Official Title:	**An Open-label Study to Evaluate Safety, Efficacy and Pharmacokinetics (PK) of Patisiran-LNP in Patients With Hereditary Transthyretin-mediated Amyloidosis (hATTR Amyloidosis) With Disease Progression Post-Orthotopic Liver Transplant**
NCT Number:	**NCT03862807**
Document Date:	**Clinical Study Protocol, 07 Oct 2018**

CLINICAL STUDY PROTOCOL
ALN-TTR02-008
DATED 07 OCTOBER 2018

Protocol Title:	An Open-label Study to Evaluate Safety, Efficacy and Pharmacokinetics (PK) of Patisiran-LNP in Patients with Hereditary Transthyretin-mediated Amyloidosis (hATTR amyloidosis) with Disease Progression Post-Orthotopic Liver Transplant
Short Title:	Patisiran-LNP in Patients with hATTR Amyloidosis Disease Progression Post-Liver Transplant
Study Drug:	patisiran-LNP (ALN-TTR02)
EudraCT Number:	2018-003519-24
Protocol Date:	07 October 2018
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: PPD
Sponsor Contact:	PPD

SPONSOR PROTOCOL APPROVAL

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

PPD

10 Oct 2018

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTR02-008 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 An Open-label Study to Evaluate Safety, Efficacy and Pharmacokinetics (PK) of Patisiran-LNP in Patients with Hereditary Transthyretin-mediated Amyloidosis (hATTR amyloidosis) with Disease Progression Post-Orthotopic Liver Transplant

Short Title Patisiran-LNP in Patients with Hereditary Transthyretin-mediated Amyloidosis (hATTR amyloidosis) with Disease Progression Post-Orthotopic Liver Transplant

Study Drug ALN-TTR02

Phase 3b

Study Centers
The study will be conducted at up to 10 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the TTR reduction of patisiran-LNP in hATTR amyloidosis patients with disease progression after OLT	• Average of Month 6 and Month 12 TTR percent reduction.
Secondary	
• To evaluate the effect of patisiran-LNP on neuropathy • To evaluate the effect of patisiran-LNP on patient reported outcomes including QoL, activities of daily living and autonomic neuropathy symptoms • To characterize the effect on nutritional status	• Change in the following parameters at 12 months o Neurologic impairment (NIS) o Patient reported measures of QoL (Norfolk QoL-DN), activities of daily living (R-ODS) and autonomic symptoms (COMPASS-31) o Nutritional status (mBMI)
Exploratory	
• To characterize exploratory measures of clinical activity (disease stage, functional status) • To evaluate PK • To assess for ADA against patisiran-LNP	• Change in the following parameters at 12 months o Disease stage (PND Score, FAP Stage) o Functional status: KPS • PK profile of ALN-18328, and the novel lipid excipients DLin-MC3-DMA and PEG_{2000}-C-DMG • Frequency and titer of anti-PEG_{2000}-C-DMG ADA

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of patisiran-LNP in hATTR amyloidosis patients with disease progression after OLT	• Frequency of adverse events

Study Design
This is a global Phase 3b open-label study designed to evaluate the safety, efficacy, and pharmacokinetics (PK) of patisiran-LNP in patients with hATTR amyloidosis with disease progression after liver transplant. The study will consist of a Screening period of up to 42 days, a 12-month treatment period and a 4-week follow up period after the last dose.

Consented eligible patients enrolled in this study will receive 0.3 mg/kg patisiran-LNP intravenously (IV) once every 3 weeks for 12 months. Patients will receive premedications at least 60 minutes before the start of the patisiran-LNP infusion in order to reduce the potential for an IRR with patisiran-LNP.

After the Day 1 visit, patients should return to the clinical site for patisiran-LNP dosing once every 3 weeks. Where applicable country and local regulations allow, eligible patients may receive the patisiran-LNP infusions at home by a healthcare professional trained on the protocol and delivery of premedications and patisiran-LNP.

Safety will be assessed throughout the study. Patients will return to the clinical site for safety evaluations at Week 12, 6 month efficacy visit, and 12 month efficacy visit. Patients will be continually assessed throughout the study for adverse events (AEs). Unscheduled visits for study assessments may occur if deemed necessary by the study personnel.

Efficacy assessments will be performed at baseline, 6 and 12 months.

Number of Planned Patients
Twenty patients are planned for enrollment in this study.

Diagnosis and Main Eligibility Criteria
This study will include adults (≥18 years of age) who have received an orthotopic liver transplant for treatment of documented hATTR amyloidosis ≥12 months before the date of informed consent, and documented increase in polyneuropathy disability (PND) score (eg, a PND change from I to II, II to IIIA, or IIIA to IIIB) compared to a pre-liver transplant assessment OR a documented increase in PND score between any 2 assessments post-liver transplant, which in the opinion of the Investigator is due to underlying disease progression.

Study Drug, Dose, and Mode of Administration
Patisiran-LNP comprises a small interfering ribonucleic acid (siRNA) which is specific for TTR, and is formulated in a lipid nanoparticle (LNP) for the hepatic delivery following an intravenous (IV) administration. Patisiran-LNP 0.3 mg/kg will be administered as an IV infusion once every 3 weeks. Dosing is based on actual body weight. For patients weighing ≥ 100 kg, the recommended dose is 30 mg.

In order to reduce the potential for an IRR with patisiran-LNP, all patients will receive premedications at least 60 minutes before the start of the patisiran-LNP infusion. Modifications

to lower the corticosteroid dose may be made to the premedication regimen as described further in the protocol.

Non-Alnylam Investigational Product, Dose, and Mode of Administration

Not applicable, open-label study.

Reference Treatment, Dose, and Mode of Administration

Not applicable, open-label study

Duration of Treatment and Study Participation

The duration of treatment with patisiran-LNP is 12 months. The estimated total time on study, inclusive of screening is up to 14.5 months, due to the requirement for an additional 4 weeks of follow-up.

Statistical Methods

Sample size assumptions included normally distributed true TTR percent reduction from baseline of 80% with a standard deviation of 18%. Given these assumptions, a sample size of 16 patients will yield a 95% confidence interval with a half-width of approximately 10%. Assuming a 20% premature discontinuation rate, approximately 20 patients will be enrolled in the study.

The populations (analysis sets) are defined as follows:

- Safety Analysis Set: All patients who received patisiran-LNP. The Safety Analysis Set will be used for the analysis of efficacy and safety assessments.
- Pharmacokinetic Analysis Set: All patients in the Safety Analysis Set who have provided at least one valid post-dose PK concentration value.

The median TTR percent reduction and 95% confidence interval will be estimated using the Hodges-Lehmann method; the TTR percent reduction will also be assessed using the Wilcoxon signed-rank test. Secondary endpoints will be analyzed using summary statistics of observed values and changes from baseline for the neuropathy impairment score (NIS) total score and component scores. Patient reported quality of life and disease burden will be assessed by summary statistics for the Norfolk QOL-DN and R-ODS. Patient reported autonomic neuropathy symptoms will be assessed by descriptive statistics for the COMPASS 31. Summary statistics will be provided for observed values and changes from baseline.

Safety data will be summarized with descriptive statistics. Adverse events will be summarized by System Organ Class (SOC) and preferred term (PT) (all events, related events, and serious events), in addition to being summarized by severity (all events). In addition, summaries will be provided for any AEs leading to discontinuation of study drug or death.

Figure 1: Study Design

Screening Period	**Open Label Treatment Period**	**Follow Up Period**
42 days	12 months	4 weeks

Table 1: Schedule of Assessments

		Screening	Baseline[a]	Dosing							6-Month Efficacy	Dosing					12-Month Efficacy		Early Termination	Safety Follow Up
Study Day (±Visit Window)	**Notes**	**D-42 to -1**	**Pre-Dose Day 1**	**D1**	**W1-2**	**W3 ±3D**	**W6 & 9 ±3D**	**W12 ±3D**	**W15 to 21 ±3D**	**W24 ±3D**	**W25 to WK 26±3D**	**W27 to W33 ±3D**	**W36 ±3D**	**W39 to W51 ±3D**	**W54 ±3D**	**W55 to W56**	**W57**	**Not applicable**	**W58 ±3D**
Informed Consent		X																	
Inclusion/ Exclusion Criteria		X	X																
Medical History	See Section 6.1	X	X																
Demographics		X																	
HIV Status Review	Section 6.1.3	X																	
Height		X																	
NYHA Classification		X																	
Karnofsky Performance Status		X									X					X		X	
PND Score and FAP Stage		X									X					X		X	
NIS		X									X					X		X	
Norfolk-DN QoL		X									X					X		X	
R-ODS		X									X					X		X	
COMPASS-31		X									X					X		X	

Table 1: Schedule of Assessments

		Screening	Baseline[a]	Dosing							6-Month Efficacy	Dosing					12-Month Efficacy		Early Termination	Safety Follow Up
Study Day (±Visit Window)	**Notes**	**D-42 to -1**	**Pre-Dose Day 1**	**D1**	**W1-2**	**W3 ±3D**	**W6 & 9 ±3D**	**W12 ±3D**	**W15 to 21 ±3D**	**W24 ±3D**	**W25 to WK 26±3D**	**W27 to W33 ±3D**	**W36 ±3D**	**W39 to W51 ±3D**	**W54 ±3D**	**W55 to W56**	**W57**	**Not applicable**	**W58 ±3D**
Echocardiogram with Doppler		X																	
12-Lead ECG	See Section 6.1.7	X																	
NT-proBNP		X																	
mBMI	See Section 6.2.6.		X								X					X		X	
Serum samples for TTR Protein	See Section 6.2.1		X		X	X				X	X				X	X			
Serum samples for anti-drug antibody	See Section 6.3.3.1		X			X				X					X				
Plasma samples for PK	See 2		X	X	X	X				X					X	X	X	.	
Pregnancy Test	See Section 6.3.3.2, Section 6.3.5.7, and Table 3	X	X			X	X	X	X	X	X	X	X	X	X			X	
Exploratory DNA Sample (optional)	See Section 6.5	X																	

Table 1: Schedule of Assessments

		Screening	Baseline[a]	Dosing							6-Month Efficacy	Dosing				12-Month Efficacy		Early Termination	Safety Follow Up
Study Day (±Visit Window)	**Notes**	**D-42 to -1**	**Pre-Dose Day 1**	**D1**	**W1-2**	**W3 ±3D**	**W6 & 9 ±3D**	**W12 ±3D**	**W15 to 21 ±3D**	**W24 ±3D**	**W25 to WK 26±3D**	**W27 to W33 ±3D**	**W36 ±3D**	**W39 to W51 ±3D**	**W54 ±3D**	**W55 to W56**	**W57**	**Not applicable**	**W58 ±3D**
Exploratory Biomarkers (plasma, serum)		X									X					X			
Full Physical Exam	See Section 6.3.2	X									X					X		X	
Symptom-Directed Physical Exam	See Section 6.3.2		X																
Vital Signs	See Section 6.3.1	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	
Serum samples for Vitamin A	See Section 6.1.1	X																	
Serum Chemistry, including LFTs	See Section 5.2.4.1	X	X (albumin only)					X			X		X			X		X	
Hematology		X						X			X		X			X		X	
Adverse Events	See Section 6.3.5.2				Continuous														
Concomitant Medications and Procedures	See Section 5.3	X			Continuous														
Liver Allograft Status	See Section 6.3.4	X						X			X		X			X		X	

Table 1: Schedule of Assessments

		Screening	Baseline[a]	Dosing							6-Month Efficacy	Dosing				12-Month Efficacy		Early Termination	Safety Follow Up
Study Day (±Visit Window)	**Notes**	**D-42 to -1**	**Pre-Dose Day 1**	**D1**	**W1-2**	**W3 ±3D**	**W6 & 9 ±3D**	**W12 ±3D**	**W15 to 21 ±3D**	**W24 ±3D**	**W25 to WK 26±3D**	**W27 to W33 ±3D**	**W36 ±3D**	**W39 to W51 ±3D**	**W54 ±3D**	**W55 to W56**	**W57**	**Not applicable**	**W58 ±3D**
Weight	See Section 6.1.4		X	X		X	X	X	X	X	X	X	X	X	X	X		X	
Premedication and Study Drug Administration	Phone contact for home infusions only			X		X	X	X	X	X		X	X	X	X				

Abbreviations: COMPASS=Composite Autonomic Symptom Score; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FAP=familial amyloidotic polyneuropathy; HIV=human immunodeficiency virus; LFT=liver function test; M=month; mBMI=modified body mass index; NIS=neurological impairment scale; NYHA=New York Heart Association; NT-proBNP=N-terminal prohormone of B-type natriuretic peptide; PK=pharmacokinetic; PND=paroxysmal nocturnal dyspnea; QoL= quality of life; R-ODS=Rasch-built Overall Disability Scale; TTR=transthyretin; W=week.
Notes: The Screening visit must be performed within 42 days before the first dose of study drug (Day 1).
Early termination visit should occur within 7 days of the decision to stop participating in the study.

Table 2: Pharmacokinetic Time Points

Study Visit	Day 1	Week 1-2	Week 3	Week 24	Week 54	Week 55-56	Week 57
Pre-Dose	X		X	X	X		
End of Infusion	X			X	X		
4 ± 1 h post EOI	X				X		
24 ± 4 h post EOI	X				X		
72 ± 6 h post EOI	X				X		
Day 7 to Day 14 post EOI		X				X	
Day 21 post EOI							X

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUCτ	Area under the plasma concentration-time curve from time zero to infinity
CLss	Systemic clearance at steady state
Cmax	Maximum (peak) plasma drug concentration
CRF	Case report form
DLin-MC3-DMA	(6Z, 9Z, 28Z, 31Z)-heptatriaconta-6, 9, 28, 31-tetraen-19-yl-4(dimethylamino) butanoate
ECG	Electrocardiogram
eCRF	Electronic case report form
GCP	Good Clinical Practice
hATTR	Hereditary transthyretin
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IB	Investigational Brochure
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion related reaction
IV	Intravenous
LFT	Liver function test
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mBMI	Modified body mass index
NIS	Neuropathy impairment score
NYHA	New York Heart Association
OLT	Orthotopic liver transplantation
os	Oral suspension

Abbreviation	Definition
PEG_{2000}-C-DMG	(R)-methoxy-PEG_{2000}-carbamoyl-di-O-myristyl-sn-glyceride
PK	Pharmacokinetic
PND	Paroxysmal nocturnal dyspnoea
PO	By mouth
RNAi	Ribonucleic acid interference
ULN	Upper limit of normal
SAE	Serious adverse event
SAP	Statistical analysis plan
siRNA	Small interfering RNA
SmPC	Summary of product characteristics
TTR	Transthyretin
wt	Wild type

1. INTRODUCTION

1.1. Disease Overview

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a rare autosomal dominant, systemic disease caused by a mutation in the transthyretin (TTR) gene leading to the extracellular deposition of amyloid fibrils containing both mutant and wild type (wt) TT [Yazaki 2000; Gillmore 2006] There are more than 120 reported TTR genetic mutations associated with hATTR amyloidosis, and almost all patients are heterozygous for the mutated TTR allele [Connors 2003; Ando 2013]. The most common genotype 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 [Ando 2013; Ando 2005; Gertz 2015].

The cardinal manifestations of hATTR amyloidosis are polyneuropathy and cardiomyopathy. The clinical manifestations of the length-dependent, symmetrical polyneuropathy are the result of amyloid-mediated injury to large and small peripheral nerve fibers [Ando 2013; Plante-Bordeneuve 2011; Benson 2007]. Sensory abnormalities include painful dysesthesias in the feet and hands, and loss of sensation leading to thermal burns involving the feet and hands and to joint injury in the lower limbs. Progressive muscle atrophy and motor weakness in both lower and upper limbs lead to impaired ambulation and inability to perform other activities of daily living, such as being able to hold eating utensils or a drinking glass, or button a shirt or zip up a coat. Autonomic dysfunction results in debilitating orthostatic hypotension, severe gastrointestinal symptoms (including early satiety, chronic nausea/vomiting, and both diarrhea and constipation), bladder dysfunction with recurrent urinary tract infections, and cardiac arrhythmias. Cardiac infiltration with amyloid leads to heart wall thickening and cardiomyopathy characterized by heart failure due to diastolic and systolic dysfunction, and conduction disturbances and arrhythmias[Ando 2013; Benson 2007; Carvalho 1992; Soares 2005; Connors 2004]. This constellation of progressive morbidity from amyloid infiltration results in severe disability, and wasting due to gastrointestinal malabsorption, malnutrition, and cardiac cachexia. Death usually results from heart failure (including sudden death caused by ventricular arrhythmias or electromechanical dissociation) or infection. The median survival is 4.7 years following diagnosis[Yazaki 2000; Plante-Bordeneuve 2011] with a reduced survival (3.4 years) for patients presenting with cardiomyopathy[Yazaki 2000; Gertz 1992; Sattianayagam 2012].

The liver is the primary source of TTR, and liver transplantation is used in some patients for treatment of hATTR amyloidosis [Stangou 2004]. More than 2000 patients have been transplanted in the world since 1990, however, morbidity and mortality are substantial. Patients require life-long immunosuppressive medications, with their attendant risks of infection and renal injury. One-year mortality rates of up to 10% have been reported [Okamoto 2009; Bispo 2009; Herlenius 2004].

Liver transplantation eliminates mutant TTR from the circulation, however, wt TTR is produced by the liver allograft. Disease progression occurs in at least one third of hATTR amyloidosis patients after a liver transplant, presumably due to continued deposition of wt TTR protein from the transplanted liver [Reines 2014; Adams 2013].

There is a need for a safe and effective treatment for patients who have disease progression following liver transplantation. By reducing mutant and wt TTR, patisiran-lipid nanoparticle (LNP) is anticipated to prevent disease progression in patients with hATTR amyloidosis who have progressive disease following orthotopic liver transplant (OLT).

1.2. Patisiran-LNP (ALN-TTR02)

Patisiran-LNP comprises a small interfering ribonucleic acid (siRNA) which is specific for TTR, and is formulated in a lipid nanoparticle (LNP) for the hepatic delivery following an intravenous (IV) administration [Akinc 2010; Coelho 2013]. It is designed to significantly suppress liver production of both wt and mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with hATTR amyloidosis.

The nonclinical pharmacology, pharmacokinetics (PK), and toxicology of patisiran-LNP were evaluated in a series of in vitro and in vivo studies that have enabled chronic dosing in clinical studies. A summary of the nonclinical data can be found in the patisiran-LNP Investigator's Brochure (IB). The clinical development program for patisiran-LNP consists of 6 studies including 2 Phase 1 studies in healthy volunteers (Studies ALN-TTR02-001 and ALN-TTR02-005) and 4 studies in patients with hATTR amyloidosis with polyneuropathy (Studies ALN-TTR02-002, ALN-TTR02-003, ALN-TTR02-004, and ALN-TTR02-006). All of the studies have been completed, with the exception of the ongoing, global open-label extension Study 006 which is evaluating the long-term safety and efficacy of patisiran-LNP in patients with hATTR amyloidosis. Patisiran-LNP reduced or halted neuropathy progression across motor, sensory and autonomic domains, with association with degree of TTR reduction, and provided evidence of favorable changes on exploratory cardiac endpoints.

On 10 August 2018, US FDA approval was granted for the treatment of the polyneuropathy of hATTR amyloidosis in adults. The Committee for Medicinal Products for Human Use adopted a positive opinion for the treatment of hATTR amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy, and the European Commission Decision was granted on 27 August 2018.

1.3. Study Design Rationale

This is a global Phase 3b open-label study designed to evaluate the safety, efficacy, and PK of patisiran-LNP in patients with hATTR amyloidosis with disease progression after liver transplant. The primary endpoint for the study is the average TTR percent reduction at Month 6 and Month 12.

The open-label design is supported by previous studies, including a pivotal Phase 3 double-blind, placebo-controlled study. The clinical benefits seen in the pivotal Phase 3 Study ALN-TTR02-004 (APOLLO) were observed in association with an 80% reduction of TTR with patisiran within 10 to 14 days after a single dose, which was maintained over the duration of the 18-month study compared to no change with placebo. The primary efficacy endpoint in the current study, TTR reduction, is an objective measurement and not susceptible to bias of clinical study center staff or study patients and therefore does not require a blinded placebo group for accurate interpretation.

All patients in this study will receive patisiran-LNP treatment. The study will consist of a 12 -month treatment period and a 4-week follow up period after the last dose. The 12-month treatment duration will enable collection of safety and efficacy data in patients with hATTR amyloidosis with disease progression after liver transplant. Previous trials support the 12-month duration, since beneficial effect on TTR reduction and efficacy endpoints including neuropathy impairment score and Norfolk QoL-DN score are evident by 9 months[Adams 2018].

1.4. Dose Rationale

The patisiran drug substance is a novel siRNA that is delivered by a LNP. The LNP facilitates siRNA delivery into hepatocytes via an ApoE dependent process. Upon internalization into hepatocytes via endocytosis, the LNP disintegrates, releasing the TTR-targeting siRNA ALN-18328 into the cytoplasm, where it reduces the production of wt and mutant TTR mRNA via the endogenous mechanism of ribonucleic acid interference (RNAi). A transplanted liver is anticipated to have a similar mechanism of LNP uptake and subsequent TTR mRNA gene silencing as native liver in hATTR patients.

The 0.3 mg/kg dose of patisiran-LNP once every 3 weeks was selected based on dose-response analysis for TTR reduction from 3 Phase 1 and Phase 2 studies. This dose was confirmed by the pivotal Phase 3 Study ALN-TTR02-004.

To minimize the risk of IRRs, patients must receive premedication prior to dosing with patisiran. Patients will receive the following premedications at least 60 minutes before the start of the patisiran-LNP infusion:

- Intravenous dexamethasone (10 mg) or equivalent
- Oral paracetamol/acetaminophen (500 mg) or equivalent
- Intravenous H2 blocker (ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose)
- Intravenous H1 blocker: diphenhydramine 50 mg (or equivalent other IV H1 blocker available at the study site). Hydroxyzine 25 mg per oral suspension (os) by mouth(PO) or fexofenadine 30 mg or 60 mg PO or cetirizine 10 mg PO may be substituted for any patient who does not tolerate IV diphenhydramine or other IV H1 blocker

These are the same premedications that were used in previous clinical trials.

1.5. Benefit-Risk Assessment

Patisiran-LNP obtained marketing approval in the US and EU based on the overall favorable risk-benefit profile in previous clinical studies, demonstrating improvement in outcomes of neuropathy, quality of life, activities of daily living, and nutritional status in hATTR patients with polyneuropathy. Previous clinical trials have shown a sustained mean serum TTR reduction of approximately 80% and a reduction of toxic misfolded TTR oligomers. The Phase 2 open label extension study showed evidence of improvement of neurologic impairment at 24 months, as assessed by the mNIS+7 [Adams D 2017]. The randomized, placebo-controlled Phase 3 study met its primary efficacy endpoint (change from baseline in mNIS+7 at 18 months) and all

secondary endpoints. Both studies had an acceptable safety profile with similar risks. Similar benefits are expected in patients who have disease progression post liver transplant.

Infusion-related reactions (IRRs) have been observed in patients treated with patisiran-LNP. To minimize the risk of IRRs, all patients must receive premedication before dosing with patisiran-LNP (Section 5). The infusion may be interrupted or slowed if an infusion related reaction (IRR) occurs (Section 5.2.2).

Patisiran-LNP is contraindicated in patients with a history of severe hypersensitivity (eg, anaphylaxis) to patisiran-LNP or any of the excipients.

Adverse drug reactions reported at a frequency of ≥1/10 (very common) in clinical trial were IRR and peripheral edema.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of patisiran-LNP may be found in the current edition of the IB. The IB is to be used as the reference safety information for this study. It will be supplemented by the summary of product characteristics (SmPC) in regions where there is an approved label.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the TTR reduction of patisiran-LNP in hATTR amyloidosis patients with disease progression after OLT	• Average of Month 6 and Month 12 efficacy TTR percent reduction.
Secondary	
• To evaluate the effect of patisiran-LNP on neuropathy • To evaluate the effect of patisiran-LNP on patient reported outcomes including QoL, activities of daily living and autonomic neuropathy symptoms • To characterize the effect on nutritional status	• Change in the following parameters at 12 months o Neurologic impairment (NIS) o Patient reported measures of QoL (Norfolk QoL-DN), activities of daily living (R-ODS) and autonomic symptoms (COMPASS-31) o Nutritional status (mBMI)
Exploratory	
• To characterize exploratory measures of clinical activity (disease stage, functional status) • To evaluate PK • To assess for ADA against patisiran-LNP	• Change in the following parameters at 12 months o Disease stage (PND Score, FAP Stage) o Functional status: KPS • PK profile of ALN-18328, and the novel lipid excipients DLin-MC3-DMA and PEG_{2000}-C-DMG • Frequency and titer of anti-PEG_{2000}-C-DMG ADA
Safety	
• To evaluate the safety and tolerability of patisiran-LNP in hATTR amyloidosis patients with disease progression after OLT	• Frequency of adverse events

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a global Phase 3b open-label study designed to evaluate the safety, efficacy, and PK of patisiran-LNP in patients with hATTR amyloidosis with disease progression after liver transplant. All eligible patients will be administered open-label patisiran-LNP.

Consented eligible patients enrolled in this study will receive 0.3 mg/kg patisiran-LNP IV once every 3 weeks for 12 months. Dosing is based on actual body weight. For patients weighing

100 kg or more, patisiran-LNP will be administered at a total dose of 30 mg IV once every 3 weeks. Eligibility for this study will be confirmed before administration of the first dose on Day 1.

Patisiran-LNP 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). In order to reduce the potential for an IRR with patisiran-LNP, all patients on this study will receive premedications at least 60 minutes before the start of the patisiran-LNP infusion. Patients who are tolerating their infusions well may be eligible to have a stepwise taper of the dose of corticosteroid premedication from 10 mg dexamethasone (or equivalent) to 5 mg during the study.

After the Day 1 visit, patients should return to the clinical site for patisiran-LNP dosing once every 3 weeks. Where applicable country and local regulations allow, eligible patients may receive the patisiran-LNP infusions at home by a healthcare professional trained on the protocol and delivery of premedications and patisiran-LNP.

Safety will be assessed throughout the study. Patients will return to the clinical site for safety evaluations at Week 12, 6 month efficacy visit, and 12 month efficacy visit. Patients will be continually assessed throughout the study for adverse events (AEs). Unscheduled visits for study assessments may occur if deemed necessary by the study personnel.

Efficacy assessments will be performed at baseline, 6 and 12 months.

3.2. Duration of Treatment

The duration of treatment with patisiran-LNP is 12 months.

3.3. Duration of Study Participants

It is anticipated that the duration of study participation for a subject or patient will be 14.5 months (inclusive of a 42-day screening period, 12-month treatment period, and a follow-up visit 4 weeks after the last dose of study drug.)

A patient is considered to have reached the end of the study when they have completed the follow up visit (4 weeks) after the last dose of patisiran-LNP.

3.4. Number of Planned Patients

The planned enrollment for this study is 20 patients.

3.5. Safety Review Committee

A safety review committee will not be utilized for this study; however, a transplant hepatologist will be available for consultation on an as needed basis.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

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

Age

1. Age 18 years (or age of legal consent, whichever is older) or older at the time of informed consent.

Patient and Disease Characteristics

2. Received an OLT for treatment of documented hATTR amyloidosis ≥12 months before the date of informed consent
3. A documented increase in polyneuropathy disability (PND) score (eg, a PND change from I to II, II to IIIA, or IIIA to IIIB) compared to a pre-liver transplant assessment OR a documented increase in PND score between any 2 assessments post-liver transplant, which in the opinion of the Investigator is due to underlying disease progression
4. On stable immunosuppressive regimen with ≤10 mg/day of prednisone for at least 3 months before the date of informed consent
5. Karnofsky performance status of ≥70% at the time of consent
6. Vitamin A level greater than or equal to lower limit of normal at Screening Visit

Informed Consent

7. Willing and able to comply with the study requirements and to provide written informed consent, per local and national requirements.

4.2. Exclusion Criteria

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

Prior/Concomitant Therapy

1. Currently taking tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out before dosing (Day 1)
2. Currently taking diflunisal; if previously on this agent, must have completed a 3-day wash-out before dosing (Day 1)
3. Received an investigational agent within the last 30 days of anticipated study drug administration or 5 half-lives of the study drug, whichever is longer, or are in follow-up of another clinical study before study enrollment
4. Current or past use of inotersen or patisiran-LNP

Medical Conditions

5. Liver allograft rejection episodes (chronic, acute, or subacute) or abnormal LFTs suggestive of possible allograft rejection in the past 6 months before the date of informed consent
6. Liver function test (including aspartate transaminase, alanine transaminase, and total bilirubin) results greater than upper limit of normal at the screening visit based on central laboratory evaluation. International normalized ratio (INR) >1.2 for patients not on anticoagulant therapy; INR >3.5 for patients receiving anticoagulant therapy
7. Known portal hypertension with ascites

8. Estimated glomerular filtration rate ≤30 mL/min/1.73 m2 (calculated by a central laboratory using the Modification of Diet in Renal Disease formula) at screening visit
9. Other known causes of sensorimotor or autonomic neuropathy (eg, autoimmune disease)
10. Known leptomeningeal amyloidosis
11. Uncontrolled diabetes (episodes of diabetic ketoacidosis or hyperglycemic, hyperosmolar nonketotic coma within the prior 9 months)
12. Active infection with hepatitis B or hepatitis C at screening visit (based on serology at central laboratory)
13. Known human immunodeficiency virus (HIV) infection based on patient's medical history
14. Hospitalizations for infections in prior 3 months from the time of informed consent, and no active infections at screening or baseline
15. New York Heart Association (NYHA) classification of >2 at screening visit
16. PND score IV (wheelchair bound or bedridden)
17. Hospitalizations for congestive heart failure or arrhythmia in the past 3 months before the date of informed consent
18. Malignancy within the last 5 years from the time of informed consent, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
19. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation
20. Unable to comply with requirements of study including premedications required prior to patisiran-LNP infusions
21. Exclude patients with organ transplants other than liver transplant

Contraception, Pregnancy, and Breastfeeding

22. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1. (NOTE: Contraception is not required in males.)
23. Female patient is pregnant or breastfeeding.

Alcohol Use

24. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine, [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer, approximately 284 mL).
25. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator.

4.3. Removal from Study Drug or Assessment

Patients are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the 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 (AE)
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

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 6.3.5.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test before 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 through the 12-month efficacy visit and approximately 4 weeks after the last dose 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), 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 6.3.5. When a patient discontinues study drug dosing, the primary reason must be recorded in the appropriate section of the eCRF. Patients who discontinue study drug

and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgment, as applicable. Safety will be captured for the entire duration of study for patients who discontinue study drug.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study-at any time. A patient considering stopping participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study for the collection of important study data as described in Section 4.3.1. If a patient still chooses to discontinue study drug and stop participation in all follow-up, every effort should be made to conduct the end of study assessments within 4 weeks of the last dose (see 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 6.3.5.

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 and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 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 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 to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of patisiran-LNP is provided in the Pharmacy Manual.

5.2.1. Description

Patisiran Solution for IV infusion is RNAi therapeutic consisting siRNA targeting TTR messenger RNA (mRNA) in the liver formulated in a LNP. The patisiran drug product is a sterile formulation of siRNA (ALN-18328), formulated as LNPs with lipid 4 excipients (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 intravenous infusion contains 2 mg/mL of patisiran.

5.2.2. Dose and Administration

Patients will receive 0.3 mg/kg patisiran-LNP IV once every 3 weeks for 12 months. Dosing is based on actual body weight. For patients weighing 100 kg or more, patisiran-LNP will be administered at a total dose of 30 mg IV once every 3 weeks. Patisiran-LNP 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).

Prior to each dose of patisiran-LNP, patients will receive the following premedications in order to reduce the risk of experiencing an IRR at least 60 minutes before the infusion:

- Intravenous dexamethasone (10 mg) or equivalent
- Oral paracetamol/acetaminophen (500 mg) or equivalent
- Intravenous H2 blocker (ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose)
- Intravenous H1 blocker: diphenhydramine 50 mg (or equivalent other IV H1 blocker available at the clinical site). Hydroxyzine 25 mg per os (PO) or fexofenadine 30 mg or 60 mg PO or cetirizine 10 mg PO may be substituted for any patient who does not tolerate IV diphenhydramine or other IV H1 blocker.

Patients will be started on the above premedication regimen. However, modifications to lower the corticosteroid dose may be made to the premedication regimen for either of the following 2 reasons:

- If a patient is having difficulty tolerating the corticosteroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the corticosteroid premedication may be allowed for that patient after consultation with the Medical Monitor.
- If a patient has tolerated 3 or more infusions of patisiran-LNP with the current steroid premedication regimen (ie, patient has not had any IRRs), then lowering of the steroid premedication is recommended.

Corticosteroid tapering should be performed in the clinic. If an individual patient's steroid premedication will be lowered, then the following steps must be followed:

1. If the current corticosteroid dose is 10 mg or less of intravenous dexamethasone or equivalent, then subsequent doses will be lowered in steps of no greater than 2.5 mg each time.
2. After each lowering of intravenous dexamethasone or equivalent, the patient must receive 3 consecutive intravenous doses of patisiran-LNP at that corticosteroid dose without experiencing an IRR and before further reductions in corticosteroid premedications.
3. The premedication corticosteroid dose will not be reduced below 5 mg intravenous dexamethasone or equivalent.

If a patient experiences an IRR, then proceed to Section 5.2.3.

5.2.2.1. Home infusion

Home infusion will be allowed if approved by local regulatory authorities. Home infusions are allowed if the patient has tolerated at least 3 infusions well in the clinic.

Patients who are receiving patisiran-LNP infusions at home will have a phone contact with the site at least every 30 (±5) days. Patients will also have visits at the clinical site at Weeks 12, 26 and 52.

5.2.3. Suggested Guidelines for Management of Infusion-Related Reactions

In the event of an IRR, the infusion of patisiran-LNP 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 patisiran-LNP administration include, but are not limited to: paracetamol/acetaminophen (or equivalent), additional histamine H1/H2 receptor antagonists (eg, ranitidine), NSAIDs, adrenaline, supplemental oxygen, IV fluids, and/or corticosteroids.

Following resolution of a mild or moderate IRR that required interruption of the patisiran-LNP infusion, resumption of administration may occur at the Investigator's discretion at a slower infusion rate for that dose and for all subsequent doses of patisiran. If the infusion is delayed, the infusion should be completed no more than 16 hours after preparation of the solution for infusion.

Patisiran-LNP administration should 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 should be increased then the following steps are recommended:

- If the IRR occurred while the patient received 10 mg intravenous 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 intravenous dexamethasone or equivalent at least 60 minutes before the infusion and/or 5 mg oral dexamethasone or equivalent the night before the intravenous infusion.
- Increased dose of premedication steroids should NOT exceed the combination of 20 mg intravenous dexamethasone or equivalent on the day of infusion and 8 mg oral dexamethasone or equivalent taken the night before the infusion.
- If the IRR occurred while the patient received less than 10 mg intravenous dexamethasone or equivalent, then the patient should return to the prior dose of intravenous 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. For categorization of IRRs, see Section 10.5.

5.2.4. Dose Modifications

Dose modifications are not permitted.

5.2.4.1. Liver Function Test Criteria for Withholding, Monitoring and Stopping patisiran-LNP Dosing

Liver function tests (LFT) will be evaluated throughout the study.

For any alanine transaminase (ALT) or aspartate transaminase (AST) elevation >3× upper limit of normal (ULN):

a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
b. Contact the patient's liver transplant doctor to discuss and agree on appropriate work-up which can include repeat lab testing (central lab), immunosuppressive drug levels, and/or liver biopsy if allograft rejection is suspected.
c. Contact the medical monitor as soon as possible and optimally within 72 hours to discuss appropriate work-up and whether patisiran administration should be continued, temporarily held or permanently discontinued.
d. If the patient has ALT or AST elevation 3×ULN or potential or confirmed event of liver transplant rejection, the Sponsor (or designee) should be notified using a supplemental AEs of Clinical Interest eCRF or serious adverse event (SAE) eCRF (Section 6.3.5).

5.2.5. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of patisiran-LNP 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 2 to 8°C. 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.

5.2.6. Packaging and Labeling

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

5.2.7. Accountability

The Investigator or designee according to local regulations 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 drug. 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

Use of concomitant medications and procedures will be recorded on the patient's case report form (CRF) as specified in the Schedule of Assessments (see Table 1). 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.

Use of the medications/treatments listed below is not permitted during the study:

- Tafamidis
- Diflunisal
- Doxycycline/TUDCA

All patients will be asked to continue to take the recommended daily allowance of vitamin A during the study. If required by local regulations, clinical sites will provide patients with a prescription for vitamin A.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

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

If available, information from a cardiac technetium scan or liver biopsy before study enrollment or during the study (as part of standard of care) should be collected and recorded as part of concomitant procedure information.

Patients will be monitored for possible liver allograft rejection; any biopsies performed to rule out allograft rejection will be evaluated and recorded as a concomitant procedure. Liver allograft status will include checking and recording immunosuppressive drug levels.

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 90 days

after last dose administration or until study completion. Pediatric/adolescent female patients must initiate contraception at menarche or must discontinue study drug.

Birth control methods which are considered acceptable 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 90 days 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 childbearing 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, contraception use by males should be consistent with local regulations 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.

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine, approximately 125 mL = 1 measure of spirits, approximately 1 fluid ounce = ½ pint of beer, approximately 284 mL) for the duration of the study.

6. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1. Additional information on the collection of study assessments will be detailed in the Study Manual.

6.1. Screening and Baseline Assessments

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

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. 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 before study drug administration. An interval medical history will be collected at the Screening and Baseline visit. Only changes since the Screening visit will be collected. Medical history will capture transplant history and evidence for disease progression.

6.1.1. Patient Demographic and Medical History/Disease History

Patient demographic data and medical history/disease history will be obtained (including any cardiac disorders, any eye disorders or previous ophthalmology test results, and prior medications). Any changes to medical history occurring between the screening assessment and Day 1 will be updated before study drug administration. An interval medical history will be collected at the Screening and Baseline visit. Only changes since the Screening visit will be collected. Medical history will capture transplant history and evidence for disease progression.

6.1.2. Vitamin A

Vitamin A levels must be obtained and evaluated at Screening. If vitamin A is not greater than or equal to lower limit of normal at Screening, it can be repleted and vitamin A level evaluation repeated during screening visit.

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 vitamin A complex. By reducing serum TTR protein, patisiran-LNP treatment leads to a decrease in vitamin A levels measured in the serum. Supplementation at the recommended daily amount of vitamin A is advised for patients taking patisiran-LNP. 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-LNP. Clinical sites may provide patients with a prescription for vitamin A depending on local requirements (Section 5.3).

6.1.3. HIV Status Review

At the Screening visit, Investigator will inquire into the patient's HIV status and will record this information.

6.1.4. 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 will be recorded in the eCRF. Weight from prior or current visit should be used for calculating dose.

6.1.5. NYHA Classification

All patients will be screened using the NYHA classification, as outlined in Table 1 .

6.1.6. Electrocardiogram

Twelve-lead electrocardiograms (ECGs) reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia corrected QT interval (QTcF) will be obtained, as specified in the Schedule of Assessments (Table 1). Patients should be supine for at least 5 minutes before each ECG is obtained. All ECGs are to be obtained in triplicate and read locally by the PI or delegated physician.

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

Recordings will be archived according to the Study Manual.

6.1.7. Echocardiogram and Biomarkers of Cardiac Function

Cardiac structure and function will be assessed through echocardiograms and measurement of serum levels of the cardiac biomarkers N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) at the time points specified in Table 1.

Echocardiograms will be performed and interpreted locally at the clinical trial center at baseline only. Image acquisition, storage, and transfer guidelines will be provided in a Study Manual.

Blood samples will be drawn to measure levels of NT-proBNP. Details on sample collection, processing, and storage will be provided in a Study Laboratory Manual.

6.2. Efficacy Assessments

Efficacy will be assessed at Baseline, Month 6, and Month 12. The specific timing for each assessment is presented in Table 1. On days that study drug is administered, efficacy assessments will be performed predose.

Further details on performing the efficacy assessments will be provided in the Study Reference Manual.

6.2.1. TTR Serum Samples

Blood for serum TTR levels will be collected at scheduled time points specified in Table 1 before the administration of patisiran-LNP. Serum TTR will be assessed using enzyme linked immunosorbent assay (ELISA). Samples for TTR measurements will be taken pre-dose on infusion days. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.2.2. Neurological Testing

Neurological testing will be performed by a neurologist and the results of these tests will be used to calculate the Neuropathy Impairment Score (NIS). The NIS, a composite neurologic

impairment score, was developed at the Mayo Clinic initially for evaluation of diabetic polyneuropathy. The NIS is an assessment of motor weakness (NIS-W), sensation (NIS-S) and reflexes (NIS-R) scored based on physical exam findings. The score range is from 0 to 244 points.

The NIS will be performed at the time points specified in Table 1

6.2.3. Norfolk Quality of Life - Diabetic Neuropathy Questionnaire

Quality of life will be assessed through the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiberneuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The version of the Norfolk QoL-DN that was used in the trial had a total score range from -4 to 136, with higher scores representing greater impairment. The questionnaire will be administered at the time points specified in Table 1 .

6.2.4. Rasch-built Overall Disability Scale

An assessment of the disability each patient experiences will be assessed through the Rasch-built Overall Disability Scale (R-ODS) at the time points specified in Table 1. The R-ODS is a questionnaire completed by the patient that consists of a 24-item linearly weighted scale that specifically captures activity and social participation limitations in patients.

6.2.5. Composite Autonomic Symptom Score

To evaluate changes in autonomic symptoms, patients will complete the Composite Autonomic Symptom Score (COMPASS 31) questionnaire. The questionnaire consists of 31 clinically selected questions evaluating 6 autonomic domains (orthostatic intolerance, secretomotor, gastrointestinal, bladder, and pupillomotor).

6.2.6. Modified Body Mass Index

Sites will measure body weight on all dosing days. Using that data, the modified body mass index (mBMI = BMI x albumin) will be calculated programmatically and does not need to be performed at the study center.

6.2.7. Familial Amyloidotic Polyneuropathy Stage and Polyneuropathy Disability Score

Changes in ambulation will be evaluated through the polyneuropathy disability (PND) score and familial amyloidotic polyneuropathy (FAP) stage as specified in Table 1 (see Section 10.3 and Section 10.4).

6.2.8. Karnofsky Scale

The Investigator will assess all patients according to the Karnofsky Scale as specified in Table 1 (see Section 10.2).

6.3. 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, and ECG findings and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.3.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, pulse rate, temperature, and respiratory rate. Vital signs will be measured predose in the supine position using an automated instrument after the patient has rested comfortably for 10 minutes. Blood pressure should be taken using the same arm throughout the study. 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. On Day 1, vital signs will also be collected post-dose.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator.

6.3.2. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1). If a physical examination is scheduled for a dosing visit, it should be conducted before 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.

6.3.3. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 5.2.4.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 3 and assessments will be assessed as specified in the Schedule of Assessments (Table 1).

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.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional.

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	Neutrophils, absolute and %
Hematocrit	Lymphocytes, absolute and %
Hemoglobin	Monocytes, absolute and %
RBC count	Eosinophils, absolute and %
White blood cell (WBC) count	Basophils, absolute and %
Mean corpuscular volume	Platelet count
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration
Serum Chemistry	
Sodium	Glucose
Potassium	Phosphate
BUN	Albumin
Creatinine	Calcium
Bicarbonate	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Immunogenicity (see Section 6.3.3.1)	
Antidrug antibodies	
Pregnancy Testing (Females of childbearing potential only, Section 6.3.3.2)	
β-human chorionic gonadotropin	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; RBC=red blood cell; WBC=white blood cell.

6.3.3.1. Immunogenicity

Serum blood samples will be collected to evaluate antidrug antibodies. Blood samples for antidrug antibody testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1). Anti-PEG_{2000}-C-DMG antibody measurements will be taken predose on infusion days.

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

6.3.3.2. Pregnancy Testing

A pregnancy test will be performed for females of childbearing potential. A serum pregnancy test will be performed at Screening and Baseline, and urine pregnancy tests at all study visits thereafter per the Schedule of Assessments and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation. Any woman with a positive 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 until the pregnancy outcome is known (see Section 6.3.5.7 for follow-up instructions).

6.3.3.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.4.1. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 1 will be performed one time, and hematology, serum chemistry, LFT, and coagulation assessments from Table 3, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring and dose modification will also be performed as outlined in Section 5.2.4.1.

6.3.4. Liver Allograft Status

Patients will be monitored for possible liver allograft rejection; any biopsies performed to rule out allograft rejection will be recorded as a concomitant procedure. Liver allograft status will include checking and recording immunosuppressive drug levels every 3 months.

6.3.5. Adverse Events

6.3.5.1. 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

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

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient 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

This study enrolls patients who have received a liver transplant. Liver function abnormalities are not an identified risk of patisiran-LNP treatment; however, for purposes of this study given the patient population, the following events will be considered events of interest: ALT or AST elevations > 3 x ULN, or potential or confirmed events of liver transplant rejections.

For information on recording and reporting of AEs of clinical interest, see Section 6.3.5.2 and Section 6.3.5.3, respectively.

Adverse Event Severity

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

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

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

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

Relationship of the Adverse Event to Study Drug

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

6.3.5.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in the patient's health since the last visit. The patient 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).

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 AE eCRF and reports or images of ophthalmological assessments should be collected as well.

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

For AEs that are considered AEs of clinical interest (Section 6.3.5.1), the Sponsor or its designee should complete the supplemental AEs of Clinical Interest eCRF. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

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

For AEs that are considered AEs of clinical interest (Section 6.3.5.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.3.5.4. 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 6.3.5.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

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

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

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

6.3.5.5. 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.

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

Suspected unexpected serious adverse reactions 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.

6.3.5.7. Pregnancy Reporting

If a patient becomes pregnant during the study through the first month 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 90 days 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 6.3.5.4.

6.3.5.8. 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.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for evaluation of PK parameters for ALN-18328 and 2 novel lipids (DLin-MC3-DMA and PEG_{2000}-C-DMG) at the visits in the Schedule of Assessments (Table 1). A detailed schedule of PK time points for the collection of blood samples is in Table 3.

Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Biomarkers, DNA Genotyping, 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 hATTR amyloidosis, and their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/EC) 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-LNP.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments Table 1. 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 principle features stated in the protocol.

7.1. Determination of Sample Size

Assuming a normally distributed true TTR percent reduction from baseline of 80% with a standard deviation of 18%, a sample size of 16 patients will yield a 95% confidence interval with a half-width of approximately 10%. Assuming a 20% premature discontinuation rate, approximately 20 patients will be enrolled in the study.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans 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:

- Safety Analysis Set: All patients who received patisiran-LNP. The Safety Analysis Set will be used for the analysis of efficacy and safety assessments.
- Pharmacokinetic Analysis Set: All patients in the Safety Analysis Set who have provided at least one valid post-dose PK concentration value.

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. Data to be tabulated will include gender, age, race, and disease-specific information.

7.2.5. Safety Analyses

A summary of exposure to patisiran, including the durations of the infusions and doses, will be produced.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarized by the MedDRA system organ class and preferred term. Separate tabulations will be produced for all treatment emergent AEs, treatment-related AEs, (SAEs, discontinuations due to AEs, and AEs by severity. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of treatment.

Prior and concomitant medications will be classified according to the World Health Organization drug dictionary. Results will be tabulated by anatomic therapeutic class and preferred term.

Descriptive statistics will be provided for clinical laboratory data, ECG, and vital signs data. Laboratory shift tables from baseline to worst values will be presented.

7.2.6. Efficacy Analyses

Summary tables and graphical displays of observed values and changes from baseline in serum TTR will be used to assess the durability of suppression over the course of the study. The primary endpoint is the average TTR percent reduction across Month 6 and Month 12. The median TTR percent reduction along with the 2-sided 95% confidence interval will be estimated using the Hodges-Lehmann method. The p-value for the TTR percent reduction will be obtained using the Wilcoxon signed-rank test

Summary statistics of observed values and changes from baseline will be provided for the NIS total score and component scores.

Patient reported quality of life and disease burden will be assessed by summary statistics for the Norfolk QOL-DN and R-ODS. Patient reported autonomic neuropathy symptoms will be assessed by descriptive statistics for the COMPASS 31. Summary statistics will be provided for observed values and changes from baseline.

Descriptive statistics will also be provided for observed values and changes from baseline in nutritional status (mBMI), functional impairment (Karnofsky Performance Status), and ambulation (FAP stage and PND score).

Results of echocardiograms will be summarized.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be performed using noncompartmental analysis methods.

The following PK parameters will be estimated: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), terminal elimination half-life ($t_{½\beta}$), area under the concentration-time curve during a dosing interval ($AUC\tau$), systemic clearance at steady state

(CLss), and apparent volume of distribution at steady state (Vss), and accumulation ratio for PK exposure parameters (R_{ac}). Additional PK parameters may be calculated, if deemed necessary.

7.2.8. Immunogenicity Analyses

Number of patients with confirmed positive antidrug antibodies (ADA) results will be summarized by visit and overall. Titer will be summarized by visit and overall. Patients with both pre- and post- treatment ADA assay results will be used to calculate incidence of treatment emergent ADA.

7.2.9. 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 6.1).

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

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.

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 approval of the protocol, and all materials approved by the IRB 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 6.3.5. 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 enrolled 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 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 designees, 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 information related to the study and the complied 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 ClincalTrials.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 reserves the right to terminate the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed at that site. 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, IEC/IRB, and regulatory authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

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

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

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities

were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor, or its 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 separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published, or following the period of 18 months after completion of the study at all centers. 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 among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined basis on 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. New York Heart Association Classification of Heart Failure

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.

10.2. Karnofsky Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

10.3. Polyneuropathy Disability Score

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.

10.4. Familial Amyloidotic Polyneuropathy Stage

Stage	Description
0	No symptoms
I	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
II	Assistance with ambulation required, mostly moderate impairment progression to the lower limbs, upper limbs, and trunk.
III	Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs.

10.5. 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, nonsteroidal anti-inflammatory drug [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.

Protocol Administrative Change 1
ALN-TTR02-008

An Open-label Study to Evaluate Safety, Efficacy and Pharmacokinetics (PK) of Patisiran-LNP in Patients with Hereditary Transthyretin-mediated Amyloidosis (hATTR amyloidosis) with Disease Progression Post-Orthotopic Liver Transplant

Purpose: The primary purpose of this administrative letter is to clarify some inconsistencies in the ALN-TTR02-008 original protocol, dated 07 Oct 2018. The clarifications are specified below; added text is **bold** font and deleted text is indicated by ~~strikethrough~~.

Section 5.2.2.1: Home infusion, page 31

There was an error in the naming of the Weekly clinical site visits in this section that has been corrected as shown for consistency with the dates provided in the Schedule of Assessments:

Home infusion will be allowed if approved by local regulatory authorities. Home infusions are allowed if the patient has tolerated at least 3 infusions well in the clinic.

Patients who are receiving patisiran-LNP infusions at home will have a phone contact with the site at least every 30 (±5) days. Patients will also have visits at the clinical site at **Week 12, 25 to 26, week 36 and week 55 to 56**. ~~Weeks 12, 26 and 52.~~

Section 6.3.5.2: Reporting Adverse Events of Clinical Interest to Sponsor/Designee, page 43

The supplemental AEs of Clinical Interest eCRF should be completed within 24 hours of notification by the Investigator/site staff that enter this data in the eCRF and not by the Sponsor or its designee.

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

Section 6.5: Biomarkers, DNA Genotyping, and Biospecimen Repository, page 45
Potential exploratory investigations of biospecimen repository and other sample will not include RNAassessment; this exploratory assessment is deleted from the list of potential investigations.

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

PPD

29 Oct 2018

Date