.7.7 for follow-up instructions).

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

6.5.6. Vital Status Check

A vital status check will be performed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

Due to the inclusion of all-cause mortality in the secondary endpoint analysis, a medical records release form will be required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries. The signing of this medical records release form is in addition to the ICF. 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.

6.5.7. Adverse Events

6.5.7.1. 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 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

An 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

No AEs of clinical interest are defined for this study.

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 AE.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. AEs 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.

6.5.7.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, 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.

All IRRs will be recorded as AEs. All information on IRRs is to be recorded on the applicable eCRF per the CRF completion guidelines.

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 to determine if an ophthalmological assessment is needed. 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.

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

Not applicable. There were no AEs of Clinical Interest identified for this study.

6.5.7.4. 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 6.5.7.1 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 Reference 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.

6.5.7.5. 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 Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.7.6. 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.

6.5.7.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 12 weeks following the last dose of study drug, 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 12 weeks after the last dose of study drug.

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 6.5.7.4.

6.5.7.8. Overdose Reporting

An overdose is defined as any dose 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. In the event of an overdose, the actual dose administered must be recorded as specified in the Pharmacy Manual.

All reports of overdose (with or without an AE) must be reported within 24 hours following the instructions outlined in the Pharmacy Manual for reporting an overdose.

6.6. Biomarkers and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this

study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of patisiran.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2). Potential exploratory investigations may include RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

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

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

The planned enrollment for this study is 300 patients. For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a mean difference between treatment groups at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment (Section 7.2.10).

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 12-month, double-blind period. More complete plans, including planned analyses for the open-label extension period, will be detailed in the SAP. 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.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug, grouped according to the randomized treatment arm.
- Safety Analysis Set: All patients who received any amount of study drug, grouped according to the treatment actually received.
- PK Analysis Set: All patients who received any amount of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- 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.

Efficacy endpoints will be analyzed using the Full Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology 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 and overall for the FAS and Safety Analysis Set.

7.2.5. Efficacy Analyses

The overall Type I error rate will be strongly controlled at a 2-sided 0.05 significance level for the primary and secondary endpoints using a fixed sequential testing procedure at the final analysis. The primary endpoint will be compared between treatment arms at the 0.05 significance level. If the test of the primary endpoint is statistically significant, then the secondary endpoints will each be tested in the order specified in the Secondary Endpoints section (see Section 2). If a test of the primary or a secondary endpoint is not statistically significant, the testing of the remaining endpoints in the sequence will stop.

For patients who were tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

7.2.5.1. Primary Endpoint

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change

from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, the treatment-by-visit interaction, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), and age (<75 vs ≥75 years) as fixed factors, and patient as a random effect. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

Sensitivity analyses will be detailed in the SAP.

7.2.5.2. Secondary Endpoints

Secondary endpoints are described in Section 2.

KCCQ-OS will be analyzed using a similar MMRM model as used for the primary endpoint.

The composite endpoint of all-cause mortality, frequency of CV-related hospitalizations and change from baseline in 6-MWT will be analyzed using a generalized rank-based win ratio method, which makes pairwise comparisons (for all possible patisiran/placebo patient pairs) of the 3 components in the hierarchical order specified above. The point estimate for the win ratio is defined as the total number of better outcomes divided by the total number of worse outcomes in the patisiran group. The detailed algorithm for assessment of this endpoint will be provided in the SAP.

The composite endpoint of all-cause mortality and all-cause hospitalizations will be analyzed using an Andersen-Gill model stratified by baseline tafamidis (yes vs no), including treatment, genotype (hATTR vs wtATTR), NYHA Class (I/II vs III), and age (<75 vs ≥75 years) as covariates.

Patients who undergo a heart transplantation and/or ventricular assist device placement after randomization will be handled in the same manner as death in the primary analyses of mortality related endpoints.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

7.2.5.3. Exploratory Endpoints

Descriptive summaries will be provided for the exploratory endpoints (Section 2), and additional analyses may be conducted. Details will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

The PD endpoint is serum TTR. Summary tables will be provided for observed values, change and percentage change from baseline for each scheduled time point. In addition, the maximum and mean percentage reduction over 12 months will be summarized.

7.2.7. Pharmacokinetic Analysis

7.2.7.1. Pharmacokinetic Analysis

Plasma concentrations of ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG will be obtained using a model-independent method. PK exposure parameters will include: maximum plasma concentration at the end of infusion (C_{max}), 30-minute post-infusion concentration ($C_{p(30min)}$), and

pre-infusion concentration (C_{min}). In addition, the steady-state C_{max} ($C_{max,ss}$), steady-state $C_{p(30min)}$ ($C_{p,ss(30min)}$), and steady-state C_{min} ($C_{min,ss}$) will be calculated as the average of the respective values at Week 24, Week 36, and Month 12.

The PK exposure parameters will be summarized by visit, and the steady-state PK parameters will be summarized.

7.2.7.2. Exposure-Response Analysis

Mean and maximum percent TTR reduction from baseline will be summarized by quartiles of the steady state PK parameters for all 3 analytes. Change from baseline at Month 12 in clinical efficacy parameters may also be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

PK exposure will be summarized by mortality status. In addition, the incidence of AEs and SAEs will be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

7.2.7.3. Population PK, PK/PD, and Disease Progression Modelling Analysis

Population PK, PK/PD, and disease progression modelling analyses may be performed, if appropriate. If performed, the analyses would be conducted according to a pre-specified analysis plan and reported separately.

7.2.8. Safety Analyses

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. The 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 and Preferred Term. The frequency and percentage of patients experiencing AEs, SAEs, related AEs, and AEs leading to discontinuation will be summarized by System Organ Class (SOC) and PT. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics will be provided for clinical laboratory data, ECG, and vital signs data, summarizing the observed values and change from baseline over time. Laboratory shift tables from baseline at the worst post-baseline values will be presented. 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. Sample Size Re-assessment

Patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period, which could result in a loss of statistical power. An interim assessment may be performed to assess the impact of tafamidis drop-in on the power and the potential need to increase the sample size. The interim assessment, if conducted, would examine the overall tafamidis drop-in rate in a blinded manner (ie, a non-comparative assessment of the drop-in rate); therefore, no impact on the type I error is expected and no multiplicity adjustment will be made. A detailed sample size re-estimation plan will be outlined in a separate document prior to implementation.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the informed consent form (see Section 4.3.2).

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 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 required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries. 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. 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 6.5.7. 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 serious 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. CRFs 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).

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10. APPENDICES

10.1. Polyneuropathy Disability (PND) Scores

Stage	Description
0	No symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capacity but ability to walk without a stick or crutches
IIIA **IIIB**	Walking with the help of one stick or crutch Walking with the help of two sticks or crutches
IV	Confined to a wheelchair or bedridden

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.

10.3. Categorization of Infusion-Related Reactions

Signs and symptoms of an IRR usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritus/itching,

rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, urticaria (hives, welts, wheals), vomiting.

Categorization of IRRs is as follows:

Categorization	**Description**
Mild	Mild reaction: infusion may be continued; if intervention is indicated it is minimal and additional treatment (other than paracetamol for delayed reactions) is not required.
Moderate	Moderate reaction: requires treatment including more intensive therapy (eg, IV fluids, NSAIDs) in addition to infusion interruption but responds promptly to medication. Treatment is indicated for ≤24 hours.
Severe	More than moderate reaction: not rapidly responsive to medication or to interruption of infusion; and/ or prolonged (treatment is indicated for >24 hours); recurrence of severe symptoms following initial improvement.

ALN-TTR02-011 PROTOCOL AMENDMENT 1
SUMMARY OF CHANGES DATED 20 DECEMBER 2019

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

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to address comments from Competent Authorities that requested changes to the protocol as part of their approval of the study.

In addition, other protocol modifications or clarifications include:

- Adding a study visit window for Week 3 (Day 22) that was erroneously left out and Adding a window for randomization to the Schedule of Assessments.
- Adding ursodeoxycholic acid to the list of prohibited medications detailed in exclusion criterion 10, as it is commonly prescribed for the same reasons as tauroursodeoxycholic acid which is already prohibited, and was left out in error.
- Clarifying instructions for the time limit for administration after study drug is prepared
- Removing reference to steroid doses the night before IV infusion as these references were included in error.
- Adding guidance to allowing for local TTR genotype testing if results are not available at Screening.
- Increasing the possible number of patients to be included in the subset who will have technetium scintigraphy during the study as an optional exploratory imaging assessment.
- Clarifying that follicle-stimulating hormone testing will be performed in all post-menopausal women to confirm suspected post-menopausal status.
- Broadening rescreening criteria to allow more flexibility.
- Clarifying that DNA will not be collected as biological samples for potential exploratory investigations.
- Removing baseline NYHA from the mixed-effects model repeated measures (MMRM) for the primary analysis to create a more parsimonious model.

A detailed summary of changes is provided in Table 1. Minor changes such as corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes between the original protocol and this amendment) are not detailed.

Table 1: Protocol Amendment 1 – Detailed Summary of Changes

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: Clarified study visit window for Week 3 (Day 22) is ±3 as this was left out in error; added a window for randomization based on questions from sites.

The primary change occurs in Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments).

Study Day ±Visit Window column header above Week 3 now reads: D22**±3**

The cell in the randomization row under the details column now reads: 3.5 **Window: 5D prior to Day 1**

Purpose: Added ursodeoxycholic acid to the list of prohibited medications as it is commonly prescribed for the same reasons as tauroursodeoxycholic acid which is already prohibited.

The primary change occurs in Section 4.2, Exclusion Criterion 10

Now reads:

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).

Section(s) also containing this change:

- 5.3. Concomitant Medications and Procedures

Purpose: Based on feedback from competent authorities, clarified that the prior TTR-lowering treatment mentioned in exclusion criterion 11 includes prior treatment with patisiran.

The primary change occurs in Section 4.2, exclusion Criterion 11

Now reads:

11. Received prior TTR-lowering treatment **(including patisiran)** or participated in a gene therapy trial for hATTR amyloidosis.

Purpose: Based on feedback from a competent authority, revised exclusion criterion 25 to broaden possible reasons that Investigators could exclude patients from the study.

The primary change occurs in Section 4.2, exclusion Criterion 25

Now reads:

25. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation**; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient**.

Purpose: Added exclusion Criterion 26 based on feedback from competent authorities.

The primary change occurs in Section 4.2, exclusion Criterion 26

Added text:

26. Has a history of severe hypersensitivity (eg, anaphylaxis) to any of the excipients in patisiran. Also see exclusion Criterion 11, which excludes all patients with prior TTR-lowering treatment including patisiran.

Purpose: Revised a category of reasons for discontinuation of study drug based on feedback from a competent authority.

The primary change occurs in Section 4.3.1, Discontinuation of Study Drug or Declining Procedural Assessments

The relevant bullet now reads:

- Significant violation of the protocol**; which includes required treatment with prohibited medication (as defined in Section 5.3) per investigator discretion**

Purpose: Clarified instructions for the time limit for administration after study drug is prepared; Removed reference to steroid doses the night before IV infusion as these references were included in error.

5.2.4. Suggested Guidelines for Management of Infusion-related Reactions

Relevant bullets now read:

- Following resolution of a mild or moderate IRR that required interruption of the study drug infusion, resumption of administration may occur at the Investigator's discretion at a slower infusion rate for that dose and for subsequent doses of study drug. If the infusion is delayed, the administration of the infusion should be completed no more than 16 hours ~~from the initial start of the infusion.~~ **after study drug is first diluted in saline (including infusion time).**
- If after consultation with the Medical Monitor it is agreed that an individual patient's steroid premedication will be increased, then the following steps are **recommended**:
  1. If the IRR occurred while the patient received 10 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and did not resolve with slowing of the infusion rate, then the patient should be increased by multiples of 5 mg IV dexamethasone or equivalent at least 60 minutes before the infusion ~~and/or 5 mg oral dexamethasone or equivalent the night before the IV infusion~~.
  2. Increased dose of premedication steroids should NOT exceed the combination of 20 mg IV dexamethasone or equivalent on the day of infusion ~~and 8 mg oral dexamethasone or equivalent taken the night before the infusion~~.

Purpose: Clarification regarding use of vitamin A added based on feedback from a competent authority.

The primary change occurs in Section 5.3, Concomitant Medications and Procedures

Now reads: All patients will be asked to take the recommended daily allowance of vitamin A for the duration of their participation in the study while being administered study drug. In countries where relevant, the clinical sites will provide patients with a prescription for vitamin A **at a dose consistent with local guidelines.**

Purpose: Clarification regarding obtaining of patient medical history/disease history added based on feedback from a competent authority.

The primary change occurs in Section 6.1, Screening Assessments

Now reads: Patient demographic data and medical history/disease history will be obtained**, including completion of ophthalmologic history in the eCRF**. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

Purpose: Guidance added to allow local genotype testing.

The primary change occurs in Section 6.1, Screening Assessments

Added text: **If a genetic test result that shows the presence or absence of a TTR pathogenic mutation, which would be consistent with either wtATTR or hATTR, is not available at Screening for the assessment of eligibility (Section 4.1, inclusion criterion 2a), genotyping may be conducted at a laboratory selected by the site in consultation with the Medical Monitor.**

Purpose: Rescreening criteria for eligibility requirements have been broadened to allow more flexibility.

The primary change occurs in Section 6.1.2, Rescreening

Now reads: A patient who does not meet all study eligibility criteria due to a transient **clinical** condition observed at screening, **or who fails to complete screening activities due to unforeseen or unavoidable circumstances, may be rescreened once after consultation with the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment.** ~~(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 will be re-consented if rescreening occurs outside of the 45-day screening window. In this case, all screening procedures must be repeated.

Purpose: Increased the possible number of patients to be included in the subset who will have technetium scintigraphy during the study as an optional exploratory imaging assessment.

The primary change occurs in 6.2.5.5. Technetium Scintigraphy Imaging

Now reads: At select sites, in a subset of ~~the~~ **approximately 100** patients ~~(≤60 patients)~~, technetium scintigraphy will be collected according to the Schedule of Assessments (Table 1 and Table 2), as an optional exploratory imaging assessment, to assess cardiac amyloid involvement.

Purpose: Clarified that follicle-stimulating hormone testing will be performed in all post-menopausal women. This was changed to match guidance in other parts of the protocol in which this was clear.

The primary change occurs in Section 6.5.5.2, Pregnancy Testing

Now reads: Follicle-stimulating hormone testing ~~may~~ **will** be performed **in all women suspected to be post-menopausal** to confirm ~~suspected~~ post-menopausal status.

Purpose: Based on feedback from a competent authority, removed text so Investigators will be able to decide whether a dose can be considered an overdose without consulting the Sponsor. In addition added language referencing the Pharmacy Manual for dose recording and reporting requirements.

The primary change occurs in Section 6.5.7.8. Overdose Reporting.

An overdose is defined as any dose 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~~ **as specified in the Pharmacy Manual**.

All reports of overdose (with or without an AE) must be reported within 24 hours ~~to the Sponsor or designee~~ **following the instructions outlined in the Pharmacy Manual for reporting an overdose**.

Purpose: Clarified that DNA will not be collected as biological samples for potential exploratory investigations.

The primary change occurs in Section 6.6, Biomarkers and Biospecimen Repository.

Now reads: Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2). Potential exploratory investigations may include ~~DNA,~~ RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

Purpose: For the primary analysis of 6-MWT, the MMRM model previously specified in the protocol included baseline NYHA class as a factor. Baseline NYHA class is associated with disease severity, however, it correlates with baseline 6-MWT which is included as a continuous covariate in the model. In the protocol amendment, baseline NYHA class has been removed from the MMRM in order to create a more parsimonious model.

The primary change occurs in 7.2.5.1, Primary Endpoint

The model description now reads: The model will include the baseline value as a covariate, treatment, visit, the treatment-by-visit interaction, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), ~~NYHA Class (I/II vs III),~~ and age (<75 vs ≥75 years) as fixed factors, and patient as a random effect.

Section(s) also containing this change:

- Synopsis

Purpose: Added details added based on a comment from a competent authority on how data from patients who undergo a heart transplantation and/or ventricular assist device placement will be treated with respect to the mortality analysis.

The primary change occurs in 7.2.5.2, Secondary Endpoints

Added text: **Patients who undergo a heart transplantation and/or ventricular assist device placement after randomization will be handled in the same manner as death in the primary analyses of mortality related endpoints.**

Purpose: Modified the interim sample size re-assessment so it is based on the overall tafamidis drop-in rate from blinded data based on a comment from a competent authority.

The primary change occurs in Section 7.2.10 Sample Size Re-assessment

Now reads:

Patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period, which could result in a loss of **statistical** power. An interim assessment may be performed to assess the impact of tafamidis drop-in on the power and the potential need to increase the sample size. The interim assessment, if conducted, would examine the **overall** tafamidis drop-in rate~~s in each treatment arm~~ in a~~n unblinded~~ **blinded** manner **(ie, a non-comparative assessment of the drop-in rate)** ~~without looking at the unblinded efficacy or safety data~~; therefore, no impact on the type I error is expected and no multiplicity adjustment will be made. ~~To maintain the blind for the study team, the interim assessment would be performed by a third party (ie, not the Sponsor) according to a prespecified plan.~~ **A detailed sample size re-estimation plan will be outlined in a separate document prior to implementation.**

Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting

These changes are not listed individually.

CLINICAL STUDY PROTOCOL
ALN-TTR02-011
DATED 18 APRIL 2019

Protocol Title:	APOLLO-B: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Short Title:	APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Study Drug:	Patisiran (ALN-TTR02)
EudraCT Number:	2019-001458-24
IND Number:	141240
Protocol Date:	Original protocol, 18 April 2019
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

[redacted]

[redacted]

18 Apr 2019

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTR02-011 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

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

Short Title

APOLLO-B: A Study to Evaluate Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Study Drug

Patisiran (ALN-TTR02)

Phase

Phase 3

Study Center(s)

The study will be conducted at approximately 65 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality and hospitalizations	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV)-related hospitalizations and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations over the 12-month double-blind period

Objectives	Endpoints
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV-related hospitalizations • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV-related hospitalizations over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI) o Cardiac magnetic resonance (CMR) parameters o Technetium scintigraphy parameters o Troponin I levels o Norfolk QoL-DN
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (AEs)

Study Design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study

population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the investigator. This group will be capped at 30% of total enrollment in the study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 12-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period.

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive intravenous (IV) treatment every 3 weeks with either patisiran or placebo. Prior to receiving randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an IRR with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. Study drug will be administered in the clinic as an approximately 80-minute IV infusion.

During the 12-month open-label extension period, all patients will receive treatment with open-label patisiran. Furthermore, patients who have received ≥3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home during the open-label extension period, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint; this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period. The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score.

Safety will be assessed throughout the double-blind and open-label extension periods of the study.

Number of Planned Patients

Approximately 300 patients are planned for enrollment in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults age 18 (or age of legal consent, whichever is older) to 85 years of age, inclusive, with ATTR amyloidosis with cardiomyopathy (hereditary or wild-type [wt]) who, at baseline, are either: 1) tafamidis naïve (on tafamidis for ≤30 days and none within 6 months prior to baseline); or 2) currently on tafamidis (for ≥6 months) with disease progression in the opinion of the investigator.

Study Drug, Dose, and Mode of Administration

Patisiran is a ribonucleic acid (RNA) interference (RNAi) therapeutic consisting of a double-stranded small interfering RNA (siRNA) targeting TTR mRNA formulated in a lipid

nanoparticle (LNP). The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG2000-C-DMG) in isotonic phosphate buffered saline.

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs.

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days. Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended patisiran dose is 30 mg.

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described above for double-blind patisiran.

Reference Treatment, Dose, and Mode of Administration

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

Duration of Treatment and Study Participation

The treatment duration in this study is up to 24 months, inclusive of a 12-month, double-blind, treatment period, and a 12-month, open-label, treatment period. The estimated total time on study for each patient is up to 26.5 months, including up to 45 days of screening, up to 24 months of treatment, and a 28-day safety follow-up period.

Statistical Methods

The planned enrollment for this study is 300 patients. Randomization (1:1) will be stratified by: 1) baseline tafamidis (yes vs no); 2) genotype (hATTR vs wtATTR); and 3) NYHA Class I or II and age < 75 years vs all other.

For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a treatment difference at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment.

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, the treatment-by-visit interaction, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), NYHA Class (I/II vs III), and age (<75 vs ≥75 years) as fixed factors, and

patient as a random effect. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

For patients who are tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

Safety data will be summarized descriptively.

Figure 1: Study Design

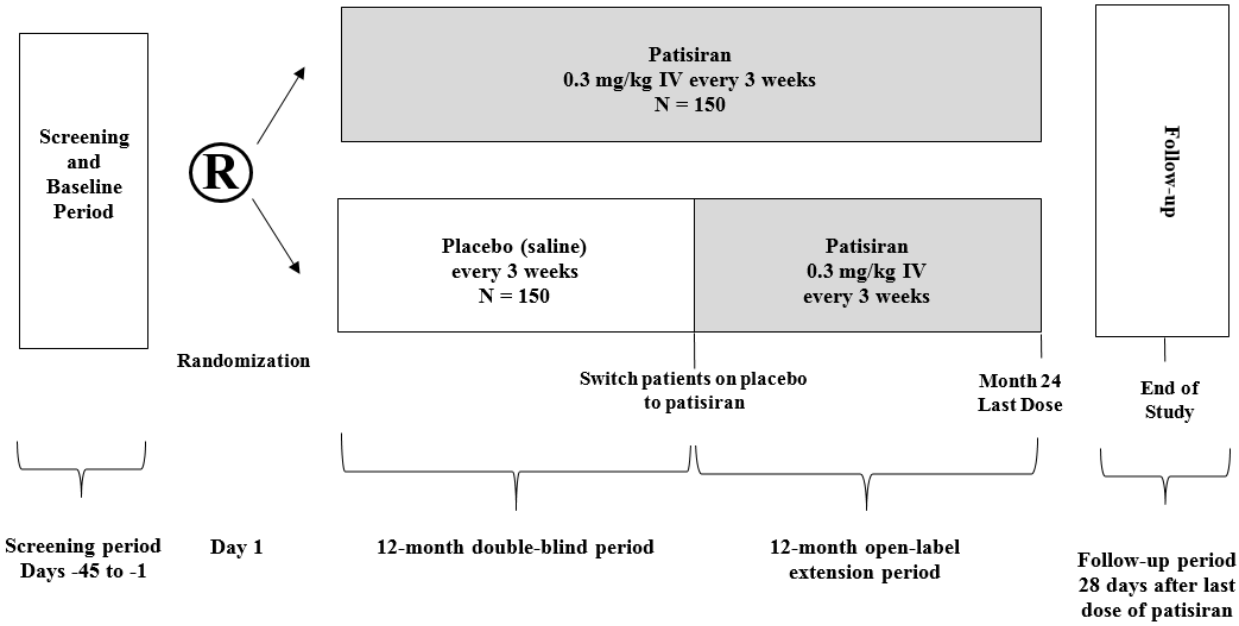

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

		Screen-ing	**Baseline**			**Double-blind Treatment Period**																					**Month 12 Efficacy Visit**	**Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]**	**Pre-tafamidis Drop-in Visit[c]**
		V1	**V2**	**Pre-dose**	**Post-dose**																								
Study Day ±Visit Window	**For Details see Section**	**Day -45 to Day -1**		**Day 1**		**D22**	**D43±3**	**D64±3**	**D85±3**	**D106±3**	**D127±3**	**D148±3**	**D169±3**	**D176-D183[a]**	**D190±3**	**D211±3**	**D232±3**	**D253±3**	**D260-D267[a]**	**D274±3**	**D295±3**	**D316±3**	**D337±3**	**D358±3**	**D365-D372[a]**		
Study Week				**Week 1**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25-26**	**27**	**30**	**33**	**36**	**37-38**	**39**	**42**	**45**	**48**	**51**	**52-53**	**52-53**	**NA[b]**
Informed Consent	6.1	X																											
Inclusion / Exclusion Criteria	4.1, 4.2	X	X																										
Demographics / Medical History	6.1	X	X																										
PND Score	6.2.7	X																											
Height	6.5.2	X																											
Efficacy Assessments																													
6-MWT	6.2.1	X	X											X [d]					X [d]						X [d]	X [d]	X [d]		
KCCQ	6.2.2			X										X					X						X	X	X		
mBMI	6.2.4			X									X										X				X		
Cardiac Biomarker Samples	6.2.5.1	NT-proBNP	X						X					X					X						X	X	X		
ATTR amyloidosis disease stage	6.2.5.2		X																						X	X	X		
NYHA Class	6.2.5.3	X												X					X						X				
Echocardiogram	6.2.5.4	X																							X				
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5		X																						X				
Norfolk QoL-DN	6.2.6		X																						X	X			

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	For Details see Section	Screen-ing	Baseline			Double-blind Treatment Period																			Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose																						
		Day -45 to Day -1		Day 1		D22	D43±3	D64±3	D85±3	D106±3	D127±3	D148±3	D169±3	D176-D183[a]	D190±3	D211±3	D232±3	D253±3	D260-D267[a]	D274±3	D295±3	D316±3	D337±3	D358±3	D365-D372[a]		
Study Week				Week 1		3	6	9	12	15	18	21	24	25-26	27	30	33	36	37-38	39	42	45	48	51	52-53	52-53	NA[b]
Pharmacodynamic Assessments																											
TTR Protein	6.3		X	X		X			X					X					X				X	X	X	X	X
Exploratory Biomarkers (plasma, serum)	6.6		X						X					X					X					X		
Safety Assessments																											
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	X		X	X
Weight	6.5.2	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed unless noted as full)	6.5.3	X Full	X			X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X Full		X Full	X
Single 12-lead ECG (unless otherwise indicated)	6.5.4		X (in triplicate, either visit)						X				X					X						X			X
Serum Chemistry, Liver Function Tests	6.5.5	X		X									X										X		X[e]	X[e]	X
Hematology	6.5.5	X		X									X										X				X
Coagulation	6.5.5	X																									
Vitamin A Levels				X																							
ADA (on dosing days, prior to dosing)	6.5.5.1			X		X			X				X											X			X

Table 1: Schedule of Assessments – Double-blind Period (Screening to Month 12 Efficacy Assessments)

Study Day ±Visit Window	For Details see Section	Screen-ing	Baseline		Double-blind Treatment Period																		Month 12 Efficacy Visit	Modified M12 Efficacy Visit (for patients w/ early treatment disc)[b]	Pre-tafamidis Drop-in Visit[c]
		V1	V2	Pre-dose	Post-dose																				
		Day -45 to Day -1		Day 1		D22	D43±3	D64±3	D85±3	D106±3	D127±3	D148±3	D169±3	D176-D183[a]	D190±3	D211±3	D232±3	D253±3	D260-D267[a]	D274±3	D295±3	D316±3	D337±3	D358±3	D365-D372[a]		
Study Week				**Week 1**		3	6	9	12	15	18	21	24	25-26	27	30	33	36	37-38	39	42	45	48	51	52-53	52-53	NA[b]
FSH (to confirm postmenopausal, if applicable)	Table 3, 6.5.5.2	X																							
Pregnancy Test	Table 3, 6.5.5.2	X		X					X				X					X					X			
Review/Record Hospitalization, Urgent Care Visits, and Procedures			----------X----------																						
Review/Record AEs, Con Meds	6.5.7, 5.3		----------X----------																						
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																											
Plasma PK	6.4			X	X				X				X					X					X			
Drug Administration																											
Randomization	3.5			X																							
Premedication/ Study Drug	5.2.1, 5.2.3			X		X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; FSH=follicle-stimulating hormone; KCCQ=Kansas City Cardiomyopathy Questionnaire; M=month; mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit.

[b] This Modified Month 12 Efficacy Visit is to be performed at Month 12 for patients who discontinued treatment early (ie, prior to Month 12), and choose to remain in the study. All patients who discontinue from study drug during the double-blind period will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including this Modified Month 12 Efficacy Visit. Such patients will also receive assessments at the Early Treatment Discontinuation Visit (7 to 14 days after their last dose of study drug); and the safety follow-up visit (28 days after the last dose of study drug) (Table 2), as described in Section 4.3.1.

[c] See Section 5.3.1; patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period. In all cases, the Pre-tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of double-blind study drug (ie, 7 to 14 days post dose). Thereafter, the patient will continue with all assessments per the Schedule of Assessments, including the Month 12 Efficacy Visit. At the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

[d] As described in Section 6.2.1, to avoid a potential training effect resulting from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be performed within each of the following time periods: Day 2 to Day 214 (includes the scheduled Weeks 25-26 assessment); Day 215 to Day 319 (includes the scheduled Weeks 37-38 assessment); and Day 320 to Day 372 (includes the scheduled Weeks 52-53 assessment). Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit [Table 2]); no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed as scheduled.

[e] Serum creatinine only.

Table 2: Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up

		Open-label Extension Period																					Early Treatment Disc Visit[b]	Follow-up
																						EOS		
Study Day ±Visit Window	**For Details see Section**	**D379±3**	**D400±3**	**D421±3**	**D442±3**	**D463±3**	**D484±3**	**D505±3**	**D526±3**	**D547±3**	**D554-D561[a]**	**D568±3**	**D589±3**	**D610±3**	**D631±3**	**D638-D645[a]**	**D652±3**	**D673±3**	**D694±3**	**D715±3**	**D736±3**	**D743-D750[a]**	**7- 14 Days after Last Dose**	**D764±10**
Study Week		**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**	**81**	**84**	**87**	**90**	**91-92**	**93**	**96**	**99**	**102**	**105**	**106-107**	**NA**	**109**
Efficacy Assessments																								
6-MWT	6.2.1										X					X						X	X	
KCCQ	6.2.2										X					X						X	X	
mBMI	6.2.4							X										X					X	
Cardiac Biomarker Samples	6.2.5.1					X					X					X						X	X	
ATTR amyloidosis disease stage	6.2.5.2																					X		

Table 2: Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																				EOS	Early Treatment Disc Visit[b]	Follow-up
		D379±3	D400±3	D421±3	D442+3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]	7- 14 Days after Last Dose	D764±10
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107	NA	109
NYHA Class	6.2.5.3										X					X						X		
Echocardiogram	6.2.5.4										X											X		
CMR, technetium (select sites only)	6.2.5.6, 6.2.5.5										X											X		
Norfolk QoL-DN	6.2.6																					X		
Pharmacodynamic Assessments																								
TTR Protein	6.3					X					X					X						X	X	X
Exploratory Biomarkers (plasma, serum)	6.6					X					X					X						X		
Safety Assessments																								
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
Weight	6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (symptom-directed)	6.5.3	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X		X	X
Single 12-lead ECG	6.5.4					X				X					X						X		X	
Serum Chemistry, Liver Function Tests	6.5.5							X										X				X[c]	X	X
Hematology	6.5.5							X										X					X	X
Pregnancy Test	Table 3, 6.5.5.2			X				X					X					X			X	X	X	
Review/Record Hospitalization, Urgent Care Visits, and Procedures		----------X----------																						

Table 2: Schedule of Assessments – Open-label Extension Period (Through Month 24), Early Treatment Discontinuation Visit, and Follow-up

Study Day ±Visit Window	For Details see Section	Open-label Extension Period																				Early Treatment Disc Visit[b]	Follow-up
																					EOS		
		D379±3	D400±3	D421±3	D442+3	D463±3	D484±3	D505±3	D526±3	D547±3	D554-D561[a]	D568±3	D589±3	D610±3	D631±3	D638-D645[a]	D652±3	D673±3	D694±3	D715±3	D736±3	D743-D750[a]	7- 14 Days after Last Dose	D764±10
Study Week		54	57	60	63	66	69	72	75	78	79-80	81	84	87	90	91-92	93	96	99	102	105	106-107	NA	109
Review/Record AEs, Con Meds	6.5.7, 5.3	----------X----------																					
Vital Status Check	6.5.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments																								
Plasma PK	6.4																						X	
Drug Administration																								
Premedication, Study Drug	5.2.1, 5.2.3	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X			

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con Meds=concomitant medications; CMR=cardiac magnetic resonance; D=day; Disc=discontinuation; ECG=electrocardiogram; EOS=End of Study (visit); KCCQ=Kansas City Cardiomyopathy Questionnaire; mBMI=modified body mass index; 6-MWT=6-minute walk test; NA=not applicable; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetics; QoL-DN=Quality of Life-Diabetic Neuropathy; TTR=transthyretin; V=visits.

[a] This efficacy visit is conducted 7 to 14 days after the prior visit.

[b] Patients who discontinue early from study drug will be asked to complete the Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug. In addition, patients discontinuing early from study drug during the double-blind period will be encouraged to remain on the study and complete assessments through Month 12 and complete the Modified Month 12 Efficacy Visit (see Table 1); they will also be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug as described in Section 4.3.1.

[c] Serum creatinine only.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALN-18328	siRNA targeting TTR
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APOLLO	Patisiran pivotal Phase 3 clinical study ALN-TTR02-004
AST	Aspartate aminotransferase
ATTR	Amyloid transthyretin
BMI	Body mass index
BUN	Blood urea nitrogen
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration at end of infusion
$C_{max,ss}$	Steady-state C_{max}
C_{min}	Minimum pre-infusion concentration
$C_{min,ss}$	Steady-state C_{min}
CMR	Cardiac magnetic resonance
Con Meds	Concomitant medication
$C_{p(30min)}$	30-minute post-infusion concentration
$C_{p,ss(30min)}$	Steady-state $C_{p(30min)}$
CRF	Case report form
CFR	Code of Federal Regulations
CV	Cardiovascular
DLin-MC3-DMA	1,2-Dilinoleyloxy-N,N-dimethylpropylamine
DMC	Data Monitoring Committee
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunoassay
EOS	End of study
FAS	Full analysis set

Abbreviation	Definition
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
HF	Heart failure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRS	Interactive Response System
IV	Intravenous(ly)
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire– Overall Summary
LNP	Lipid nanoparticle
LS	Least squares
mBMI	Modified body mass index
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 neurological impairment score +7
mRNA	Messenger ribonucleic acid
6-MWT	6-minute walk test
NA	Not applicable
Norfolk QoL-DN	Norfolk Quality of Life - Diabetic Neuropathy
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association

Abbreviation	Definition
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEG_{2000}-C-DMG	3-N-[(ω-methoxy poly(ethylene glycol)2000) carbamoyl]-1,2-dimyristyloxy-propylamine
PK	Pharmacokinetic
PND	Polyneuropathy disability
PT	Preferred term
RBC	Red blood cell
RBP	Retinol binding protein
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
siRNA	Small interfering RNA
Tc	Technetium
TTR	Transthyretin
ULN	Upper limit of normal
US	United States
V30M	Valine to methionine mutation at position 30
V122I	Valine to isoleucine mutation at position 122
wt	Wild type
wtTTR	Wild type transthyretin

1. INTRODUCTION

1.1. Disease Overview

Transthyretin (TTR)-mediated amyloidosis (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 (ageing) causes, respectively. In ATTR amyloidosis, deposition of TTR in various organs results in progressive, chronically debilitating morbidity and mortality. The most common manifestations of ATTR amyloidosis are polyneuropathy and cardiomyopathy (ie, ATTR amyloidosis with cardiomyopathy).

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]

In hATTR amyloidosis, 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. These misfolded TTR monomers can then self-assemble into oligomers and form amyloid fibrils and plaques in the extracellular space of various tissues [Hou 2007], including the peripheral nervous system, heart, gastrointestinal tract, kidney, central nervous system and eye, leading to cellular injury and organ dysfunction with corresponding clinical manifestations. Since almost all patients are heterozygous for the mutated TTR allele, the amyloid fibrils typically consist of both mutant and wtTTR.

There are over 120 reported TTR genetic mutations associated with hATTR amyloidosis, and almost all patients are heterozygous for the mutated TTR allele.[Ando 2013; Connors 2003] The phenotypic expression varies depending on the predominant site of deposition of the amyloid fibrils with some mutations associated with predominantly polyneuropathy manifestations and others associated with predominantly cardiomyopathy manifestations. However, most patients experience both over the course of their disease.

The most common TTR mutation is the valine to methionine mutation at position 30 (V30M), accounting for approximately 50% of cases worldwide, and occurring primarily in families with heritage from Portugal, Sweden, Japan, and Brazil.[Parman 2016] This genotype is most commonly associated with multisystemic polyneuropathy. The valine to isoleucine at position 122 (V122I) mutation is most commonly associated with cardiomyopathy and occurs primarily in African Americans. In these individuals, the mean age at diagnosis is approximately 65 to 70 years, with symptom onset typically occurring after the age of 65.[Jacobson 2011; Quarta 2015] While there appears to be an association between carrier status and the development of heart failure (HF) and echocardiographic features of cardiac amyloidosis, the exact penetrance of this particular allele is unknown, and estimates vary widely.

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] Patients with this

condition do not have a pathogenic mutation in the TTR gene and the amyloid fibrils consist only of wtTTR protein, which form amyloid deposits typically found in heart tissue.

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 preserved until late stages of the disease.[Castano 2015; Dungu 2012; Mohty 2013; Ruberg 2012] Cardiac infiltration by amyloid can also lead to conduction disturbances and arrhythmias.[Adams 2016; Ando 2013; Benson and Kincaid 2007; Connors 2004] Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, in addition to clinical measurements of ambulation, and quality of life. Progression of disease in this population can be seen over a period of 12 months as demonstrated by differences in 6-minute walk test (6-MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary (KCCQ-OS) in the Phase 3 ATTR-ACT study.[Maurer 2018] Based on natural history data, patients typically experience progressive symptoms of HF resulting in hospitalization and with death typically occurring 2.5 to 5 years after diagnosis.[Castano 2015; Damy 2015; Dungu 2012; Hawkins 2015]

1.2. Current Treatments

The treatment of ATTR amyloidosis requires a multidisciplinary approach primarily involving cardiology, neurology, and gastroenterology specialties. While there are treatments for polyneuropathy that are available to hATTR amyloidosis patients, for most regions no treatments are currently available for the cardiomyopathy phenotype for either the hATTR or wtATTR forms. Palliative/symptomatic therapies directed at specific symptoms, including volume control and treatment of cardiac arrhythmias and conduction system disturbances, including cardiac pacemakers where appropriate, have been the mainstay of treatment despite their limited effectiveness.

Given that the liver is the primary source of TTR, orthotopic liver transplantation (OLT) has been used for hATTR amyloidosis patients since the early 1990s. However, OLT is intended to eliminate mutant TTR from circulation, but has no effect on the hepatic production of wtTTR, which continues to be made by the transplanted liver and can continue to deposit in the heart. OLT has also only been shown to be effective in slowing the progression of disease in patients with an early age of onset (<50 years of age) [Okamoto 2009], and especially for those with the V30M mutation and short disease duration before transplant. Consequently, almost two-thirds of patients with hATTR amyloidosis are not transplant-eligible.

Tafamidis, a TTR tetramer stabilizer that acts by binding to the thyroxine-binding site on TTR to reduce its dissociation into misfolded amyloidogenic monomers, is currently approved in Europe, Japan, Mexico, and select countries in South America, but not in the United States (US), for the treatment of patients with hATTR amyloidosis with polyneuropathy.[Coelho 2016] Recently, tafamidis was evaluated in the Phase 3 ATTR-ACT trial in patients with ATTR amyloidosis with cardiomyopathy (including hereditary and wt).[Maurer 2018] This study demonstrated that tafamidis treatment over 30 months was associated with lower all-cause mortality and cardiovascular (CV)-related hospitalizations compared with placebo treatment. Additionally, tafamidis treatment resulted in a slowing of the decline in functional capacity

(6-MWT) and quality of life (KCCQ-OS) compared to placebo. However, consistent with the expected pharmacodynamic (PD) effect of TTR stabilization, the effects of tafamidis on mortality outcomes was not observed until late in treatment, with differentiation between treatment groups occurring only after 18 months of treatment. Furthermore, although improvements with tafamidis relative to placebo were observed in 6-MWT and KCCQ-OS, minimal changes in echocardiographic parameters were observed, and tafamidis-treated patients still progressed during the study.

As of early 2019, tafamidis was not approved in the US for patients with ATTR amyloidosis (neither polyneuropathy nor cardiomyopathy phenotypes); however, it is anticipated that tafamidis may become available for patients with the cardiomyopathy phenotype in the US and in other regions, based on the ATTR-ACT study results. In Japan, tafamidis was approved in 2019 for use in transthyretin-type cardiac amyloidosis (wt and mutant), in addition to approval for transthyretin-type familial amyloid polyneuropathy.

The results of the ATTR-ACT study 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 a ribonucleic acid (RNA) interference (RNAi) therapeutic, may be required to halt or reverse the debilitating and ultimately fatal course of disease.

1.3. Patisiran Clinical Development

Patisiran is a small interfering RNA (siRNA) specific for TTR, which is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration.[Akinc 2010] The patisiran drug product (ALN-TTR02; patisiran-LNP, hereafter referred to as "patisiran") is designed to significantly suppress liver production of both wt and all mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with ATTR amyloidosis.

Patisiran utilizes the mechanism of RNAi to selectively degrade TTR messenger RNA (mRNA) and thereby reduce the expression of its corresponding protein.[Bumcrot 2006] Patisiran is formulated (via the LNP) to target delivery to hepatocytes in the liver, the primary source of TTR protein in circulation. Following IV infusion, opsonization of the LNP by apolipoprotein E facilitates binding to the low-density lipoprotein receptor on hepatocytes and subsequent endocytosis. Fusion of the ionizable lipid component of the LNP with the endosomal membrane then leads to release of the siRNA into the cytoplasm where it can bind to and activate the RNA-induced silencing complex (RISC). Upon binding and activation of RISC in the cytoplasm within hepatocytes, the siRNA duplex unwinds, and the antisense strand specifically binds to a genetically conserved sequence in the 3' untranslated region of wt and mutant TTR mRNA. The Argonaute-2 endonuclease within the RISC/siRNA enzyme complex catalytically degrades wt and mutant TTR mRNA, resulting in a reduction of wt and mutant TTR protein.

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing patisiran for the treatment of patients with ATTR amyloidosis. Based on results from the pivotal Phase 3 APOLLO study (Section 1.3.1), patisiran is approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults and in the European Union for the treatment of hATTR

amyloidosis in adult patients with stage 1 and stage 2 polyneuropathy. Ongoing development is intended to establish patisiran for the treatment of ATTR (hereditary and wt) amyloidosis with cardiomyopathy based on exploratory cardiac results from the APOLLO study (Section 1.3.1.1), which provides preliminary evidence in support of the use of patisiran for the treatment of the cardiomyopathy manifestations of the disease.

The nonclinical pharmacology, pharmacokinetics (PK), and toxicology of patisiran were evaluated in a series of in vitro and in vivo studies that have enabled chronic dosing in clinical studies.

1.3.1. The Phase 3 APOLLO Study

The safety and efficacy of patisiran was shown in a Phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study (ALN-TTR02-004, APOLLO) that met the primary and all secondary endpoints.[Adams 2018] This study demonstrated that, in patients with hATTR amyloidosis who exhibited a broad range of disease severity and TTR genotypes, treatment with patisiran leads to a significant improvement in neuropathy (modified neurological impairment score +7 [mNIS+7]) relative to placebo at 18 months (primary endpoint), as well as significant improvement in quality of life (Norfolk Quality of Life - Diabetic Neuropathy [Norfolk QoL-DN], key secondary endpoint) relative to placebo at 18 months. Significant improvement in neuropathy and quality of life were also observed at Month 9. This study furthermore demonstrated that treatment with patisiran is associated with an improvement in overall health (gait speed, nutritional status, and disability), with improvement in these endpoints seen as early as at Month 9.

In the patisiran group, serum TTR reduction was seen after the first dose and was stably maintained over the duration of the study; the mean TTR percent reduction from baseline was 82.6% and 84.3% at Months 9 and 18, respectively. A correlation (Pearson's r, 0.59; 95% CI, 0.49-0.68) was observed between the degree of TTR reduction from baseline and the change in the mNIS+7 at 18 months.

Patisiran showed an acceptable safety profile in the APOLLO study. Common adverse events (AEs) occurring more frequently with patisiran compared to placebo included peripheral edema (30% versus 22%) and infusion related reactions (IRRs) (19% versus 9%, respectively).

1.3.1.1. Cardiac Results and Cardiac Subpopulation Data from APOLLO

In APOLLO, evidence of potential cardiac amyloid involvement was seen in most patients in the study; 80% had left ventricular wall thickness >13 mm and 79% had abnormal levels of the cardiac biomarker N-terminal prohormone B-type natriuretic peptide (NT-proBNP).[Solomon 2018] As well, 56% of the population met the prespecified criteria for inclusion in a subpopulation of patients with evidence of cardiac amyloid involvement (ie, the cardiac subpopulation, with baseline left ventricular wall thickness ≥13 mm and no history of hypertension or aortic valve disease). In these patients, treatment with patisiran for up to 18 months resulted in improvement relative to placebo in important measures of cardiac structure and function. These included reduction in ventricular wall thickness and decrease (improvement) in global longitudinal strain.[Solomon 2018] In addition, patisiran treatment led to a reduction (improvement) in NT-proBNP and an improvement in functional capacity, as measured by 10-meter walk test assessment of gait speed, relative to the placebo group.

Overall, patisiran had an acceptable safety profile, based on an in-depth analysis of cardiac events in both the overall (modified intent-to-treat) population and the cardiac subpopulation. Importantly, in a post hoc analysis of safety data in the modified intent-to-treat population, rates of any hospitalization and/or all-cause death were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups respectively, while the rates of cardiac hospitalizations and/or all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups respectively. This approximates a reduction in event rate of approximately 50% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality for patients in the patisiran group compared to those in the placebo group.[Solomon 2018] Similar reductions in the event rates were observed in the cardiac subpopulation in APOLLO (approximately 55% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality; data on file).

The observed cardiac data from the APOLLO study support the therapeutic hypothesis that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis and warrant ongoing development for this indication.

1.3.2. Phase 3, Open-label Extension Study

Study ALN-TTR02-006 is an ongoing multicenter, open-label extension study designed to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis who have completed a prior Phase 2 or 3 parent study with patisiran (ALN-TTR02-003 or ALN-TTR02-004 [APOLLO]). The interim data from this open-label extension study were consistent with, and extended, the acceptable safety profile and clinical efficacy of patisiran observed in the Phase 3 APOLLO study.

No new safety signals have emerged for patients with long-term patisiran treatment.

1.4. Study Design Rationale

This study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of patisiran in adult patients with ATTR amyloidosis with cardiomyopathy. The efficacy of patisiran on functional capacity will be evaluated via change at Month 12 in the 6-MWT (primary endpoint). The study will include patients with wtATTR and hATTR amyloidosis with cardiomyopathy who, at baseline, are either tafamidis naïve or have been on tafamidis for ≥6 months with disease progression, in the opinion of the investigator.

Confidence in a beneficial treatment effect with patisiran in this patient population with ATTR amyloidosis with cardiomyopathy comes from the Phase 3 APOLLO study of patisiran in patients with hATTR amyloidosis with polyneuropathy. As described in Section 1.3.1 and Section 1.3.1.1, TTR lowering with patisiran demonstrated multiple benefits in a broad range of disease manifestations, including a substantial improvement in neuropathy and quality of life, as well as autonomic symptoms, motor strength, ambulatory ability, disability, and nutritional status.[Adams 2018] Furthermore, in a prespecified subgroup of patients with evidence of cardiac involvement, which was a majority (56%) of the overall study population, a beneficial treatment effect of patisiran compared to placebo was observed for assessments of cardiac structure and function as well as the cardiac biomarker NT-proBNP.[Solomon 2018]

The 6-MWT (primary endpoint assessment) 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 2014] The KCCQ-OS (first secondary endpoint assessment) 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 et al. 2006) Both 6-MWT and KCCQ-OS were shown to rapidly and consistently decline over time in cardiac ATTR amyloidosis patients and, in the 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 primary and key secondary endpoints, respectively.

Assessment of the primary endpoint at Month 12 is supported by placebo-arm data from the ATTR-ACT study showing substantial disease progression (via the 6-MWT) over an equivalent time; as well, data from APOLLO demonstrated a patisiran treatment effect as early as 9 months on multiple manifestations of hATTR amyloidosis (neuropathy, quality of life, NT-proBNP, and functional capacity [ie, gait speed]).[Maurer 2018]

The inclusion of placebo as a control allows for a rigorous analysis of the treatment effect of patisiran. If tafamidis becomes an approved therapy for ATTR amyloidosis with cardiomyopathy in a given region while this study is in progress, patients who are naïve to tafamidis treatment at baseline may commence concomitant on-label tafamidis during the study (ie, tafamidis drop-in) (Section 5.3.1).

1.5. Dose Rationale

The approved and recommended dosage of patisiran for the treatment of the polyneuropathy in patients with hATTR amyloidosis is 0.3 mg/kg administered IV every 3 weeks for patients weighing <100 kg and a fixed dose of 30 mg administered every 3 weeks for patients weighing 100 kg or more. This dosage was selected based on dose-response analyses from three Phase 1 and 2 studies demonstrating dose-dependent TTR reduction, with the maximum reduction achieved at 0.3 mg/kg. This regimen was further confirmed in the pivotal Phase 3 APOLLO study, where this dosage showed significant clinical activity and was well tolerated by patients with hATTR amyloidosis with polyneuropathy, including those in the cardiac subpopulation. The approved dosing regimen used in the treatment of polyneuropathy is being employed in this study since the mechanism of action of patisiran (ie, serum TTR lowering) for treatment of polyneuropathy and cardiomyopathy is the same.

1.6. Benefit-risk Assessment

ATTR amyloidosis with cardiomyopathy is a rare, serious, life-threatening, multisystemic disease characterized by deposition of TTR in various organs. Without treatment, the disease progresses, resulting in chronically debilitating morbidity and mortality, with the most common manifestations being cardiomyopathy and polyneuropathy. Patients with symptomatic HF experience rapid progression of their amyloidosis with cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, ambulation, and quality of life seen over a period of 18 months or less.[Ruberg and Berk 2012]

The benefit-risk profile of patisiran has been established in extensive clinical development; in Phase 1, 2, and 3 clinical studies, patisiran administered IV demonstrated a potent, dose-dependent inhibition of TTR. In the Phase 3 APOLLO study of patisiran, the primary and all secondary endpoints were met.[Adams 2018] Furthermore, exploratory cardiac results from the APOLLO study suggest that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon 2018] and provide preliminary evidence in support of the use of patisiran for the treatment patients with ATTR amyloidosis with cardiomyopathy (Section 1.3.1.1).

In APOLLO, as well as in the ongoing Phase 3, open-label extension study (ALN-TTR02-006), an acceptable safety profile with patisiran was demonstrated. Most AEs were mild or moderate in severity. Transient infusion-related reactions (IRRs) were observed, but all IRRs were mild or moderate in severity, none were reported as serious AEs (SAEs). No clinically significant laboratory or hematologic changes were observed. Furthermore, in APOLLO, an acceptable safety profile was also observed in a prespecified subgroup of patients with evidence of cardiac amyloid involvement. [Solomon 2018]

For patisiran, important identified risks include IRRs. To minimize this risk, all patients must receive premedication with a corticosteroid, paracetamol/acetaminophen, and H1 and H2 blockers prior to patisiran administration (Section 5.2.1). The infusion may be interrupted or slowed if an IRR occurs (Sections 5.2.3 and 5.2.4). Important potential risks also include severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients. Patisiran is contraindicated in patients with a history of severe hypersensitivity (eg, anaphylaxis or anaphylactoid reactions) to patisiran or any of the excipients.

Vitamin A deficiency is also considered an important potential risk. Nonclinical and clinical data with patisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in 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 (Section 5.3). 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 patisiran.

Detailed information about the known and expected benefits and risks of patisiran may be found in the current edition of the Investigator's Brochure.

During the study, patients will be monitored, including evaluation of laboratory monitoring for liver function test abnormalities, renal function, and other standard hematology and blood chemistries. As the risk of embryofetal toxicity is currently unknown, females of child-bearing potential participating in the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception as specified in the protocol.

An external, independent Data Monitoring Committee (DMC) will monitor and ensure the safety of trial participants (see Section 3.7).

In conclusion, exploratory cardiac results from the APOLLO study suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of hATTR amyloidosis [Solomon

2018] (Section 1.3.1.1) together with the established benefit-risk profile of patisiran demonstrated in the Phase 3 APOLLO study (and supportive data from the ALN-TTR02-003 and ALN-TTR02-006 studies), support the evaluation of patisiran in a Phase 3 study in adult patients with ATTR amyloidosis (wtATTR and hATTR) cardiomyopathy.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-minute walk test [6-MWT]) in patients with ATTR amyloidosis with cardiomyopathy	Change from baseline at Month 12 in 6-MWT
Secondary	
To evaluate the efficacy of patisiran compared with placebo treatment on: • Health status and health-related quality of life • Patient mortality and hospitalizations	• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score • Composite endpoint of all-cause mortality, frequency of cardiovascular (CV)-related hospitalizations and change from baseline in 6-MWT over the 12-month double-blind period • Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations over the 12-month double-blind period
Exploratory	
To evaluate the efficacy of patisiran compared with placebo treatment on: • All-cause mortality and CV-related hospitalizations • Cardiac biomarkers and biomarker-based risk assessment • Manifestations of cardiac amyloid involvement	• Composite endpoint of all-cause mortality and frequency of CV-related hospitalizations over the 12-month double-blind period • Change from baseline at Month 12 in: o N-terminal prohormone B-type natriuretic peptide (NT-proBNP) o ATTR amyloidosis disease stage • Change from baseline at Month 12 in: o New York Heart Association (NYHA) Class o Echocardiographic parameters o Modified body mass index (mBMI)

Objectives	Endpoints
	○ Cardiac magnetic resonance (CMR) parameters ○ Technetium scintigraphy parameters ○ Troponin I levels ○ Norfolk QoL-DN
Pharmacodynamics (PD) and Pharmacokinetics (PK)	
• To evaluate the PD effect of patisiran on transthyretin (TTR) reduction • To determine the plasma concentration of patisiran and 2 lipid excipients • To assess presence of anti-drug antibodies (ADA)	• Change from baseline in serum TTR levels through Month 12 • Plasma PK exposure parameters (maximum plasma concentration at end of infusion [C_{max}], 30-minute post-infusion concentration [$C_{p(30min)}$], and pre-infusion concentration [C_{min}] • Frequency and titer of ADA
Safety	
• To evaluate the safety and tolerability of patisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of adverse events (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 patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:

- Tafamidis naïve; or
- Currently on tafamidis (for ≥6 months), with disease progression in the opinion of the investigator. This group will be capped at 30% of total enrollment in the study.

In addition to patients who have never taken tafamidis, patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve for this study.

The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 12-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period (Figure 1).

After screening, during the 12-month double-blind period, eligible patients will be randomized to receive IV treatment every 3 weeks with either patisiran (0.3 mg/kg for patients weighing <100 kg; 30-mg fixed dose for patients weighing ≥100 kg) or placebo. Prior to receiving

randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an IRR with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. (Patients randomized to placebo will also receive premedications to maintain the blind.) Study drug will be administered in the clinic as an approximately 80-minute IV infusion.

During the 12-month open-label extension period, all patients will receive treatment with open-label patisiran. Furthermore, patients who have received ≥3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion.

To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint (Section 2); this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period at the time points noted in the Schedule of Assessments (Table 1 and Table 2). The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score.

Safety will be assessed throughout the study, as described in the Schedule of Assessments for the double-blind period (Table 1) and for the open-label extension period (Table 2).

3.2. Duration of Treatment

The treatment duration in this study is up to 24 months, inclusive of a 12-month, double-blind, treatment period, and a 12-month, open-label, treatment period.

3.3. Duration of Study Participation

The estimated total time on study for each patient is up to 26.5 months, including up to 45 days of screening, up to 24 months of treatment (see Section 3.2), and a 28-day safety follow-up period.

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:

- the patient has completed the end of study (EOS; Month 24) visit, or
- the patient has completed the follow-up visit 28 days after the last dose of patisiran.

3.4. Number of Planned Patients

The planned enrollment for this study is 300 patients with wtATTR and hATTR amyloidosis with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR.

3.5. Method of Assigning Patients to Treatment Groups

Using the interactive response system (IRS), patients will be randomized 1:1 to the patisiran or placebo arm. Randomization will be stratified by:

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

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 IRS. The Investigator or his/her designee will contact the IRS to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

3.6. Blinding

During the double-blind period of the study, all site personnel will be blinded to the study treatment, except the pharmacist and designated pharmacy personnel who will set-up, dispense, and prepare the infusion. Patisiran confers a slightly opalescent color relative to the clear saline (placebo) infusate; therefore, all infusion bags and lines will be covered with amber bags and line covers by the unblinded personnel to prevent visualization by the blinded study personnel and patient, as described in detail in the Pharmacy Manual.

After the pharmacist (and designated pharmacy personnel) has prepared the infusion, separate blinded personnel will administer study drug and monitor the patient during and after the infusion. All patients will be blinded to treatment and will receive an IV infusion once every 3 weeks using identical volumes for patisiran and placebo.

Study personnel performing assessments related to the primary and secondary endpoints will be different from the Investigator and other personnel managing the patient, and all of these study personnel will be blinded to any clinical laboratory results that could potentially unblind them (eg, TTR levels). In addition, the study personnel performing assessments related to the primary and secondary efficacy endpoints will also be blinded to the results of any previous assessments.

Furthermore, unblinded source documentation containing all descriptions of pharmacy preparations and infusions or distribution of study drug or randomization data will be stored separate from all other study data/records and from other pharmacy staff not participating on the study.

Blinding will be maintained until the last patient completes their Month 12 visit.

3.6.1. Emergency Unblinding

During the double-blind period of the study, 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. 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 IRS instructions for details on emergency unblinding.

3.7. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study through the double-blind period (through Month 12), providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.8. Adjudication Committee

An independent Adjudication Committee will review deaths and hospitalizations and will attribute a cause (CV versus non-CV) according to the responsible underlying disease process rather than the immediate mechanism. Deaths and hospitalizations will be classified as specified in the Adjudication Committee 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 and Sex

1. Age 18 (or age of legal consent, 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:

   Hereditary ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

   a. TTR pathogenic mutation consistent with hATTR.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at screening).
   c. 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] or ^{99m}Tc-pyrophosphate [PYP-Tc]) with Grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) has been excluded.
   d. If MGUS, confirm TTR protein in tissue with immunohistochemistry (IHC) or mass spectrometry.

Wild-type ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:

a. Absence of pathogenic TTR mutation.
b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at screening).
c. Amyloid deposits in cardiac tissue with TTR precursor identification by IHC, mass spectrometry, **OR** technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc] or ^{99m}Tc-pyrophosphate [PYP-Tc]) with Grade 2 or 3 cardiac uptake, if MGUS has been excluded.
d. If MGUS, confirm TTR protein in cardiac tissue with IHC or mass spectrometry

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; in addition to patients who have never taken tafamidis, those who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.
   b. Currently on tafamidis (for ≥6 months) and has demonstrated disease progression, as determined by the Investigator. (At the time of study entry, tafamidis treatment must be on-label use of commercial tafamidis.)
5. Patient is clinically stable, with no CV-related hospitalizations within 6 weeks prior to randomization, as assessed by the Investigator.
6. Able to complete ≥150 m on the 6-MWT at screening.
7. Screening NT-proBNP >600 ng/L and <8500 ng/L.

Informed Consent

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent; and patient agrees to sign the medical records release form for collection of vital status.

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) or leptomeningeal amyloidosis.

2. NYHA Class III **AND** ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3000 ng/L and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2).[Gillmore 2018]
3. NYHA Class IV at the Screening visit.
4. Has a polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires cane or stick to walk, or is wheelchair bound) at the Screening visit.

Laboratory Assessments

5. Has any of the following laboratory parameter assessments at screening:
   a. Aspartate transaminase (AST) or alanine transaminase (ALT) levels >2.0 × the upper limit of normal (ULN).
   b. Total bilirubin >ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if total bilirubin <2 × ULN.
   c. International normalized ratio (INR) >1.5 (unless patient is on anticoagulant therapy, in which case excluded if INR >3.5).
6. Has eGFR <30 mL/min/1.73 m^2 (using the modification of diet in renal disease [MDRD] formula).
7. Has known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.

Prior/Concomitant Therapy

8. Tafamidis naïve patients (at baseline) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
9. Is currently taking diflunisal; if previously on this agent, must have at least a 6-month wash-out prior to dosing (Day 1).
10. Is currently taking doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 30-day wash-out prior to dosing (Day 1).
11. Received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR amyloidosis.
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 6 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 calcium channel blockers (eg, verapamil, diltiazem) or digitalis.

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 electrocardiogram [ECG] changes).

15. Has non-amyloid disease affecting exercise testing (eg, severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation).
16. Recent or planned orthopedic procedure during the double-blind period (eg, lower extremity or back surgery) that could impact 6-MWT.
17. Unstable congestive heart failure (CHF) (eg, no adjustment of diuretics at time of screening required to achieve optimal treatment of CHF).
18. Had acute coronary syndrome or unstable angina within the past 3 months.
19. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.
20. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
21. Has persistent elevation of systolic (>180 mmHg) and diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.
22. Has untreated hypo- or hyperthyroidism.
23. Prior or planned heart, liver, or other organ transplant.
24. Had a malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
25. Has other medical conditions or comorbidities 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 5.5.1.
27. Female patient is pregnant or breast-feeding.

Alcohol Use

28. Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (for females, more than 14 units of alcohol per week; for males, more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer]);
29. 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 or their legal guardians 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 electronic case report form (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 6.5.7.7 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 is captured in the final analyses.

If this occurs, 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 and Table 2), 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 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 6.5.7. 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 from study drug during the 12-month double-blind period, defined as the time the first dose of study drug is administered on Day 1 through completion of the Month 12 Efficacy Visit (primary endpoint assessment), will be encouraged to remain on the study and complete assessments through Month 12 (excluding PK assessments), including a Modified Month 12 Efficacy Visit (Table 1). They will also be asked to complete an Early

Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, 28 days after the last dose of study drug (Table 2); see Section 3.3.1.

Patients who discontinue patisiran during the open-label extension period will be asked to complete an Early Treatment Discontinuation Visit (7-14 days after their last dose) and the safety follow-up visit, per the Schedule of Assessments (Table 2), 28 days after the last dose of patisiran; see Section 3.3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop the patient's participation in the study-at any time. A patient or legal guardian 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, through the Modified Month 12 Efficacy Visit, and the 28-day follow-up visit, or alternatively may complete any minimal assessments for which the patient or legal guardian consents as described in Section 4.3.1. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 12 visit, every effort should be made to conduct the assessments scheduled to be performed at the Modified Efficacy Visit (Table 1).

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, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and 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.

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 6.5.7.

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 fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian 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 or legal guardian (where possible, 3 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 or legal guardian 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 can search publicly available records (where permitted and allowed by local law) to ascertain survival status. 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 preparation, administration, and storage of study drug (patisiran and placebo) is provided in the Pharmacy Manual.

All patients will be instructed to take the recommended daily allowance of vitamin A while on the study.

5.2.1. Premedication

All patients will receive premedication prior to study drug administration to reduce the risk of IRRs. Each of the following medicinal products should be given on the day of study drug infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

If a patient is having difficulty tolerating the steroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the steroid premedication may be allowed for that patient after consultation with the medical monitor at any time during the study (double-blind and open-label periods).

In the open-label extension period only, for patients who are tolerating their drug infusions well with their current corticosteroid premedication regimen (ie, no IRRs during the past 3 or more infusions), corticosteroid dose may be reduced in 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (IV) or equivalent.

Infusions during corticosteroid tapering (and the 2 infusions after the new and stable lower corticosteroid dose is established) should be performed in the clinic, as described in detail in the Pharmacy Manual.

Additional or higher doses of 1 or more of the premedications may be administered to reduce the risk of IRRs, if needed. For suggested guidelines for management of IRRs, see Section 5.2.4; further details can be found in the Pharmacy Manual.

5.2.2. Study Drug Description

Patisiran is a RNAi therapeutic consisting of a double-stranded siRNA targeting TTR mRNA formulated in an LNP. The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline. Patisiran Solution for IV infusion contains 2 mg/mL of patisiran.

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

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

5.2.3. Dose and Administration

Detailed instructions for study drug preparation and administration are found in the Pharmacy Manual.

5.2.3.1. Double-bind Study Drug (Patisiran or Placebo)

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days.

The amount (in mg) of double-blind patisiran to be administered should be determined based on the patient's weight (kg). Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended dose is 30 mg.

Weight from the previous visit may be used for calculating dose. Weight must be collected prior to dosing with study drug. Study drug will be administered as an approximately 80-minute IV infusion (approximately 1 mL/minute for the first 15-minutes followed by approximately 3 mL/minute for the remainder of the infusion). The patient's infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments.

Missed doses of double-blind study drug

If a patient does not receive a dose of study drug within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit (with the following infusion taken on schedule, per the Schedule of Assessments), after consultation with the Medical Monitor.

A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study.

5.2.3.2. Open-label Extension Period (Patisiran)

The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described in Section 5.2.3.1 for double-blind patisiran.

As noted in Section 3.6, blinding will be maintained until the last patient completes their Month 12 visit.

During the open-label extension period, patients who have received at least 3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home, where applicable country and local regulations allow. Home administration of patisiran

will be performed by a healthcare professional trained on the protocol and administration of premedications and patisiran infusion.

All patients will receive premedications prior to open-label patisiran administration to reduce the risk of IRRs (Section 5.2.1).

Missed doses of open-label patisiran

If a patient does not receive a dose of open-label patisiran within the dosing window (±3 days), the delayed dose may be taken up to 7 days after the scheduled visit (with the following infusion taken on schedule, per the Schedule of Assessments), after consultation with the Medical Monitor.

5.2.4. Suggested Guidelines for Management of Infusion-related Reactions

Criteria for categorizing IRRs are provided in Section 10.3.

- In the event of an IRR, the infusion of study drug may be slowed or stopped and the patient closely monitored until resolution of the reaction. Drugs that may be used to facilitate resolution and permit resumption of study drug administration include but are not limited to: paracetamol/acetaminophen (or equivalent), additional histamine H1/H2 receptor antagonists (eg, ranitidine), nonsteroidal anti-inflammatory drugs (NSAIDs), adrenaline, supplemental oxygen, IV fluids, and/or corticosteroids.
- Following resolution of a mild or moderate IRR that required interruption of the study drug infusion, resumption of administration may occur at the Investigator's discretion at a slower infusion rate for that dose and for subsequent doses of study drug. If the infusion is delayed, the administration of the infusion should be completed no more than 16 hours from the initial start of the infusion.
- Study drug administration will not be resumed for any patient following a severe IRR until the case is discussed with the Medical Monitor.
- If after consultation with the Medical Monitor it is agreed that an individual patient's steroid premedication will be increased, then the following steps are **recommended**:
    1. If the IRR occurred while the patient received 10 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and did not resolve with slowing of the infusion rate, then the patient should be increased by multiples of 5 mg IV dexamethasone or equivalent at least 60 minutes before the infusion and/or 5 mg oral dexamethasone or equivalent the night before the IV infusion.
    2. Increased dose of premedication steroids should NOT exceed the combination of 20 mg IV dexamethasone or equivalent on the day of infusion and 8 mg oral dexamethasone or equivalent taken the night before the infusion.
    3. If the IRR occurred while the patient received less than 10 mg IV dexamethasone or equivalent, then the patient should return to the prior dose of IV dexamethasone or equivalent that did not result in an IRR.

Patients will be instructed to call the Investigator if they experience symptoms such as fever, chills, myalgia, or nausea/vomiting after discharge from the site.

5.2.5. 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.

5.2.6. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of study drug (patisiran and placebo) doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately (5 ±3°C) until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

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 will be provided in the Pharmacy Manual.

5.2.7. 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. Additional details will be available in the Pharmacy Manual.

5.2.8. 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, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.3. Concomitant Medications and Procedures

All patients will receive premedications prior to study drug administration to reduce the risk of IRRs (Section 5.2.1).

Use of the following medications/treatments are prohibited during study participation:

- Any investigational agent other than study drug.

- Inotersen, doxycycline, tauroursodeoxycholic acid, and diflunisal are also prohibited during the study.

All patients will be asked to take the recommended daily allowance of vitamin A for the duration of their participation in the study while being administered study drug. In countries where relevant, the clinical sites will provide patients with a prescription for vitamin A.

Standard vitamins and topical medications are permitted. Any concomitant medication or treatment that is required for the patient's welfare may be given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the CRF, as specified in the Schedule of Assessments (Table 1 and Table 2). Concomitant medications include 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 CRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Concomitant Tafamidis Use

Per inclusion Criterion 4, at baseline patients are either: 1) tafamidis naïve or 2) currently on tafamidis for ≥6 months with demonstrated disease progression, as determined by the Investigator. Patients who have been on tafamidis for ≤30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.

For patients on tafamidis at baseline, the reasons for considering the patient to have demonstrated disease progression will be recorded in the eCRF. Patients who are on tafamidis at baseline are encouraged, if it is medically appropriate in the opinion of the investigator, to remain on tafamidis for the duration of the double-blind period.

Per exclusion Criterion 8, patients who are tafamidis naïve at baseline, for whom the investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period (taking into consideration clinical status, patient preference, and/or commercial availability of tafamidis), should not be enrolled in the trial.

However, if tafamidis is granted approval by a Health Agency for treatment in patients with ATTR amyloidosis with cardiomyopathy in a given region, all enrolled patients in this region will be made aware of its potential benefits and risks at the time of regulatory approval and all patients will be reconsented. In such circumstances, tafamidis is not considered prohibited and the investigator may, using their medical judgement, commence concomitant on-label tafamidis during the study, if it is felt to be in the best interest of the patient and if it is commercially available in the country.

Patients who are tafamidis naïve at baseline, but begin taking commercial tafamidis (ie, "tafamidis drop-in"), will remain in the study. 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). In all cases, the Pre tafamidis Drop-in Visit should occur prior to starting concomitant tafamidis; where possible, this visit should occur between 1-2 weeks after the last dose of study drug (ie, 7 to 14 days post study drug dose). Thereafter, the patient will continue with all

assessments per the Schedule of Assessments (Table 1 and Table 2). In addition, at the time of tafamidis drop-in, the reason for starting tafamidis will be recorded in the CRF.

Initiation of TTR stabilizer therapies other than tafamidis (eg, diflunisal) is not allowed during the double-blind period of this study.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

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 12 weeks after the last dose of study drug in this study.

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.
- 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 12 weeks after the last dose of study drug.

Investigators should advise females of childbearing 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 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 6.5.5.2).

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 (double-blind period) and Table 2 (open-label extension period). Additional information on the collection of study assessments will be detailed in the respective reference manuals.

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient or legal guardian before the Screening procedures are initiated. All patients or their legal guardians will be given a copy of the signed and dated ICF. In addition, a medical records release form will be required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries.

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

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening (once) 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. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

The study eligibility biopsies and technetium scintigraphy noted in inclusion Criterion 2 are intended to be historical, as part of the patient's clinical care and diagnosis, and are not performed as part of the study.

An echocardiogram will be performed at screening Visit 1 and results confirmed centrally to assess study eligibility, as indicated in the Schedule of Assessments (Table 1).

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. Any additional repeat testing may be considered 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. A patient will be re-consented, if rescreening occurs outside of the 45-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

6.2.1. 6-Minute Walk Test (6-MWT)

The 6-MWT, which will be assessed as the primary endpoint, is an assessment of functional exercise capacity. The 6-MWT will be administered by staff trained in the procedure per the relevant study manual. The staff administering the 6-MWT will be different from the Investigator or designee managing the care of the patient.

The 6-MWT will be performed at each of the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). At screening Visit 1, the 6-MWT will be administered for study eligibility purposes (per inclusion Criterion 6 [Section 4.1]). At screening Visit 1, prior to conducting the 6-MWT, 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.

On Day 1 (baseline), which is a dosing day, the 6-MWT will be performed prior to study drug administration. (No other dosing days have a 6-MWT assessment.)

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 within the permitted visit window.

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 6MWT should be repeated as soon as possible within the allowed visit window.

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

A 1.5-month window will be used to group 6-MWT assessments to the Month 6 (Weeks 25-26), Month 9 (Weeks 37-38), and Month 12 (Weeks 52-53) visits. During the double-blind period, a patient may opt to begin tafamidis treatment or to discontinue study treatment, in which case they would complete a Pre-tafamidis Drop-in Visit (Table 1) or Early Treatment Discontinuation Visit (Table 2), respectively. To avoid the potential training effect from repeated assessments of the 6-MWT within a short period of time, only one 6-MWT assessment should be collected for the following time periods: Day 2 to Day 214 (for Month 6), Day 215 to Day 319 (for Month 9), and Day 320 to Day 372 (for Month 12).

Within a given time period, the 6-MWT assessment should be performed at whichever visit occurs first (scheduled assessment, Pre-tafamidis Drop-in Visit, or Early Treatment Discontinuation Visit; no additional 6-MWT assessments should be made in that time period. In later time periods, the 6-MWT should be assessed per the Schedule of Assessments (Table 1).

6.2.2. 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-OS will be assessed for the first secondary endpoint.

The KCCQ questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

6.2.3. Deaths and Hospitalizations

All deaths and hospitalizations will be recorded at Day 1 post dose and throughout the study as specified as part of AEs monitoring (see Section 6.5.7) and per the Schedule of Assessments (Table 1 and Table 2).

Reasons for deaths and hospitalizations will be adjudicated by an independent Adjudication Committee (see Section 3.8).

6.2.4. Modified Body Mass Index (mBMI)

The nutritional status of patients is evaluated using the mBMI, calculated as the product of body mass index (BMI) (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

Weight, height, and serum albumin (collected as part of the serum chemistry panel) will be collected pre-dose at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). The site will not perform the calculation for mBMI.

6.2.5. Cardiac Assessments

Manifestations of cardiac amyloid involvement will be assessed via cardiac biomarker, NYHA class, echocardiograms, CMR, and technetium scintigraphy imaging, as described.

Qualified personnel will be required to administer cardiac imaging assessments as specified in the respective reference manuals.

6.2.5.1. Cardiac Biomarkers

The cardiac biomarkers NT-proBNP and troponin I will be used to assess cardiac stress and heart failure severity. These biomarkers have been shown to be prognostic of outcomes in HF, including in ATTR amyloidosis.[Damy 2016; Kristen 2017; Merlini 2016] Blood samples will be drawn to measure cardiac biomarker levels at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2) and will be measured at a central laboratory. At screening Visit 1, only NT-proBNP will be assessed for eligibility purposes.

Details on cardiac biomarker sample collection, processing, and storage will be provided in a Study Laboratory Manual.

6.2.5.2. ATTR Amyloidosis Disease Stage

Based on published data from Gillmore et al, the ATTR amyloidosis disease staging used for this protocol stratifies patients with ATTR amyloidosis with cardiomyopathy (both hATTR and wtATTR) into prognostic categories using the serum biomarkers NT-proBNP and eGFR.[Gillmore 2018] Patients are categorized as follows:

- Stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min/1.73 m^2
- Stage 2 (intermediate risk): all other patients not meeting criteria for Stages 1 or 3
- Stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 ml/min/1.73 m^2

Based on published data, this staging system discriminates between patients with median survival of ~6 years, ~4 years, and ~2 years for Stage 1, Stage 2, and Stage 3, respectively.

6.2.5.3. 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 Schedule of Assessments (Table 1 and Table 2). The score collected at screening will be used to determine eligibility.

6.2.5.4. Echocardiogram

Echocardiographic parameters will be used for assessment of cardiac structure and function. Echocardiograms will be performed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2), and analyzed at a central cardiac imaging core lab.

Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

6.2.5.5. Technetium Scintigraphy Imaging

At select sites, in a subset of the patients (≤60 patients), technetium scintigraphy will be collected according to the Schedule of Assessments (Table 1 and Table 2), as an optional exploratory imaging assessment, to assess cardiac amyloid involvement. Based on local practice standards, either ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc], or ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) can be used as the tracer. Technetium scintigraphy images will be interpreted at a central imaging core laboratory. Image acquisition, storage, and transfer guidelines will be provided in the relevant study manual.

For patients in whom technetium scintigraphy is performed as a study efficacy parameter, the results of the baseline scan must be reviewed by the central reader and confirmed to be consistent with the diagnosis of ATTR amyloidosis prior to randomization.

At select sites where technetium scintigraphy is being performed as an exploratory efficacy assessment, patients may be exempt from the baseline scan if technetium scintigraphy has been performed prior to study entry as part of the patient's clinical care within 6 months prior to the baseline assessment. In such cases, the historical technetium scintigraphy examination performed prior to study entry as part of the patient's clinical care should be collected and transferred to the central imaging core laboratory for interpretation; if the historical scan cannot

be transferred to the central reader, or is deemed by the central reader to be of inadequate quality for interpretation, the patient should not participate in this optional efficacy assessment.

6.2.5.6. Cardiac Magnetic Resonance (CMR)

At select sites, in a subset of patients (≤60 patients), CMR will be collected according to the Schedule of Assessments (Table 1 and Table 2), as an optional exploratory imaging assessment to assess cardiac amyloid involvement. CMR imaging with late gadolinium enhancement will only be performed on patients without contraindications (ie, pacemakers, severe renal failure with eGFR <30 mL/min/1.73 m^2, defibrillators, or allergy to gadolinium).

Details for image acquisition and upload for central review can be found in the relevant study manual.

6.2.6. Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN)

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that assesses 5 domains: physical function, large-fiber neuropathy, activities of daily living, symptoms, small-fiber neuropathy, and autonomic neuropathy. The total score ranges from -4 (best possible quality of life) to 136 points (worst possible quality of life).[Vinik 2005; Vinik 2014]

The Norfolk QoL-DN questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

6.2.7. Polyneuropathy Disability (PND)

Physician assessment of ambulation via PND score [Coutinho 1980; Yamamoto 2007] will be evaluated only at screening to assess eligibility for the study as specified in the Schedule of Assessments (Table 1). PND scoring is described in Section 10.1.

6.3. Pharmacodynamic Assessments

In this study, serum samples for measurement of TTR levels will be collected for the assessment of PD effects. TTR levels will be determined by a validated enzyme-linked immunoassay (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 Schedule of Assessments (Table 1 and Table 2).

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of plasma concentrations of ALN-18328 (siRNA component of patisiran) and 2 lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) during the double-blind period at the timepoints specified in the Schedule of Assessments (Table 1). Plasma PK samples will be collected: predose (within 1 hour of planned study drug dosing); at the end of the infusion (+5 minutes); and 30 minutes after the end of the infusion (+15 minutes) at the specified visits.

For patients who discontinue treatment early during the double-blind period, a single PK sample will be taken at any time during the Early Treatment Discontinuation Visit, per the Schedule of Assessment (Table 2).

Actual dates and times of sample collection will be recorded.

Plasma concentrations of the 3 analytes will be determined using validated assay methods. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

PK parameters will be analyzed, whenever possible, as outlined in Section 7.2.7.

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 in addition an independent DMC as described in Section 3.7.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, 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 10 minutes. Blood pressure should be taken using the same arm. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary 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 sign 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 Schedule 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 Schedule 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.

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.

6.5.4. Electrocardiogram

12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval will be obtained, as specified in the Schedule of Assessments (Table 1 and Table 2). Patients should be supine for at least 5 minutes before each ECG is obtained. The 12-lead ECGs will be performed in triplicate at baseline, with readings approximately 1 minute apart. At all other time points, a single 12-lead ECG will be performed.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn, when possible.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator. Recordings will be archived in the patient's files.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. 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 laboratory tests and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 3 and will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 3, which are performed at the clinic 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.

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 3: 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 and eGFR (using the MDRD formula)	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Coagulation (at Screening)	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.5.5.1)	
Antidrug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.5.2)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; MDRD=modification of diet in renal disease; PCR=polymerase chain reaction; RBCs=red blood cells; RNA=ribonucleic acid.

6.5.5.1. Immunogenicity

Serum samples will be collected to evaluate the presence of antidrug antibodies (ADA) as outlined in the Schedule of Assessments (Table 1). Details regarding the blood volume, processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

A validated ELISA will be used that specifically detects antibodies to PEG_{2000}-C-DMG, which is a component of patisiran-LNP. Serum samples will first be analyzed with a screening assay. Samples testing positive for ADA in the screening assay will be further evaluated in a confirmatory assay. For the samples that tested positive for ADA in the confirmatory assay, the ADA titer will then be determined as the reciprocal of the highest dilution of the sample that yielded a positive ADA test result.

6.5.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2). More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. 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 6.5.7.7 for follow-up instructions).

Follicle-stimulating hormone testing may be performed to confirm suspected post-menopausal status.

6.5.6. Vital Status Check

A vital status check will be performed at the timepoints specified in the Schedule of Assessments (Table 1 and Table 2).

Due to the inclusion of all-cause mortality in the secondary endpoint analysis, a medical records release form will be required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries. The signing of this medical records release form is in addition to the ICF. 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.

6.5.7. Adverse Events

6.5.7.1. 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 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

An 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

No AEs of clinical interest are defined for this study.

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 AE.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. AEs 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.

6.5.7.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, 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.

All IRRs will be recorded as AEs. All information on IRRs is to be recorded on the applicable eCRF per the CRF completion guidelines.

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 to determine if an ophthalmological assessment is needed. 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.

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

Not applicable. There were no AEs of Clinical Interest identified for this study.

6.5.7.4. 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 6.5.7.1 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 Reference 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.

6.5.7.5. 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 Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.7.6. 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.

6.5.7.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 12 weeks following the last dose of study drug, 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 12 weeks after the last dose of study drug.

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 6.5.7.4.

6.5.7.8. Overdose Reporting

An overdose is defined as any dose 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.

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

6.6. Biomarkers and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of patisiran.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2). Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

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

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

The planned enrollment for this study is 300 patients. For the change from baseline at Month 12 in the 6-MWT, assuming a treatment difference of 33 meters between patisiran and placebo in the treatment-naïve group and 20 meters in patients with baseline tafamidis, the weighted average treatment difference between patisiran and placebo in the overall population is approximately 29 meters (standard deviation = 75 meters) assuming 70% are in the treatment-naïve group and 30% are in the baseline tafamidis group. A sample size of 300 patients provides >90% power for a 2-sided test to detect a mean difference between treatment groups at a 2-sided alpha = 0.05. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim assessment (Section 7.2.10).

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 12-month, double-blind period. More complete plans, including planned analyses for the open-label extension period, will be detailed in the SAP. 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.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug, grouped according to the randomized treatment arm.
- Safety Analysis Set: All patients who received any amount of study drug, grouped according to the treatment actually received.
- PK Analysis Set: All patients who received any amount of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- 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.

Efficacy endpoints will be analyzed using the Full Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology 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 and overall for the FAS and Safety Analysis Set.

7.2.5. Efficacy Analyses

The overall Type I error rate will be strongly controlled at a 2-sided 0.05 significance level for the primary and secondary endpoints using a fixed sequential testing procedure at the final analysis. The primary endpoint will be compared between treatment arms at the 0.05 significance level. If the test of the primary endpoint is statistically significant, then the secondary endpoints will each be tested in the order specified in the Secondary Endpoints section (see Section 2). If a test of the primary or a secondary endpoint is not statistically significant, the testing of the remaining endpoints in the sequence will stop.

For patients who were tafamidis treatment-naïve at baseline and start tafamidis during the double-blind period, the primary analysis of the primary endpoint will censor data collected after the initiation of tafamidis treatment post-randomization.

7.2.5.1. Primary Endpoint

The primary endpoint, change from baseline at Month 12 in the 6-MWT, will be analyzed using a mixed-effects model repeated measures (MMRM) approach. The outcome variable is change from baseline in the 6-MWT. The model will include the baseline value as a covariate, treatment, visit, the treatment-by-visit interaction, baseline tafamidis (yes vs no), genotype (hATTR vs wtATTR), NYHA Class (I/II vs III), and age (<75 vs ≥75 years) as fixed factors, and patient as a random effect. The primary comparison is the contrast (difference in least squares [LS] means) between the patisiran and placebo groups at Month 12.

Sensitivity analyses will be detailed in the SAP.

7.2.5.2. Secondary Endpoints

Secondary endpoints are described in Section 2.

KCCQ-OS will be analyzed using a similar MMRM model as used for the primary endpoint.

The composite endpoint of all-cause mortality, frequency of CV-related hospitalizations and change from baseline in 6-MWT will be analyzed using a generalized rank-based win ratio method, which makes pairwise comparisons (for all possible patisiran/placebo patient pairs) of the 3 components in the hierarchical order specified above. The point estimate for the win ratio is defined as the total number of better outcomes divided by the total number of worse outcomes in the patisiran group. The detailed algorithm for assessment of this endpoint will be provided in the SAP.

The composite endpoint of all-cause mortality and all-cause hospitalizations will be analyzed using an Andersen-Gill model stratified by baseline tafamidis (yes vs no), including treatment,

genotype (hATTR vs wtATTR), NYHA Class (I/II vs III), and age (<75 vs ≥75 years) as covariates.

To control the overall Type I error rate, secondary endpoints will be tested in a prespecified hierarchical order.

7.2.5.3. Exploratory Endpoints

Descriptive summaries will be provided for the exploratory endpoints (Section 2), and additional analyses may be conducted. Details will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

The PD endpoint is serum TTR. Summary tables will be provided for observed values, change and percentage change from baseline for each scheduled time point. In addition, the maximum and mean percentage reduction over 12 months will be summarized.

7.2.7. Pharmacokinetic Analysis

7.2.7.1. Pharmacokinetic Analysis

Plasma concentrations of ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG will be obtained using a model-independent method. PK exposure parameters will include: maximum plasma concentration at the end of infusion (C_{max}), 30-minute post-infusion concentration ($C_{p(30min)}$), and pre-infusion concentration (C_{min}). In addition, the steady-state C_{max} ($C_{max,ss}$), steady-state $C_{p(30min)}$ ($C_{p,ss(30min)}$), and steady-state C_{min} ($C_{min,ss}$) will be calculated as the average of the respective values at Week 24, Week 36, and Month 12.

The PK exposure parameters will be summarized by visit, and the steady-state PK parameters will be summarized.

7.2.7.2. Exposure-Response Analysis

Mean and maximum percent TTR reduction from baseline will be summarized by quartiles of the steady state PK parameters for all 3 analytes. Change from baseline at Month 12 in clinical efficacy parameters may also be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

PK exposure will be summarized by mortality status. In addition, the incidence of AEs and SAEs will be summarized by quartiles of the steady-state PK parameters for all 3 analytes.

7.2.7.3. Population PK, PK/PD, and Disease Progression Modelling Analysis

Population PK, PK/PD, and disease progression modelling analyses may be performed, if appropriate. If performed, the analyses would be conducted according to a pre-specified analysis plan and reported separately.

7.2.8. Safety Analyses

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. The 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 and Preferred Term. The frequency and percentage of patients experiencing AEs, SAEs, related AEs, and AEs leading to discontinuation will be summarized by System Organ Class (SOC) and PT. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics will be provided for clinical laboratory data, ECG, and vital signs data, summarizing the observed values and change from baseline over time. Laboratory shift tables from baseline at the worst post-baseline values will be presented. 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. Sample Size Re-assessment

Patients who are tafamidis-naïve at baseline may opt to begin tafamidis treatment (ie, "tafamidis drop-in") during the double-blind period, which could result in a loss of power. An interim assessment may be performed to assess the impact of tafamidis drop-in on the power and the potential need to increase the sample size. The interim assessment, if conducted, would examine the tafamidis drop-in rates in each treatment arm in an unblinded manner without looking at the unblinded efficacy or safety data; therefore, no impact on the type I error is expected and no multiplicity adjustment will be made. To maintain the blind for the study team, the interim assessment would be performed by a third party (ie, not the Sponsor) according to a prespecified plan.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the informed consent form (see Section 4.3.2).

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 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 required of all patients for the purpose of obtaining vital status information from the patient's physician or from death registries. 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. 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 6.5.7. 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 serious 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. CRFs 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).

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10. APPENDICES

10.1. Polyneuropathy Disability (PND) Scores

Stage	Description
0	No symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capacity but ability to walk without a stick or crutches
IIIA **IIIB**	Walking with the help of one stick or crutch Walking with the help of two sticks or crutches
IV	Confined to a wheelchair or bedridden

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.

10.3. Categorization of Infusion-Related Reactions

Signs and symptoms of an IRR usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritus/itching,

rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, urticaria (hives, welts, wheals), vomiting.

Categorization of IRRs is as follows:

Categorization	**Description**
Mild	Mild reaction: infusion may be continued; if intervention is indicated it is minimal and additional treatment (other than paracetamol for delayed reactions) is not required.
Moderate	Moderate reaction: requires treatment including more intensive therapy (eg, IV fluids, NSAIDs) in addition to infusion interruption but responds promptly to medication. Treatment is indicated for ≤24 hours.
Severe	More than moderate reaction: not rapidly responsive to medication or to interruption of infusion; and/ or prolonged (treatment is indicated for >24 hours); recurrence of severe symptoms following initial improvement.