EU RISK MANAGEMENT PLAN
FOR
ONPATTRO® (PATISIRAN)

RMP version to be assessed as part of this application:

RMP version number:	3.0
Data lock point for this RMP:	09 August 2023
Date of final sign off:	01 February 2024
Rationale for submitting an updated RMP:	To update the Risk Management Plan (RMP) to address the comments received in EMA's request for supplementary information (RSI) for procedure number EMEA/H/C/004699/II/0034 concerning submission of the final study report for ALN-TTR02-006 (Study 006) listed as a Category 3 study in the RMP.

Summary of significant changes in this RMP:

Part	Module	Significant Change in Each Module
Part I	Product Overview	No Change
Part II	Module SI Epidemiology of the Indication and Target Population	Amended text on existing treatment options for hATTR amyloidosis
	Module SII Nonclinical Part of the Safety Specification	No Change
	Module SIII Clinical Trial Exposure	Updated information for Study ALN-TTR02-006 (Study 006), based on the final CSR, dated 27 June 2023 (Final Database lock: 07 December 2022); and for Study ALN-TTR02-011 (Study 011) based on the 09 August 2023 data cutoff date
	Module SIV Populations Not Studied in Preauthorization Clinical Trials	Updated information for Study 006, based on the final CSR data dated 27 June 2023 and for Study 011 based on the 09 August 2023 data cutoff date

	Module SV Post-Authorization Experience	Updated with new information on commercial exposure to patisiran and on patient exposure from Early Access Programs and Compassionate Use Programs based on the current DLP (09 August 2023)
	Module SVI Additional EU Requirements for the Safety Specification	No Change
	Module SVII Identified and Potential Risks	Reverted Section SVII.1 to its original text from the initial RMP v1.0 (dated 25 July 2018) due to inadvertent modifications in later versions. Additionally, Section SVII.3 was updated with Study 006 data, based on the final CSR, dated 27 June 2023 (final database lock: 07 December 2022); and Study 011 data based on the 09 August 2023 data cutoff date
	Module SVIII Summary of Safety Concerns	No Change
Part III **Pharmacovigilance Plan**		Updated the due date for the first Study 009 full interim analysis report to align with the basic interim reports and revised the date formatting for all milestones to align with guidance
Part IV **Plan for Post-authorization Efficacy Studies**		No Change
Part V **Risk Minimization Measures**		Updated Part V.3 with additional pharmacovigilance activity for the important potential risk of consequences of vitamin A deficiency and study milestone for the additional pharmacovigilance activities for the risks. Additionally, updated the first full interim analysis and final study report due dates for Study 009
Part VI **Summary of RMP**		Updated based on the changes made in the corresponding sections of the RMP
Part VII Annexes	Annex 1 EudraVigilance Interface	Not Applicable

	Annex 2 Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Program	Updated the version number for Study 010 and the due date for the first Study 009 full interim analysis report
	Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	Updated the version number for Study 010
	Annex 4 Specific Adverse Drug Reaction Follow-up Forms	No Change
	Annex 5 Protocols for Proposed and Ongoing Studies in the RMP Part IV	Not Applicable
	Annex 6 Details of Proposed Additional Risk Minimization Activities (if Applicable)	No Change
	Annex 7 Other Supporting Data (including referenced material)	No Change
	Annex 8 Summary of Changes to the Risk Management Plan over time	Updated with details of the current changes to the RMP

Other RMP versions under evaluation:

RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:

Version number:	2.1
Approved with procedure:	EMEA/H/C/004699/IB/0032
Date of approval (opinion date):	23 January 2023

QPPV name: Natalia Kalousová Kocankova

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization applicant´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification
ATTR	Amyloid transthyretin
AUC	Area under the plasma concentration-time curve
CNS	Central nervous system
CRP	C-reactive protein
CUP	Compassionate Use Program
CYP	Cytochrome P450
DLin-MC3-DMA	Patisiran lipid excipient; (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate
DSPC	Patisiran lipid excipient; 1,2-distearoyl-*sn*-glycero-3-phosphocholine
EAP	Expanded Access Protocol
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EPAR	European Public Assessment Report
EU	European Union
FAC	Familial amyloidotic cardiomyopathy
FAP	Familial amyloidotic polyneuropathy
hATTR	Hereditary ATTR
INN	International Nonproprietary Name
IRR	Infusion-related reaction
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
mNIS+7	modified neuropathy impairment score +7
mRNA	messenger RNA
MTD	Maximum tolerated dose
N/A	Not applicable

Abbreviation	Definition
NOAEL	No observed adverse effect level
Norfolk QOL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NYHA	New York Heart Association
OLT	Orthotopic liver transplant
Patisiran-LNP	Patisiran-lipid nanoparticle; drug name for the initial RMP, as described in Part II: Module SVII.1.1, Module SVII.1.2, and Part III.2
PEG_{2000}-C-DMG	Patisiran lipid excipient; (R)-2,3-bis(tetradecyloxy)propyl 1-(methoxy poly(ethylene glycol)2000)propylcarbamate
q2w	Once every 2 weeks
q3w	Once every 3 weeks
q4w	Once every 4 weeks
QPPV	Qualified Person for Pharmacovigilance
RBP	Retinol binding protein
RMP	Risk Management Plan
RNAi	RNA interference
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBILI	Total bilirubin
TTR	Transthyretin
UK	United Kingdom
ULN	Upper limit of normal
US/USA	United States of America
V30M	Valine to methionine at position 30
V122I	Valine to isoleucine mutation at position 122 in human transthyretin gene
wt	Wild type
wtATTR	wt transthyretin-mediated amyloidosis

PART I. PRODUCT OVERVIEW

Table 1: Product Overview

Active substance: **(INN or common name)**	patisiran
Pharmacotherapeutic group **(ATC Code):**	N07XX12
Marketing Authorization Applicant:	Alnylam Netherlands B.V. Antonio Vivaldistraat 150 Amsterdam 1083 HP Netherlands Tel: +31 20 36 97 868
Medicinal products to which this RMP refers:	1
Invented name in the European Economic Area (EEA):	Onpattro
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: siRNA
	Summary of mode of action: Onpattro contains patisiran, a double-stranded small interfering RNA (siRNA) that uses RNA interference (RNAi) to inhibit the synthesis of wild type (wt) and variant transthyretin (TTR) protein in hepatocytes, leading to the reduction of the serum TTR protein that forms amyloid deposits in patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).
	Important information about its composition: Each mL of Onpattro contains patisiran (2 mg) and lipid excipients DLin-MC3-DMA, DSPC, cholesterol, and PEG_{2000}-C-DMG formulated as lipid nanoparticles (LNPs) in isotonic phosphate buffered saline for intravenous (IV) administration.
Hyperlink to the Product Information	Refer to 1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet
Indication in the EEA	Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy

Dosage in the EEA	The recommended dose of Onpattro is 300 micrograms per kg body weight administered via intravenous (IV) infusion once every 3 weeks. Dosing is based on actual body weight. For patients weighing ≥100 kg, the maximum recommended dose is 30 mg.
Pharmaceutical form and strength	Concentrate for solution for infusion (sterile concentrate) Each mL contains patisiran sodium equivalent to 2 mg patisiran) Each vial contains patisiran sodium equivalent to 10 mg patisiran formulated as lipid nanoparticles
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC=Anatomical Therapeutic Chemical classification; DLin-MC3-DMA=patisiran lipid excipient: (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate; DSPC=patisiran lipid excipient: 1,2-distearoyl-*sn*-glycero-3-phosphocholine; EEA=European Economic Area; EU=European Union; hATTR amyloidosis=hereditary amyloid transthyretin-mediated amyloidosis; INN=International Nonproprietary Name; IV=intravenous; LNP=lipid nanoparticle; PEG_{2000}-C-DMG=patisiran lipid excipient: (R)-2,3-bis(tetradecyloxy)propyl 1-(methoxy poly(ethylene glycol)2000)propylcarbamate; RMP=risk management plan; RNAi=RNA interference; siRNA=small interfering RNA; TTR=transthyretin; wt=wild type.

PART II. SAFETY SPECIFICATION

Part II: Module SI Epidemiology of the Indication and Target Population

Indication in adults for the treatment of:

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a rapidly progressive, multisystem, debilitating, and ultimately fatal disease.[Adams 2021; Gertz 2017; Grodin 2019; Lane 2019; Parman 2016] hATTR amyloidosis results from genetic variants in the transthyretin (*TTR*) gene. In hATTR amyloidosis, the tetrameric TTR protein becomes destabilized and disassociates into dimers and monomers, which subsequently misfold and deposit as amyloid in various organs and tissues, including the heart, peripheral nerves, and the gastrointestinal tract.[Hou 2007] Progressive, chronically debilitating morbidity and mortality ensue. Historically, 2 clinical syndromes of hATTR amyloidosis have been described: hATTR amyloidosis with polyneuropathy (also known as familial amyloidotic polyneuropathy [FAP]) and hATTR amyloidosis with cardiomyopathy (also known as familial amyloidotic cardiomyopathy [FAC]), both of which are characterized by TTR amyloid deposits.[Ando 2013] As hATTR amyloidosis is a systemic disease with amyloid deposition in multiple organs, individual patients with hATTR amyloidosis often manifest signs and symptoms of both neuropathy and cardiomyopathy and thus the terminology has evolved, referring to 1 hereditary disease with a spectrum of clinical manifestations rather than attempting to classify the disease into 2 distinct syndromes.[Swiecicki 2015]

The literature provides very limited incidence and prevalence data for hATTR amyloidosis. This is due to the fact that this is a rare disease with varying endemicity by region. For instance, hATTR amyloidosis is familial and therefore is identified with elevated prevalence in certain endemic foci within specific regions (each associated with a specific TTR genotype). Due to its rarity, hATTR amyloidosis is not yet well known outside of certain specialty centers in a limited number of countries. Often this disease is misdiagnosed, adding to the challenge in providing accurate incidence and prevalence data, and individuals carrying a TTR variant may not necessarily manifest the disease, further contributing to the challenges in estimating incidence and prevalence of the disease.

The epidemiology of hATTR amyloidosis is summarized in Table 2.

Table 2: Epidemiology of hATTR Amyloidosis

Incidence
Estimates of incidence of hATTR amyloidosis are scarce. Prevalence has been reported somewhat more commonly and is discussed below. While incidence may be estimated from prevalence data in conjunction with survival data, the usefulness of doing so is limited by variability in both regional prevalence estimates and estimates of survival.
Prevalence
hATTR amyloidosis The prevalence of hATTR amyloidosis varies depending on the prevalence of individual TTR genotypes and the penetrance of those genotypes in a given population. As the prevalence and

penetrance of individual *TTR* genotypes differ across geographic regions, the overall prevalence of the disease also shows regional variation. Further, although terminology has evolved to refer to 1 hereditary disease with a spectrum of symptoms, as most patients with hATTR amyloidosis experience both cardiomyopathy and polyneuropathy over the course of their disease, prevalence data often distinguish between hATTR amyloidosis with polyneuropathy and hATTR amyloidosis with cardiomyopathy, reflecting a historical view of the disease as having these 2 distinct subtypes, or are reported in a genotype-specific manner. Accordingly, the estimated prevalence of hATTR amyloidosis by dominant phenotype at diagnosis (polyneuropathy or cardiomyopathy) or by genotype is presented below for various regions.

hATTR amyloidosis with polyneuropathy:

In Europe, the largest endemic foci of hATTR amyloidosis with polyneuropathy are in areas with an elevated prevalence of carriers of the change from valine to methionine at position 30 (V30M) TTR variant. These foci include Portugal (Póvoa de Varzim and Vila do Conde), where the prevalence of the V30M variant is estimated to be 1 in 538 individuals,[Sousa 1995] and northern Sweden where the estimated number of V30M TTR carriers was 7500 in a total population of 500,000 .[Holmgren 1994] As the phenotypic penetrance of the V30M variant in Northern Portugal was not reported in association with the variant prevalence estimate of 1 in 538, it is not possible to discriminate between healthy V30M variant carriers and individuals with V30M-hATTR amyloidosis with polyneuropathy, and thus estimate the actual prevalence of clinically evident disease, in this population. In the previously mentioned northern Swedish population of 500,000, there were 152 known prevalent cases of V30M-hATTR amyloidosis with polyneuropathy, corresponding to a disease prevalence rate of 31 cases per 100,000 population (and a phenotypic penetrance rate of approximately 2% among the 7500 V30M carriers).

The prevalence of hATTR amyloidosis with polyneuropathy in other European countries including France, Italy, and Germany is lower than that reported in endemic areas, ranging from 0.06 to 0.82 per 100,000. Estimation of prevalence across the European Union (EU) based on available by-country prevalence data, together with application of reported prevalence from France (which has a national referral network, high disease awareness among physicians, and no endemic foci) to other countries without a directly estimated, country-specific prevalence figure, resulted in an estimated overall prevalence of hATTR amyloidosis with polyneuropathy of 1.02 per 100,000 in the EU.[Dardiotis 2009; Lobato 2003; Munar-Ques 2005; Parman 2016; Plante-Bordeneuve 2007; Rapezzi 2013; Reilly 1995]

In Japan, hATTR amyloidosis with polyneuropathy is also endemic in some areas as it is in Portugal and Sweden; however, the overall prevalence throughout Japan is estimated to be lower than in Europe, at approximately 1 in 1,000,000 individuals (0.1 in 100,000).[Kato-Motozaki 2008]

In the United States (US), the prevalence of hATTR amyloidosis with polyneuropathy is estimated to be approximately 2 in 100,000 individuals, based on a 2018 estimate from Coelho and colleagues of 6400 patients nationwide.[Coelho 2016]

hATTR amyloidosis with cardiomyopathy:

The worldwide prevalence of hATTR amyloidosis with cardiomyopathy is unknown, but it is almost certainly underdiagnosed, particularly in individuals of African descent who carry the change from valine to isoleucine at position 122 (V122I) TTR variant and are older than 65 years.[Buxbaum 2010; Dharmarajan 2012]

The frequency of the V122I TTR genotype in the African American population is 3% to 3.9%, with most individuals developing late-onset cardiac amyloidosis in cases where this genotype is clinically penetrant. The frequency of V122I in Caucasian and Hispanic populations in the US is 0.44% and 0%, respectively.[Jacobson 1997; Yamashita 2005] Data on disease penetrance in V122I carriers suggests that hATTR amyloidosis with cardiomyopathy in the US population is prevalent in as many as 52,000 patients (approximately 16 per 100,000). This is an indirect estimate calculated using the total number of African American residents 65 or older, an allele frequency of 3.43%, and a clinical penetrance (that

is, a probability of the mutation causing the disease) of 33%. This method is contrasted with the method used below to estimate the prevalence of cardiomyopathy in the European Community, which relied on directly estimated, country-specific prevalence figures obtained from the published literature and other sources. Therefore, the calculated estimate of prevalence of hATTR amyloidosis with cardiomyopathy in the US is likely to be an overestimate of the actual prevalence.

The prevalence of hATTR amyloidosis with cardiomyopathy is lower in the European Community with an estimated prevalence of 0.12 per 100,000; this estimate is based on data in the literature,[Frederiksen 1962; Rapezzi 2013] data from the National Amyloidosis Centre in the UK, and information from recognized European experts in the field of amyloid transthyretin (ATTR) amyloidosis.

Summary:

The genotypes that tend to present initially with polyneuropathy contribute more to the overall prevalence of hATTR amyloidosis in the EU, while the genotypes that present initially with cardiomyopathy are estimated to be more prevalent in the US. The overall prevalence of hATTR amyloidosis can be estimated as approximately 1.02 in 100,000 in the EU and 18 in 100,000 in the US. As noted above, the estimate of prevalence of hATTR amyloidosis in the US is likely to be higher than the actual prevalence because of the indirect method utilized to derive the US population prevalence of hATTR amyloidosis with cardiomyopathy. The prevalence of hATTR amyloidosis with polyneuropathy in Japan is estimated to be approximately 0.1 in 100,000; Japanese prevalence estimates for hATTR amyloidosis with cardiomyopathy are not available. While prevalence data are not readily available for regions other than Europe, US, and Japan, it can be concluded that hATTR amyloidosis is a rare disease worldwide.

Demographics of the Target Population (Age, Sex, Race/Ethnic Origin)

hATTR amyloidosis

Sex and age at disease onset and diagnosis:

Overall, hATTR amyloidosis clinical symptoms tend to manifest in adults, and thus the disease is typically diagnosed at the adult stage of life.[Ando 2013] The onset of disease-related symptoms varies across different populations and genotypes, with the onset of symptoms potentially occurring anywhere from 20 years of age onward. Adult patients with the V30M TTR genotype can manifest the disease at age 30-50 years (early onset) or after age 50 years (late-onset). Patients with non-V30M TTR genotypes typically manifest the disease after age 50 years. The Transthyretin Amyloidosis Outcomes Survey is a global, multicenter, longitudinal, observational survey to collect data on TTR amyloidosis (both hereditary and wt). An evaluation of patients with hATTR amyloidosis who enrolled in this registry between December 2007 and September 2011 illustrated the variability among different countries and genotypes in not only age at onset, but distribution between male and female patients. The median age of onset of symptoms for patients with the V30M mutation was 33.9 years, compared with 54.5 years for patients with other variants, producing a bimodal age-of-onset distribution overall. The male-to-female ratios reported in countries other than the US ranged from 0.7 in Portugal to 1.9 in Germany. The male-to-female ratio of patients from the US was 4.6.[Coelho 2013] The age, gender distribution, and percentage of patients with V30M in the 225 patients with hATTR amyloidosis in the randomized, global, double-blind, placebo-controlled, Phase 3 pivotal study of patisiran (ALN-TTR02-004; Study 004) further illustrate the variability among analyses of populations of patients with hATTR amyloidosis. Median age at entry was 62 years (range 24 to 83), median time since diagnosis was 1.37 years, and 74.2% of patients were male. A total of 96 patients (42.7%) possessed the V30M variants.

Race/ethnic origin of patients with hATTR amyloidosis:

Hereditary ATTR amyloidosis is a world-wide disease and therefore occurs in patients across a range of races and ethnic origins.

The V30M variants occurs primarily in families with heritage from Portugal, Sweden, and Japan. Those patients with the V30M variant and a relatively early age of disease onset (30-50 years) are usually from endemic regions within those 3 countries and present with sensory neuropathy, autonomic dysfunction, and cardiac conduction disturbances.[Carvalho 1992; Soares 2005]

Patients with late onset V30M (after age 50) and most non-V30M variants, found in multiple different non-endemic regions throughout the world, typically present with motor neuropathy, in addition to sensory and autonomic neuropathy, and often have cardiomyopathy and/or heart wall thickening from cardiac amyloid involvement.[Ando 2013]

Certain genotypes, such as the T60A variant, which is associated with persons of Irish descent, the I68L variant in Italy, and the V122I variants in persons of west African descent, manifest as hATTR amyloidosis that usually starts with a cardiac-predominant phenotype but can include polyneuropathy in a large fraction of patients.[Buxbaum 2017; Jacobson 1997; Maurer 2016]

Existing Treatment Options

The treatment of hATTR amyloidosis requires a multidisciplinary approach primarily involving neurology, gastroenterology, and cardiology specialties. Historically, palliative/symptomatic therapies directed at specific symptoms such as pain, nausea, vomiting, and diarrhea have been the mainstay of treatment.

Patisiran and vutrisiran, RNA interference (RNAi) therapeutics, are approved in the US, EU, Japan, and other regions for the treatment of the polyneuropathy of hATTR amyloidosis in adults. These therapeutics suppress the production of TTR in the liver by targeting the messenger RNA (mRNA) for degradation through RNAi. Treatment with patisiran or vutrisiran, has been shown to result in improvements in neuropathy (modified neuropathy impairment score +7 [mNIS+7]), quality of life (Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QOL-DN]), and multiple other disease manifestations compared to placebo in patients with hATTR amyloidosis who exhibited a broad range of disease severity and *TTR* genotypes.[Adams 2018; Adams 2021; Adams 2023] In Study 004 (APOLLO; which was the basis for the approval of patisiran), the magnitude of TTR reduction correlated with the improvement in mNIS+7 score at 18 months, where a higher magnitude of TTR reduction led to greater improvements in mNIS+7 score at a population level. In a threshold analysis of mNIS+7 (change from baseline of < 0 points), 56.1% of patisiran-treated patients compared to only 3.9% of placebo-treated patients experienced improvement in polyneuropathy based on mNIS+7 score at 18 months. In ALN-TTRSC02-002 (HELIOS-A; which was the basis for the approval of vutrisiran), treatment with vutrisiran led to rapid and sustained lowering of circulating TTR across all TTR variants studied.

TTR tetramer stabilizers (including tafamidis and diflunisal) act by binding to the thyroxine-binding site on TTR to reduce the dissociation of TTR tetramers into misfolded amyloidogenic monomers. Tafamidis, an oral TTR tetramer stabilizer, received approval from the European Medicines Agency under exceptional circumstances in November 2011 ‘for the treatment of transthyretin amyloidosis in adult patients with stage I symptomatic polyneuropathy to delay peripheral neurologic impairment.[Pfizer Limited 2011] Tafamidis has also been authorized for the treatment of hATTR amyloidosis with polyneuropathy in Japan and a number of other countries; however, tafamidis has not been approved for this use in the US. Long-term follow-up of early stage patients with the V30M variant after initiating tafamidis treatment showed continued neuropathy progression over time.[Barroso 2017] Tafamidis has been reported to be generally well tolerated.[Coelho 2012]

Diflunisal, a generic, oral, nonsteroidal, anti-inflammatory drug that has been demonstrated to bind to and stabilize the TTR tetramer in a manner similar to tafamidis, was shown to slow neuropathy progression compared with placebo in patients with V30M and non-V30M hATTR amyloidosis with both early and late stage neuropathy in a Phase 3 US National Institutes of Health-sponsored study (N=130).[Berk 2013] While used off-label in some countries where available, diflunisal is not an

approved treatment for hATTR amyloidosis in any country.[Berk 2013] In the US, diflunisal carries boxed warnings for cardiovascular thrombotic events, gastrointestinal risk, and renal injury.[Cadila Healthcare Limited 2017] Overall, the data to date with TTR tetramer stabilizers indicate some slowing of neuropathy progression, with effects limited in the case of tafamidis to early stage V30M patients.

The TTR-targeting antisense oligonucleotide inotersen, was authorized in the European Economic Area (EEA) on 05 July 2018 for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy and authorized in the US on 05 October 2018 for the treatment of the polyneuropathy of hATTR amyloidosis in adults. It is also approved for marketing in Brazil for the treatment of stage 1 or 2 polyneuropathy in adult patients with hATTR amyloidosis and in Canada for the treatment of polyneuropathy of hATTR in adults. Inotersen showed statistically significant slowing of neuropathy progression (measured using a version of the modified Neurologic Impairment Score +7) and quality of life (Norfolk QOL-DN) relative to placebo in a randomized Phase 3 trial,[Dyck 2017]. From the Phase 3 clinical trial, 28 adverse event (AE) data including thrombocytopenia, glomerulonephritis, liver enzyme elevations, and 1 case of fatal intracranial hemorrhage have resulted in regulatory requirements for routine laboratory monitoring (eg, platelets, kidney function, and liver function) and dosing adjustments for at-risk patients. The fibril-disrupting drug combination of doxycycline and tauroursodeoxycholic acid,[Adams 2012] is also currently under development, which to date has only been tested in small single-arm Phase 2 studies. A small molecule and an antibody against serum amyloid P, a component common to amyloid deposits in systemic amyloidosis, are also in early-stage development for the treatment of hATTR amyloidosis.[Pepys 2017; Pepys 2002; Richards 2015]

Orthotopic liver transplantation (OLT) eliminates variant TTR from the circulation but does not affect the production of wt TTR, which continues to be made by the transplanted liver. Orthotopic liver transplantation is only effective in slowing the progression of disease in patients with an early age of onset (<50 years of age),[Okamoto 2009] especially for those with the V30M variant and short disease duration before transplant. Consequently, almost two-thirds of patients with hATTR amyloidosis are not transplant-eligible. Even when OLT is possible, 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.[Bispo 2009; Herlenius 2004; Okamoto 2009]

Natural History of hATTR Amyloidosis

Overall, hATTR amyloidosis is a rapidly progressive, multisystem disease that results in poor quality of life and premature death.

Polyneuropathy classically manifests as a length-dependent, symmetrical sensorimotor neuropathy involving large and small peripheral nerve fibers.[Ando 2013; Benson 2007; Carvalho 1992; Connors 2004; Soares 2005] Patients experience painful dysesthesias, loss of sensation, progressive muscle atrophy, and motor weakness in both lower and upper limbs. These symptoms subsequently lead to ambulation impairment, frequent falls, and inability to perform activities of daily living such as holding eating utensils, buttoning a shirt, or zipping a coat. Loss of sensation can lead to burns and joint injury in the lower limbs. Furthermore, sensorimotor neuropathy is accompanied by autonomic dysfunction, which results in debilitating orthostatic hypotension, severe gastrointestinal symptoms (including early satiety, chronic nausea/vomiting, and both diarrhea and constipation), and bladder dysfunction with recurrent urinary tract infections. Amyloid infiltration into cardiac tissue leads to cardiomyopathy characterized by heart failure due initially to diastolic dysfunction, followed by systolic dysfunction, as well as conduction disturbances, and arrhythmias.[Ando 2013; Benson 2007; Carvalho 1992; Connors 2004; Soares 2005] Renal amyloid deposition resulting in proteinuria and renal insufficiency can occur with V30M as well as other genotypes such as Gly47Glu and Ser77Tyr.[Lobato 2012] Ocular abnormalities such as keratoconjunctivitis sicca, secondary glaucoma, vitreous deposits, and pupillary abnormalities are commonly observed in patients with hATTR amyloidosis due to the underlying

disease.[Conceicao 2016; Martins 2015; Rousseau 2013] The constellation of progressive morbidity from amyloid infiltration results in severe disability, wasting due to gastrointestinal malabsorption, malnutrition, and cardiac cachexia, and profound loss of quality of life. 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, [Plante-Bordeneuve 2011; Swiecicki 2015] with a reduced survival (3.4 years) for patients with ATTR cardiomyopathy.[Gertz 1992; Sattianayagam 2012; Swiecicki 2015]

Important comorbidities

Patients with hATTR amyloidosis often have poor nutritional status and overall wasting due in part to severe gastrointestinal manifestations including frequent episodes of diarrhea.[Ando 2013] Furthermore, as late-onset disease manifests in the elderly, diseases commonly associated with aging such as osteoarthritis, ocular events, thyroid dysfunction, and malignancies are important co-morbidities. Depression may also be an important co-morbidity as a result of this debilitating disease.[Lopes 2015]

In addition to the ocular symptoms that present as manifestations of hATTR amyloidosis,[Rousseau 2013] dry eye has been reported as well, and decreases in visual acuity are noted as the disease progresses.[Ando 2013]

Neuromuscular diseases are known risk factors for osteoporosis, which may be further exacerbated by the gastrointestinal manifestations of the disease leading to malabsorption. In a study conducted on 12 patients with V30M FAP, 6 were diagnosed as osteoporotic, and 2 had osteopenia.[Conceicao 2005] In a study of patients with diabetes who had neuropathy (N=19) or did not have neuropathy (N=22), cortical bone mass in hands and feet was found to be significantly lower in patients with neuropathy. Metatarsal fractures were reported in 6 out of 19 patients who had neuropathy, but in none of the 22 patients who did not have neuropathy.[Cundy 1985]

Baseline comorbidities in patients in the Phase 3 study of patisiran in patients with hATTR amyloidosis with polyneuropathy (Study 004 described above; N=225), as reported in medical history at baseline (according to Medical Dictionary for Regulatory Activities [MedDRA] System Organ Classes [SOCs] and High-Level Terms), were consistent with those reported in the literature and included cardiac disorders in 67% (myocardial disorders, cardiac conduction disorders, supraventricular arrhythmias, among others); eye disorders in 44% (including cataracts in 24% and dry eye in 8% of patients); gastrointestinal disorders in 71% (primarily diarrhea and gastrointestinal atonic and hypomotility disorders); general disorders and administration site conditions in 27% (including asthenic conditions in 12% and oedema in 12%); renal and urinary disorders in 28% (bladder and urethral symptoms in 11%); and vascular disorders in 56% (28% with vascular hypertensive disorders and 28% with vascular hypotensive disorders). Musculoskeletal and connective tissue disorders were reported in 45% of patients at baseline, including intervertebral disc disorders in 9% and metabolic bone disorders in 8%.

Part II: Module SII Nonclinical Part of the Safety Specification

Executive Summary of Important Nonclinical Findings

The siRNA in patisiran binds to a conserved sequence in humans and monkeys, and thus is pharmacologically active in humans and monkeys, but not in rodents or rabbits. Liver and spleen were the primary organs of toxicity in nonclinical species following intravenous (IV) administration of patisiran. The liver is the primary site of patisiran uptake and accumulation. Hepatotoxicity determined the no observed adverse effect levels (NOAELs) in all of the nonclinical species. Other target organs included the lymph nodes (rats only), adrenal gland, infusion sites, and testes and epididymis (rats only). Adverse microscopic changes in the liver were correlated with increases in liver-related enzymes in serum and were reversible. In the spleen, histomorphological changes associated with toxicity included lymphoid hyperplasia as well as atrophy and necrosis; these changes also tended to recover after treatment. The incidence and severity of these findings did not progress with increased study duration. Adrenal gland, lymph node, and testicular/epididymal findings were confined to the 6-week studies only. The toxicities observed in rats and in monkeys with patisiran were similar to those seen for AF-011-1955 (same LNP formulation as patisiran but containing an siRNA directed against insect luciferase), overall suggesting that the toxicity is primarily due to the LNP, and potentially mostly contributed by the DLin-MC3-DMA component of the LNP rather than the siRNA. Transient activation of complement was observed in cynomolgus monkeys, but did not result in long-term complement depletion. Transient increases in some circulating cytokines (interleukin-1RA and interleukin-6) were also observed but were not associated with any adverse clinical signs.

Given the role of TTR as a carrier of retinol binding protein (RBP) and thus vitamin A, and of thyroxine, studies in monkeys with ALN-TTR01 (a first generation LNP with same siRNA [ALN-18328] as patisiran) or with patisiran, confirmed the secondary pharmacological effects associated with reductions in TTR, namely reductions, relative to baseline, in RBP (60%), vitamin A (90%), and thyroxine (41%). There were no toxic sequelae to the reductions of vitamin A or thyroxine in monkeys after chronic administration of patisiran.

In safety pharmacology studies in monkeys, there were no observed effects on electrocardiogram parameters (including QT intervals) and mean arterial blood pressure at ≤6 mg/kg, although heart rate and body temperature were increased at ≥3 mg/kg. Respiratory parameters and neurological examinations were not affected at 3 mg/kg, the only dose evaluated.

Patisiran was not mutagenic or clastogenic in genetic toxicity studies and was not carcinogenic in TgRasH2 mice. There were no developmental, reproductive, or perinatal/postnatal effects of patisiran (or its pharmacologically active rodent surrogate) in rats or rabbits at minimally toxic maternal doses. However, in a dose range-finding embryo-fetal toxicity study in rabbits, increases in spontaneous abortions, early resorptions, post-implantation loss, and reductions in litter size, embryo-fetal survival, and fetal body weights were observed at doses ≥1 mg/kg, but were considered to be secondary to the maternal toxicity observed at these doses.

Key safety findings from nonclinical studies and the relevance to human usage are summarized in Table 3.

Table 3: Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Toxicity:	
Target Organ Toxicity Identified from Acute and Repeat-Dose Toxicity Studies	
Liver: Necrosis (single cell and/or hepatocellular) was observed in mice, rats, and monkeys and was considered adverse when accompanied by increases in 1 or more liver-associated enzymes in serum (eg, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyltransferase, lactate dehydrogenase) and/or total bilirubin (TBILI). The high dose in the 39-week monkey study was lowered from 3.0 to 2.0 mg/kg once every 3 weeks (q3w) after the first dose because of adverse elevations in ALT and AST. Increased hepatocellular vacuolation was observed in mice, rats, and monkeys. Inflammatory changes were seen in mice, rats (highest severity), and monkeys and were often accompanied by changes in hematology (eg, total and/or differential white blood cell counts), fibrinogen, and serum chemistry (albumin and globulin). Sinus histiocytosis and reactive sinusoidal lining cells (including Kupffer cells) were seen in nonclinical species. Hepatic findings were partially or completely reversible. Maximum tolerated dose (MTD) or no observed adverse effect levels (NOAELs) in repeat-dose studies were based on hepatotoxicity observed at higher doses and were 6 mg/kg once every 2 weeks (q2w) (MTD) in mice, 0.1 mg/kg/q2w (NOAEL) in rats, and 1.0 mg/kg/q2w or q3w in monkeys.	The liver and spleen are the primary target organs of patisiran uptake and target organs of toxicity in rats and monkeys. There was no progression of toxicity with chronic dosing, and there appeared to be a trend toward recovery/reversibility in the nonclinical studies. In the clinical trials, analysis of hepatic AEs has shown no clinically important difference between placebo- and patisiran-treated patients and no increase in the overall pooled experience across the studies. A small increase of ALT and AST was observed in the patisiran group compared to placebo that remained stable over the 18-month treatment period. The mean change from baseline in ALT and AST was not associated with changes in ALP or TBILI. Across the 3 studies, ALT and AST have continued to remain stable over time for periods up to 84.9 months. As hepatotoxicity was observed in the nonclinical studies in rodents and monkeys and clinical data on longer term use are unknown, hepatic disorders are addressed as an important potential risk as summarized in Section Part II: Module SVII.
Spleen and Lymph Nodes: Lymphoid depletion/atrophy/necrosis was seen in the white pulp and marginal zone of the spleen in mice at 10 mg/kg/q2w and rats (≥0.15 mg/kg/q2w and 1 mg/kg once every 4 weeks [q4w]) and was considered adverse at ≥0.8 mg/kg/q2w in rats because of marked	Evaluation of AE data from the clinical trials reveals no safety concerns with respect to infections or malignancies related to abnormal lymphoid function.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
severity. Histiocytosis was observed in the white pulp of spleen in rats at ≥0.15 mg/kg/q2w and at 0.1 mg/kg/q4w. No decreases in circulating lymphocytes or other signs of immunotoxicity were seen. Increased extramedullary hematopoeisis, at times deemed secondary to inflammation, was seen in rats at ≥0.15 mg/kg/q2w and mice at ≥1 mg/kg/q2w. Non-adverse red pulp hypocellularity was seen in monkeys at 3 mg/kg/q2w and 3.0/2.0 mg/kg/q3w. Splenic changes in rodents and monkeys were reversible. In rats, reversible lymphoid and stromal cell hyperplasia, histiocytosis, and inflammation in lymph nodes were observed in the 6-week toxicity study at ≥0.15 mg/kg/q2w only. No lymph node findings were noted in mice or monkeys.	
<u>Adrenal Gland:</u> In a 6-week rat study, reversible cortical hypertrophy was observed at the end of the dosing phase at ≥0.8 mg/kg/q2w; degeneration/necrosis at corticomedullary junction was observed after 60-day recovery period at ≥0.15 mg/kg/q2w. In a 6-week monkey study, reversible decreases in cortical vacuolation were observed at 3 mg/kg/q2w. No findings were noted in subsequent rat and monkey studies of longer duration.	Clinical trial data revealed no safety concerns related to decreased adrenal cortical function.
<u>Injection/Infusion Sites:</u> Reversible vascular/perivascular inflammation occurred in mice at ≥1 mg/kg/q2w, in rats at ≥0.03 mg/kg/q2w, and in monkeys at 3 mg/kg/q2w and was associated with inflammatory changes in hematology (total and differential white blood cell count), fibrinogen, and serum chemistry (albumin and globulin).	Clinical trial data revealed no safety concerns related to the infusion sites.
<u>Testes and Epididymis:</u> In a 6-week rat study, adverse uni- or bilateral degeneration/atrophy of seminiferous epithelium and oligo/aspermia in epididymis were observed at low incidence at the end of dosing and recovery phases at ≥0.15 mg/kg/q2w. No findings were noted in subsequent rat studies or in any of the	Clinical trial data revealed no safety concerns related to nonclinical findings in the testes and epididymis.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
monkey studies, including the 39-week study that employed sexually mature animals in which male reproductive parameters (ie, volume, color, appearance, sperm concentration, motility and morphology, and testis measurement) and spermatogenic cycle were evaluated. No effects were observed in a male fertility study at ≤0.3 mg/kg/q2w (highest dose tested) in which rats were dosed for 10 weeks (a full cycle of spermatogenesis) prior to mating.	
Reproductive and developmental toxicity:	
Fertility: No effects on mating or fertility were observed at ≤0.3 mg/kg/q2w (highest dose tested) in male rats (patisiran was administered q2w for 10 weeks prior to mating) or on estrus cycling, mating, or fertility at ≤1.5 mg/kg (highest dose tested) in female rats (patisiran was administered 15, 8, and 1 day prior to mating). No effects on male reproductive parameters in sexually mature monkeys were observed at ≤3.0/2.0 mg/kg/q3w (highest dose tested). Embryo-Fetal and Developmental Toxicology: Little to no fetal exposure to ALN-18328, DLin-MC3-DMA, or PEG_{2000}-C-DMG was observed in rats and rabbits. No effects on pregnancy or embryo-fetal development were observed in rats at ≤1.5 mg/kg when patisiran was administered 15, 8, and 1 day prior to cohabitation and on Gestation Days (GDs) 6, 13, and 19. No effects were observed on pregnancy or embryo-fetal development when a rodent-specific surrogate formulated in the same LNP as patisiran was administered at 1.5 mg/kg by the same schedule and elicited reductions in serum TTR protein (>95% from baseline) and vitamin A (88% from controls). No effects were observed on embryo-fetal development in rabbits at ≤0.6 mg/kg (patisiran administered on GDs 7, 13, and 19). In a dose range-finding study in rabbits, increases in spontaneous abortions, early	In animal studies, patisiran had no adverse effects on male or female fertility, pregnancy, or embryo-fetal development at doses that did not result in maternal toxicity. Despite marked reductions in circulating vitamin A in rats after administration of the rodent-specific surrogate, there were no effects on fertility, reproductive outcomes, embryo-fetal or postnatal/perinatal development. Components of the LNP formulation were detected in the milk of rats in low levels relative to their concomitant plasma levels. No data are available on the use of patisiran in pregnant or lactating women. The effects of maternal serum TTR reduction or serum vitamin A reduction on the human fetus are unknown. There are no data on the effects of patisiran on human fertility. No impact on male or female fertility was detected in animal studies. The use of patisiran in pregnant or lactating women is considered missing information as summarized in Part II: Module SVII.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
resorptions, postimplantation loss, reductions in litter size, embryo-fetal survival, and fetal body weights at ≥1 mg/kg (patisiran administered on GDs 7, 13, and 19) were considered to be secondary to the maternal toxicity observed at these doses. <u>Peri/Postnatal Developmental Toxicity in Rats:</u> No ALN-18328 was detected in milk from rats at 2 hours post-dose on Lactation Day (LD) 12. Milk DLin-MC3-DMA and PEG_{2000}-C-DMG concentrations were ≤7% of concomitant maternal plasma concentrations. There were no effects on gestation, parturition, lactation, or maternal behavior or on peri/postnatal development in offspring at ≤1.5 mg/kg (highest dose tested) when patisiran administered on GDs 7, 13, and 19 and on LDs 6, 12, and 18. No effects were observed on these parameters in rats administered the rat-active surrogate LNP at 1.5 mg/kg by the same schedule despite reductions in serum TTR protein (90-100% from baseline), vitamin A (67-75% from control), and thyroxine (66% from baseline).	
Carcinogenicity and Genotoxicity	
Patisiran was not carcinogenic at ≤6 mg/kg/q2w (highest dose tested) in a 26-week study in TgRasH2 mice. Patisiran was not genotoxic in bacterial mutagenesis, chromosomal aberration, or mouse bone marrow micronucleus tests.	There is no evidence that patisiran is carcinogenic in humans based on the nonclinical studies. The pharmacologic mode of action does not pose an increased risk for carcinogenicity. In clinical studies, malignancies were reported in similar percentages of patients treated with patisiran and placebo and were at a rate consistent with the expected rate for the general population. No cases of malignancy were considered related to treatment.
Drug Abuse and Liability Assessment	
Based on a review of the nonclinical findings, there was no evidence of significant drug distribution to the brain, effects on central nervous system (CNS) activity, behavior, or neurological examinations.	There is no evidence that patisiran has a potential for abuse in humans, based on findings in both the nonclinical and clinical programs.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Safety Pharmacology:	
Based on its physiochemical properties, patisiran has a low likelihood of direct cardiac ion channel interactions or delaying ventricular repolarization. Single intravenous (IV) doses at ≤6 mg/kg (highest dose tested) did not result in QT prolongation or electrocardiogram abnormalities in monkeys. Heart rate and body temperature were increased at ≥3 mg/kg; these did not fully recover to baseline values. No effects were seen on the respiratory or central nervous systems at 3 mg/kg (only dose tested). No CNS-related or respiratory system-related clinical observations were noted in repeat-dose monkey toxicity studies at ≤3 mg/kg/q2w or at ≤3/2 mg/kg/q3w (highest doses tested).	There is no evidence that patisiran causes corrected QT interval prolongation, as findings from nonclinical and clinical studies do not suggest that patisiran has the potential to delay ventricular repolarization.
Other Toxicity-related Information:	
Drug-drug interactions: The components of patisiran were not inhibitors or inducers of cytochrome P450 (CYP) enzymes or transporters in in vitro assays. ALN-18328 and PEG_{2000}-C-DMG are not substrates of CYP enzymes. Although approximately 26% of DLin-MC3-DMA was metabolized by CYP3A4 (in an in vitro assay with human CYP supersomes), clinically relevant drug-drug interactions are not expected.	No formal drug interaction clinical studies have been performed. Patisiran is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of CYP. The components of patisiran are not inhibitors or inducers of CYP enzymes or transporters.
Secondary pharmacology: Repeated administration of patisiran to monkeys at ≤3 mg/kg/q2w or ≤3/2 mg/kg/q3w resulted in mean maximum reductions, relative to baseline, in vitamin A (90%) and thyroxine (41%) as well as mean maximum reductions in the primary pharmacodynamics effect of serum TTR (98%). No effects were noted on the eye or thyroid gland.	The risk of development of vitamin A deficiency in patients receiving patisiran is expected to be low, as transport and tissue uptake of vitamin A can occur in the absence of RBP.[Biesalski 1999; Episkopou 1993; van Bennekum 2001] In the patisiran program, there have been no safety concerns related to apparent vitamin A deficiency, either in the evaluation of reported AEs or in serial ophthalmic evaluations (including electroretinography). As was done in the clinical studies, patients should be instructed to take the daily recommended amount of supplemental vitamin A. Because of a theoretical risk, despite the lack of evidence in the clinical development program, consequences of vitamin A deficiency is addressed as

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
	an important potential risk as summarized in Part II: Module SVII.
Immunogenicity: Antidrug antibodies (ADA) measured as IgG, IgM, or IgG+IgM directed against the PEG_{2000}-C-DMG component of patisiran were observed in rats and monkeys. In the 6- and 4-week rat and in the 6-and 39-week studies in monkeys, there were no apparent effects on exposure or any associated clinical signs. In the 26-week study in rats, ADA were detected in approximately 50% of the rats (all dose groups), and systemic exposure to ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG was altered. This may have explained the lack of target organ toxicity observed in this study (NOAEL=0.3 mg/kg/q2w, the highest dose tested).	Immunogenicity to biotherapeutic drugs in nonclinical species is not generally predictive of the potential immunogenicity in humans. The immunogenic response to patisiran in humans was evaluated in a placebo-controlled Phase 3 study through measurement of ADA directed against PEG_{2000}-C-DMG, a lipid component of patisiran. The overall frequency of treatment-emergent ADAs in patients treated with patisiran group was 3.6%. ADA titers were low and transient with no evidence of an effect on clinical response or on the pharmacokinetic and pharmacodynamic profiles of patisiran. There was no association of ADA with any safety concerns, including infusion-related reactions (IRRs), anaphylactic reactions, or hypersensitivity events.
Immunostimulation: Transient (<24 h) increases, relative to control, were observed in circulating interleukin 6, interferon gamma-induced protein 10, chemokine (C-X-C motif) ligand 1, and monocyte chemoattractant protein-1, in mice after a single dose at ≥7.5 mg/kg. Increased serum/plasma levels of complement split product Bb and/or C3a, cytokines interleukin-6 and interleukin-1 receptor antagonist, and C-reactive protein (CRP) were observed in monkeys 15 min to 48 h after patisiran at ≥1.0 mg/kg/q2w. No associated clinical signs were observed. No depletion of Factor B, C3, and CH50 (functional complement) occurred in monkeys dosed for 39 weeks at ≤3.0/2.0 mg/kg/q3w (highest dose tested).	Changes in CRP and complement split product Bb were seen in early clinical studies; however, these findings were not correlated with clinical signs.

Nonclinical findings that may have relevance to humans are the following:

- Important potential risks:
  - Consequences of vitamin A deficiency
  - Hepatic Disorders
- Missing information: Use in pregnancy and lactation

Part II: Module SIII Clinical Trial Exposure

The clinical development program for patisiran consists of 2 clinical trials in healthy volunteers (ALN-TTR02-001; Study 001 and ALN-TTR02-005; Study 005), 5 clinical trials in patients with hATTR amyloidosis with polyneuropathy: a Phase 2 multiple ascending dose study (ALN-TTR02-002; Study 002), a Phase 2 open-label extension study (ALN-TTR02-003; Study 003), a double-blind, randomized, placebo-controlled pivotal Phase 3 study (ALN-TTR02-004 [APOLLO]; Study 004), a global open-label Phase 3 extension study (ALN-TTR02-006; Study 006), and an open-label study in patients post liver transplant (ALN-TTR02-008; Study 008), and 1 clinical trial in patients with ATTR amyloidosis with cardiomyopathy: a Phase 3, double-blind, randomized, placebo-controlled, multicenter study in patients with ATTR amyloidosis with cardiomyopathy (ALN-TTR02-011 [APOLLO-B]; Study 011). Patisiran was also given as a reference comparator in Study ALN-TTRSC02-002 in patients with hATTR amyloidosis with polyneuropathy. See Table 4 for study details.

In addition to the clinical trials described above, patisiran was also administered to patients with hATTR amyloidosis with polyneuropathy via an Expanded Access Protocol (EAP, ALN-TTR02-007; Study 007) in the US and under Compassionate Use Programs (CUPs) worldwide and to patients with ATTR amyloidosis with cardiomyopathy via EAP, ALN-TTR02-014; Study 014) conducted in the US. These programs are further described in Part II: Module SV.

Table 4: Clinical Studies with Patisiran

Study Number Phase Status	Study Description/ Number of Study Centers and Regions	Dose and Duration[a,b]	Number Dosed		Objective
			Placebo	Patisiran	
Patients with hATTR Amyloidosis					
Placebo-controlled – included in pooled data					
ALN-TTR02-004 Phase 3 (Study 004, APOLLO) Completed	Randomized, double blind, placebo-controlled study of patisiran in patients with hATTR amyloidosis with polyneuropathy 44 centers in United States, Canada, Europe, Asia, and South America	Patisiran 0.3 mg/kg or placebo q3w IV; 18 months	77	148	To evaluate the efficacy and safety of patisiran
Long term open-label – included in pooled data					
ALN-TTR02-006 Phase 3 (Study 006) Completed	Multicenter, open-label, extension study of patisiran in patients who completed clinical study ALN-TTR02-004 or ALN-TTR02-003 43 centers worldwide in 19 countries in North America, South America, Europe, and Asia	Patisiran 0.3 mg/kg q3w IV; up to ~5 years	N/A	211 (includes 186 patients who completed Study 004 (49 patients previously on placebo and 137 patients previously on patisiran), and 25 patients who completed Study 003	To evaluate longer-term safety and efficacy of patisiran

Study Number Phase Status	Study Description/ Number of Study Centers and Regions	Dose and Duration[a,b]	Number Dosed		Objective
			Placebo	Patisiran	
ALN-TTR02-003 Phase 2 (Study 003) Completed	Open-label extension study of patisiran in patients previously dosed in ALN-TTR02-002 9 centers in Europe, United States, and South America.	Patisiran 0.3 mg/kg q3w IV; 24 months	N/A	27 (all previously treated in Study 002)	To evaluate long-term safety, PD, PK, and clinical activity of patisiran
Open-label –included in pooled data					
ALN-TTR02-008 Phase 3b (Study 008) Completed	Open-label study to evaluate safety, efficacy, and pharmacokinetics of patisiran in patients with hATTR amyloidosis with disease progression post-orthotopic liver transplant 9 centers in Europe	Patisiran 0.3 mg/kg q3w IV; 12 months	N/A	23	To evaluate the efficacy and safety of patisiran in patients with disease progression after orthotopic liver transplant

Study Number Phase Status	Study Description/ Number of Study Centers and Regions	Dose and Duration[a,b]	Number Dosed		Objective
			Placebo	Patisiran	
ALN-TTRSC02-002 Phase 3 Ongoing	Randomized, open-label, global study to evaluate the efficacy and safety of ALN-TTRSC02 (vutrisiran) in patients with hATTR amyloidosis, with patisiran as the reference comparator to vutrisiran 80 centers worldwide	Patisiran 0.3 mg/kg IV infusion once every 3 weeks ±3 days during the 18 months treatment period (reference comparator only). All active patients have been switched to vutrisiran	N/A	42	To determine the efficacy of ALN-TTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment
Multiple ascending dose – not included in pooled data					
ALN-TTR02-002 Phase 2 (Study 002) Completed	Open-label, multiple-dose, dose escalation study of patisiran in patients with hATTR amyloidosis with polyneuropathy 10 centers in 7 countries in Western Europe, North America, and South America.	Patisiran 0.01 to 0.3 mg/kg q3w or q4w IV; 2 doses	N/A	29 0.01 mg/kg (n=4) 0.05 and 0.15 mg/kg (n=3 each) 0.3 mg/kg (n=19)	To evaluate safety, PK, and PD of multiple doses of patisiran

Study Number Phase Status	Study Description/ Number of Study Centers and Regions	Dose and Duration[a,b]	Number Dosed		Objective
			Placebo	Patisiran	
Patients with ATTR Amyloidosis					
Placebo-controlled –included in pooled data					
ALN-TTR02-011 Phase 3 (Study 011) DB Period: Completed OLE Period: Ongoing	Randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of patisiran in patients with ATTR amyloidosis with cardiomyopathy. 69 centers worldwide in 21 countries in North America, South America, Europe, Asia, and Australia	Patisiran 0.3 mg/kg for patients weighing <100 kg; 30 mg fixed dose for patients weighing ≥100 kg up to 48 months (12-month DB period and 36-month OLE period)	178	347[c]	To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6-MWT) in patients with ATTR amyloidosis with cardiomyopathy
Healthy Volunteers					
Single-ascending dose					
ALN-TTR02-001 Phase 1 (Study 001) Completed	Randomized, single blind, single ascending dose study of patisiran in healthy volunteers 2 centers in the United Kingdom.	Patisiran 0.01 to 0.5 mg/kg or placebo; single dose	4	13 0.01, 0.05, 0.15, and 0.3 mg/kg (n=3 each) 0.5 mg/kg (n=1)	To evaluate the safety, PK, and PD of a single dose of patisiran

Study Number Phase Status	Study Description/ Number of Study Centers and Regions	Dose and Duration[a,b]	Number Dosed		Objective
			Placebo	Patisiran	
ALN-TTR02-005 Phase 1 (Study 005) Completed	Randomized, double-blind, placebo-controlled, single ascending dose study of patisiran in healthy volunteers of Japanese descent 1 center in the United Kingdom.	Patisiran 0.05 to 0.3 mg/kg or placebo; single dose	3	9 0.05, 0.15, and 0.3 mg/kg (n=3 each)	To evaluate safety, tolerability, and PK of a single dose of patisiran in healthy volunteers of Japanese descent

Abbreviations: 6-MWT=6-minute walk test; ATTR amyloidosis=amyloid TTR-mediated amyloidosis; DB=Double-Blind; hATTR amyloidosis=hereditary amyloid TTR-mediated amyloidosis; IV=intravenous; N/A=not applicable; OLE=Open-Label Extension; PD=pharmacodynamic; PK=pharmacokinetic; q3w=every 3 weeks; q4w=every 4 weeks; TTR=transthyretin.

[a] All patients, including patients who received placebo in Study 004, received a premedication regimen prior to each dose that included a corticosteroid, paracetamol, an H1 blocker, and an H2 blocker.

[b] The rate of infusion was approximately 3.3 mL/min in Study ALN-TTR02-001. In Study ALN-TTR02-002, Cohorts 1 through 6 received the IV infusion at the rate of 3.3 mL/min (approximately 60-minute infusion), while a rate of 1.1 mL/min during the first 15 minutes, and approximately 3.3 mL/min for the remainder of the infusion (approximately 80-minute infusion) was used with Cohorts 7 through 9. For all other studies, the rate of approximately 1 mL/min for the first 15 minutes followed by approximately 3 mL/min for the remainder of the infusion was utilized; the total infusion time was approximately 80 minutes.

[c] This includes all patients who received at least 1 dose of patisiran, including patients treated with patisiran during the DB Period (N=181) and patients initially treated with placebo during the DB Period and switched to patisiran during the OLE Period (N=166; data cutoff date 09 August 2023).

Sources: Study 004 (final data: 14 September 2017), Study 003 (final data: 27 September 2016), Study 006 (final database lock: 07 December 2022), Study 008 (final data: 11 December 2020), ALN-TTRSC02-002 (interim data: 20 October 2021; all active patients who received patisiran as a reference comparator have been switched to vutrisiran), and Study 011 (interim data: 09 August 2023).

In the patisiran development program, a total of 291 patients with hATTR amyloidosis with polyneuropathy (Studies 002, 003, 004, 006, 008, and the patisiran arm of ALN-TTRSC02-002), 347 patients with ATTR amyloidosis with cardiomyopathy (Study 011), and 22 healthy volunteers have received at least 1 dose of patisiran. The healthy volunteers received single doses as described in Table 4.

The 29 patients in Study 002 each received 2 doses in the dosing groups described above. All but 2 of those patients enrolled in the completed Phase 2 extension study (Study 003) and, as for all remaining patients receiving patisiran in the clinical development program (Study 004 and Study 006), received doses of 0.3 mg/kg every 3 weeks. Exposure data from the 2 patients from Study 002 who did not enroll in Study 003 are not included in the pooled data (see below). One of the patients in the 0.3 mg/kg dose q3w cohort withdrew from Study 002 early after receiving 1 dose of patisiran, and 1 patient in the 0.3 mg/kg q4w cohort completed the 2 doses of patisiran in Study 002 then moved to another country and did not wish to continue patisiran treatment.

A total of 23 patients with hATTR amyloidosis with disease progression post-OLT received at least 1 dose of patisiran (0.3 mg/kg every 3 weeks) in Study 008. Twenty-two patients completed the study. One of the patients discontinued study treatment after receiving 1 dose of patisiran due to a patient decision. Exposure data from Study 008 are included in the pooled data.

Additionally, 42 patients have been exposed to patisiran as the comparator in an ongoing Phase 3, global, randomized, open-label clinical study investigating vutrisiran with hATTR amyloidosis with polyneuropathy (ALN-TTRSC02-002) during the 18 months treatment period. Vutrisiran is being developed for the same indication as patisiran but with a subcutaneous route of administration. In ALN-TTRSC02-002, patients were randomized in a 3:1 ratio to receive vutrisiran or patisiran, respectively, and patient enrollment is complete. Patisiran exposure data from ALN-TTRSC02-002 are included in the pooled data.

Exposure data are summarized in further detail for the 289 patients with hATTR amyloidosis with polyneuropathy who have been exposed to at least 1 dose of patisiran in Studies 003, 004, 006, 008, or ALN-TTRSC02-002. All exposure data are final with Study 006 (open-label Phase 3 extension study) completed on 23 November 2022 (Final Database lock: 07 December 2022).

Exposure data are also summarized for the 347 patients with wt transthyretin-mediated amyloidosis (wtATTR) or hATTR amyloidosis with cardiomyopathy who have been exposed to at least 1 dose of patisiran in Study 011 as of the data cutoff date of 09 August 2023.

Clinical trial exposure to patisiran in ATTR amyloidosis patients is presented in Table 5, Table 6, and Table 7.

The overall cumulative patient exposure to patisiran based on the Pooled Data (N=636) was 1887.1 patient-years.

Table 5: Duration of Patient Exposure to Patisiran

Duration of exposure	Polyneuropathy Studies[a] N=289		Cardiomyopathy Study[b] N=347		Total N=636	
	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]
On patisiran for at least:						
≥1 day	289 (100)	1224.6	347 (100)	662.5	636 (100)	1887.1
≥6 months	273 (94.5)	1221.0	329 (94.8)	657.9	602 (94.7)	1878.9
≥12 months	267 (92.4)	1216.9	313 (90.2)	645.4	580 (91.2)	1862.3
≥18 months	238 (82.4)	1185.0	224 (64.6)	532.1	462 (72.6)	1717.1
≥24 months	192 (66.4)	1110.3	174 (50.1)	445.3	366 (57.5)	1555.6
≥30 months	181 (62.6)	1085.6	79 (22.8)	228.3	260 (40.9)	1313.9
≥36 months	174 (60.2)	1066.5	21 (6.1)	69.9	195 (30.7)	1136.4
≥42 months	169 (58.5)	1050.3	7 (2.0)	25.3	176 (27.7)	1075.6
≥48 months	167 (57.8)	1042.8	0	-	167 (26.3)	1042.8
≥54 months	159 (55.0)	1008.5	0	-	159 (25.0)	1008.5
≥60 months	144 (49.8)	935.0	0	-	144 (22.6)	935.0
≥66 months	131 (45.3)	869.0	0	-	131 (20.6)	869.0
≥72 months	125 (43.3)	833.9	0	-	125 (19.7)	833.9
≥78 months	111 (38.4)	744.7	0	-	111 (17.5)	744.7
≥84 months	24 (8.3)	170.4	0	-	24 (3.8)	170.4

[a] Includes patients with hATTR amyloidosis with polyneuropathy who received patisiran in Studies 003, 004, 006, 008, or the patisiran arm of ALN-TTRSC02-002.

[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received patisiran in Study 011.

[c] Patient-years are defined as the sum of the years that patients in the study population have been exposed to patisiran.

Sources: Study 004 (final data: 14 September 2017), Study 003 (final data: 27 September 2016), Study 006 (final database lock: 07 December 2022), Study 008 (final data: 11 December 2020), ALN-TTRSC02-002 (interim data: 20 October 2021), and Study 011 (interim data: 09 August 2023).

Table 6: Exposure to Patisiran by Age Group and Gender

	Polyneuropathy Studies[a] N=289				Cardiomyopathy Study[b] N=347				Total N=636			
Age group	**Patients Number (%)**		**Patient-years[c]**		**Patients Number (%)**		**Patient-years[c]**		**Patients Number (%)**		**Patient-years[c]**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
0 to <18 years	0	0	0	0	0	0	0	0	0	0	0	0
≥18 to 64 years	120 (58.8)	50 (58.8)	540.0	207.8	24 (7.7)	5 (13.5)	46.9	7.4	144 (28.0)	55 (45.1)	586.9	215.2
≥65 to 74 years	70 (34.3)	26 (30.6)	302.4	101.2	106 (34.2)	6 (16.2)	211.6	12.8	176 (34.2)	32 (26.2)	514.0	114.1
≥75 years	14 (6.9)	9 (10.6)	46.6	26.5	180 (58.1)	26 (70.3)	332.1	51.7	194 (37.7)	35 (28.7)	378.7	78.2
Total (%)	204 (100.0)	85 (100.0)	889.1	335.5	310 (100.0)	37 (100.0)	590.6	71.9	514 (100.0)	122 (100.0)	1479.6	407.4

Abbreviations: F=female; M=male.

[a] Includes patients with hATTR amyloidosis with polyneuropathy who received patisiran in Studies 003, 004, 006, 008, or the patisiran arm of ALN-TTRSC02-002.

[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received patisiran in Study 011.

[c] Patient-years are defined as the sum of the years that patients in the study population have been exposed to patisiran.

Sources: Study 004 (final data: 14 September 2017), Study 003 (final data: 27 September 2016), Study 006 (final database lock: 07 December 2022), Study 008 (final data: 11 December 2020), ALN-TTRSC02-002 (interim data: 20 October 2021), and Study 011 (interim data: 09 August 2023).

Table 7: Exposure to Patisiran by Race or Ethnic Origin

Race/ethnic origin	Polyneuropathy Studies[a] N=289		Cardiomyopathy Study[b] N=347		Total N=636	
	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]
White	225 (77.9)	964.2	272 (78.4)	516.8	497 (78.1)	1481.0
Black or African American	8 (2.8)	28.0	26 (7.5)	47.0	34 (5.3)	75.1
Asian	50 (17.3)	204.7	37 (10.7)	79.3	87 (13.7)	284.0
Other[d]	6 (2.1)	27.6	7 (2.0)	13.0	13 (2.0)	40.7
Not Reported	0	-	5 (1.4)	6.3	5 (0.8)	6.3

[a] Includes patients with hATTR amyloidosis with polyneuropathy who received patisiran in Studies 003, 004, 006, 008, or the patisiran arm of ALN-TTRSC02-002.

[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received patisiran in Study 011.

[c] Patient-years are defined as the sum of the years that patients in the study population have been exposed to patisiran.

[d] Includes any patient who had indicated 'other', or 'unknown', or more than 1 race group.

Sources: Study 004 (final data: 14 September 2017), Study 003 (final data: 27 September 2016), Study 006 (final database lock: 07 December 2022), Study 008 (final data: 11 December 2020), ALN-TTRSC02-002 (interim data: 20 October 2021), and Study 011 (interim data: 09 August 2023).

Part II: Module SIV Populations Not Studied in Preauthorization Clinical Trials

SIV.1 Exclusion Criteria in the Pivotal Clinical Studies within the Development Program

The exclusion criteria used in the pivotal Phase 3 placebo-controlled Study 004 in polyneuropathy were selected primarily to enroll patients able to withstand the rigors of participating in a clinical study and to avoid enrolling patients with medical conditions or treatments that could potentially confound the assessment of the safety or efficacy of patisiran.

Key exclusion criteria from the pivotal Phase 3 Study 004 are presented in Table 8 with a determination of whether the criterion is considered as missing information.

Other exclusion criteria from Study 004 that were designed to ensure patients could participate in the study or to avoid confounding efficacy and safety results not presented in Table 8 are listed below. Based on nonclinical and clinical observations, patients with these criteria are not expected to be at a higher risk of adverse drug reactions (ADRs) from patisiran than the overall population.

- Other known causes of sensorimotor or autonomic neuropathy (Study 004).
- Type I diabetes (any length of time)
- Type II diabetes (for ≥5 years)
- Vitamin B_{12} deficiency
- Untreated hypo- or hyperthyroidism
- Previous investigational agents or devices (within 30 days or 5 half-lives, whichever is longer), antisense oligonucleotide therapy (within 3 months), or (Study 004) TTR tetramer stabilizers (within 14 days [3 days for diflunisal])
- Has had (within 3 months) or was planning a major surgery
- HIV or any infections requiring systemic antiviral treatment
- Malignancies within 2 years (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that was successfully treated),
- Acute coronary syndrome within 3 months
- Uncontrolled cardiac arrhythmia or unstable angina
- Known history of alcohol abuse within the past 2 years or daily heavy consumption
- An anticipated survival less than 2 years

Table 8: Key Exclusion Criteria from the Pivotal Phase 3 Study 004

Criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale if not considered missing information
Had a prior liver transplant or is planning to undergo liver transplant during the study period	To avoid confounding the assessment of the safety and efficacy of patisiran	Yes	-
Has known primary amyloidosis or leptomeningeal amyloidosis	Because patisiran specifically targets TTR to reduce its levels, it is unlikely to benefit patients with polyneuropathy due to causes other than hATTR amyloidosis. Furthermore, patisiran is not distributed to the CNS and would not be effective in leptomeningeal disease. This exclusion criterion aligns with the inclusion criterion defining the qualified population as patients with hATTR amyloidosis.	No	Patisiran would not be expected to be effective in these conditions. These conditions are not within the indication for the drug.
Has a New York Heart Association (NYHA) heart failure classification >2	To avoid confounding the assessment of safety of patisiran	No	Though patients with NYHA heart failure classification greater than 2 were excluded from at entry in Studies 003 and 004, patients with higher classifications were allowed entry into the open-label extension Study 006. Among the 211 patients who entered Study 006 from Study 004 or Study 003 , 15 (7.1%) and 4 (1.9%) had NYHA classifications 3 and 4, respectively at the time

Criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale if not considered missing information
			they entered Study 006. An evaluation of cardiac events in patients with a history of cardiac involvement revealed no safety concerns in these patients to suggest an increased risk of ADRs. On the contrary, the overall data from Study 004 suggest a beneficial effect on cardiac amyloid involvement based on improvement with patisiran compared to placebo on measures of cardiac structure (mean left ventricular wall thickness), cardiac function (longitudinal strain), and the cardiac biomarker N-terminal prohormone of brain natriuretic peptide.
Is unable to take the required premedications	All patients were required to receive premedications to reduce the potential of infusion-related reactions (IRRs), including placebo. patients to maintain the blind.	No	Premedication is required to be used with patisiran treatment to reduce the risk of IRRs. Information on the use of premedication is provided in the Summary of Product Characteristics (SmPC). It is not expected that patients will receive patisiran without premedication.
Female patients who were pregnant or were considering becoming pregnant during the study	Unknown effect	Yes	-
Female patients who were breastfeeding	Unknown effect	Yes	-

Abbreviations: ADR=adverse drug reaction; CNS=central nervous system; hATTR amyloidosis=hereditary amyloid TTR-mediated amyloidosis; NYHA=New York Heart Association; OLT=orthotopic liver transplant; SmPC=summary of product characteristics; TTR=transthyretin.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Trial Development Program

In the pooled data across Studies 003, 004, 006, 008, 011, and the patisiran arm of ALN-TTRSC02-002, 636 patients with wtATTR or hATTR amyloidosis were exposed to patisiran for approximately 1887.1 person-years (Table 5); the clinical safety data would enable detection of very common (incidence of ≥1/10) and common (≥1/100 to <1/10) ADRs and ADRs with a frequency as low as 1 in 514 per patient-years of exposure associated with patisiran. The patisiran clinical safety data are unlikely to allow detection of ADRs that are rare (≥1/10,000 to <1/1000) or very rare (<1/10,000).

In the pooled patient population, 580 patients have been exposed to patisiran for ≥12 months, 366 patients for ≥24 months, 195 patients for ≥36 months, 167 patients for ≥48 months, 144 patients for ≥60 months, 125 patients for ≥72 months, and 24 patients for ≥84 months (Table 5). Based on the available data, there are no known patisiran ADRs that have a long latency, are due to prolonged exposure, or are due to cumulative effects.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Development Programs

Table 9 presents exposure data in special populations from the patisiran Pooled Population (N=636).

Table 9: Exposure of Special Populations in Clinical Development Programs

Type of Special Population	Polyneuropathy Studies[a] N=289		Cardiomyopathy Study[b] N=347		Total N=636	
	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]
Pregnant women	0	-	0	-	0	-
Breastfeeding women	0	-	0	-	0	-
Patients with relevant comorbidities:						
Renal impairment[d]						
Mild	74 (25.6)	279.0	145 (41.8)	296.0	219 (34.4)	574.9
Moderate	35 (12.1)	98.4	136 (39.2)	245.6	171 (26.9)	344.0
Severe	1 (0.3)	1.1	7 (2.0)	9.4	8 (1.3)	10.5
Hepatic impairment[e]						
Mild	15 (5.2)	66.6	56 (16.1)	102.3	71 (11.2)	168.9
Moderate	2 (0.7)	4.4	12 (3.5)	15.9	14 (2.2)	20.3
Severe	0	-	1 (0.3)	0.8	1 (0.2)	0.8
Cardiac impairment						
NYHA Classification ≤2	281 (97.2)	1201.9	297 (85.6)	577.7	578 (90.9)	1779.6
NYHA Classification >2	6 (2.1)	14.6	50 (14.4)	84.8	56 (8.8)	99.4
Missing	2 (0.7)	8.1	0	-	2 (0.3)	8.1
Type of Amyloidosis						
wtATTR	0	-	279 (80.4)	537.8	279 (43.9)	537.8
hATTR	289 (100.0)	1224.6	68 (19.6)	124.7	357 (56.1)	1349.3
V30M	135 (46.7)	589.5	2 (0.6)	4.3	137 (21.5)	593.8
non-V30M	154 (53.3)	635.1	66 (19.0)	120.4	220 (34.6)	755.5
PND score >3b	8 (2.8)	17.0	0	-	8 (1.3)	17.0

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; eGFR=estimated glomerular filtration rate; hATTR=hereditary transthyretin-mediated amyloidosis; NYHA=New York Heart Association; PND=polyneuropathy disability; TBILI=total bilirubin; TTR=transthyretin; ULN=upper limit of normal; V30M=valine to methionine variant at position 30; wtATTR=wild type transthyretin-mediated amyloidosis.

[a] Includes patients with hATTR amyloidosis with polyneuropathy who received patisiran in Studies 003, 004, 006, 008, or the patisiran arm of ALN-TTRSC02-002.
[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received patisiran in Study 011.
[c] Patient-years are defined as the sum of the years that patients in the study population have been exposed to patisiran.
[d] Renal impairment: Mild: eGFR ≥60 to <90 mL/min/1.73m^2; Moderate: eGFR ≥30 to <60 mL/min/1.73m^2; Severe: eGFR=0 to <30 mL/min/1.73m^2.
[e] Hepatic impairment for patients without Gilbert's syndrome: Mild: (TBILI ≤ ULN and AST >ULN) or (TBILI >1.0×ULN to ≤1.5×ULN), Moderate: TBILI >1.5×ULN to ≤3.0×ULN, Severe: TBILI >3×ULN. Hepatic impairment for patients with Gilbert's syndrome: Mild: AST >ULN.

Sources: Study 004 (final data: 14 September 2017), Study 003 (final data: 27 September 2016), Study 006 (final database lock: 07 December 2022), Study 008 (final data: 11 December 2020), ALN-TTRSC02-002 (interim data: 20 October 2021), and Study 011 (interim data: 09 August 2023).

Part II: Module SV Post-Authorization Experience

Patisiran is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Cumulative global patient exposure to patisiran from marketing experience was calculated from internal sales data and patient counts collected since the International Birth Date of patisiran through 09 August 2023 (sales data) and 31 July 2023 (patient counts).

The following methodology for estimating post-marketing patient-years exposure to patisiran was used.

Patisiran is supplied in vials, each containing 10,000 µg patisiran. The recommended dose of patisiran is 300 µg/kg administered via IV infusion once every 21 days. Considering the average patient weight of 68 kg, the average daily dose of patisiran taken by a single patient is approximately 971.43 µg/day. The 365.25 days per year estimate was used to convert exposure from patient-days to patient-years.

Therefore, the following formula was used for the calculation of the estimated patient-years exposure to patisiran in the post-marketing experience:

$$\textbf{Number of patient-years} = \frac{\textbf{Number of vials sold} \times \textbf{10,000 µg patisiran}}{\textbf{Average daily dose} \times \textbf{365.25 days}}$$

The estimate of the number of patients treated with patisiran is based on the best available information from multiple sources, from firm and verifiable numbers to unverifiable numbers (eg, internal sources at a region or country level).

SV.1 Post-authorization Exposure

Commercial exposure to patisiran

Cumulatively, as of 09 August 2023, 297,025 vials of patisiran had been sold worldwide, corresponding to an estimated 8371.27 patient-years exposure, and cumulatively, as of 31 July 2023, it was estimated that 2834 patients had been treated with patisiran.

The cumulative number of patisiran vials sold, estimated patient-years exposure, and estimated number of patients treated are presented by region/country in Table 10.

Table 10: Cumulative Patisiran Sales and Estimated Exposure Data from Marketing Experience

Region/Country	Number of Vials Sold	Estimated Patient Exposure (Patient-Years)	Estimated Number of Patients Treated
Europe			
Austria	1404	39.57	15
Belgium	2135	60.17	19
Bulgaria	1086	30.61	21
Cyprus[a]	1829	51.55	19
Denmark	223	6.28	3
Finland[a]	93	2.62	1
France	39,758	1120.53	290
Germany	17,315	488.00	135
Greece	819	23.08	8
Ireland	808	22.77	12
Italy	21,587	608.40	280
Luxembourg	1460	41.15	11
Netherlands	7199	202.89	53
Poland[a]	55	1.55	1
Portugal	11,159	314.50	188
Romania	1582	44.59	23
Slovakia[a]	128	3.61	3
Slovenia	82	2.31	2
Spain	17,133	482.87	218
Sweden	5320	149.94	61
Switzerland	3922	110.54	41
Turkey[a]	148	4.17	4
UK (Great Britain, Northern Ireland, Scotland)	17,245	486.03	167
North America			
Canada	8047	226.79	81
USA	108,986	3071.63	816

Region/Country	Number of Vials Sold	Estimated Patient Exposure (Patient-Years)	Estimated Number of Patients Treated
Rest of the world			
Argentina[a]	419	11.81	10
Bolivia[a]	286	8.06	6
Brazil[a]	2873	80.97	53
Israel[a]	1679	47.32	13
Japan	21,938	618.29	260
Singapore[a]	58	1.63	1
Taiwan	249	7.02	19
Total	**297,025**	**8371.27**[b]	**2834**[c]

Abbreviations: UK=United Kingdom; USA=United States of America

[a] Patisiran was being supplied via named-patient sales in these countries as of 09 August 2023.

[b] Total corresponds to the sum of unrounded person time and therefore may not correspond to a simple sum of individual patient-years within the table.

[c] Estimated number of patients treated: through 31 July 2023.

Exposure from Early Access Programs in patients with hATTR Amyloidosis with polyneuropathy

Prior to being marketed, an open-label expanded access protocol ALN-TTR02-007 in the US and CUPs in Europe for patisiran generated preliminary safety data comparable to the information collected in the post-authorization setting. Exposure information pertaining to these programs is presented in this section.

The EAP Study ALN-TTR02-007 in patients with hATTR amyloidosis with polyneuropathy had a first patient enrolled in December 2016 in the US. Exposure data as of 28 January 2021 (ALN-TTR02-007 summary report date) were calculated based on 154 patients enrolled and dosed in the EAP. The median duration of patisiran exposure in Study ALN-TTR02-007 was 336 days (range, 21 to 777), with 41 (26.6%) patients receiving 271 to 360 days of patisiran. Cumulative study drug exposure was 159.3 patient-years.

The EAP Study ALN-TTR02-014 in patients with ATTR amyloidosis with cardiomyopathy had an additional 191 new patients that received patisiran as of the DLP of this report.

Cumulatively, as of 09 August 2023, 25,243 vials of patisiran had been distributed to 572 patients enrolled in early access programs and CUPs worldwide, corresponding to an estimated 711.44 patient-years exposure.

The cumulative exposure data from the early access programs by country are presented in Table 11.

Table 11: Cumulative Exposure Data from Early Access Programs as of 09 August 2023

Country	Total Patients Treated	Total Number of Vials Distributed	Total Patient-Years
Argentina	1	18	0.51
Australia	7	874	24.63
Belgium	9	462	13.02
Brazil	3	295	8.31
Canada	2	42	1.18
France	52	737	20.77
Germany	32	894	25.20
Ireland	5	663	18.69
Italy	46	2000	56.37
Netherlands	6	92	2.59
Malaysia	1	108	3.04
Mexico	4	228	6.43
Republic of Korea	6	361	10.17
Spain	13	1042	29.37
Sweden[a]	0	0	0.00
Taiwan	9	432	12.18
UK	29	1787	50.36
USA[b]	346	15,092	425.35
Vietnam	1	116	3.27
Total	**572**	**25,243**	**711.44**[c]

Abbreviation: ATTR=transthyretin-mediated amyloidosis; CT=clinical trial; DLP=data lock point; EAP=Expanded Access Protocol; UK=United Kingdom; USA=United States of America.

[a] A compassionate use program was approved in Sweden, but it did not enroll any patients.

[b] In the USA, the early access program conducted under the protocol of CT ALN-TTR02-007 was originally approved under the Investigational New Drug application for patisiran. As such, patient exposure (154) from CT ALN-TTR02-007 is captured. One additional patient received patisiran for the indication of wild-type ATTR amyloidosis as part of an individual patient expanded access Investigational New Drug application. An additional 191 new patients received patisiran under EAP ALN-TTR02-014 as of the DLP of this report.

[c] Total corresponds to the sum of unrounded person time and therefore may not correspond to a simple sum of individual patient-years within the table.

Part II: Module SVI Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

Patisiran is a double-stranded, liver-directed siRNA that reduces TTR. Given the size of patisiran drug substance (~14 kDa), it is unable to pass through the blood-brain barrier and is not expected to exert any direct effect on the central nervous system. As such, patisiran is unlikely to affect neurotransmitter systems associated with abuse potential. From the clinical trial data, the safety profile does not suggest any type of rewarding/stimulatory effects or other abuse-related behaviors with patisiran use.

Based on the chemical properties, mechanism of action, route of administration, and evaluations of AEs associated with the potential for drug abuse, patisiran has a low potential for abuse, and there is no potential for misuse of patisiran for illegal purposes.

Other Safety Topics

The following safety topics are also considered unlikely to pose a risk with patisiran: overdose, transmission of infectious agents, medication errors, off-label use, and pediatric issues. Patisiran is manufactured and prepared in controlled settings and administered by healthcare professionals; these measures minimize the potential for overdose, medication errors, misuse, abuse, off-label use, and transmission of infectious agents. Because hATTR amyloidosis manifests in adults, patisiran is not anticipated nor recommended to be administered to pediatric patients.

Part II: Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Potential safety areas of interest based on therapeutic class, observations from nonclinical studies, the mechanism of action of patisiran-LNP, and disease-related pathophysiology of hATTR amyloidosis were identified and evaluated in the patisiran-LNP clinical development program. Particular attention was given to the double-blind, randomized, placebo-controlled pivotal Phase 3 study ALN-TTR02-004 (Study 004), because this study afforded an opportunity to compare AEs in patients receiving patisiran-LNP with those in patients receiving placebo, thus isolating drug effects from disease- and age-related effects. Among the areas of interest listed below, only infusion-related reactions (IRRs) emerged as an important identified risk, due to an imbalance in the occurrence of IRRs between treatment groups (see Observed Adverse Drug Reactions, below). The other categories of events listed occurred in similar percentages of patients in both treatment groups and are therefore not considered safety concerns for patisiran-LNP. Hepatic disorders has been included as an important potential risk based on the nonclinical observations. Refer to 2.7.4, Section 2.1.5 Analysis of Adverse Events by Organ System or Syndrome.

- Based on nonclinical observations: hepatobiliary events and thyroid disorders
- Based on known occurrence with lipid nanoparticle drugs: IRRs
- Based on disease manifestations: cardiac events, renal events, ocular events, and metabolic bone disorders
- Considering a common comorbidity of hATTR amyloidosis: depression/suicidality
- Considering the overall age of the patient population: malignancies.

The Medical Dictionary for Regulatory Activities (MedDRA) groupings of System Organ Classes (SOCs) and Standardized MedDRA Queries (SMQs) were utilized to summarize groupings of AEs, as were individual preferred terms and, in the case of IRRs, specific instructions were given to investigators to evaluate whether an AE was considered an IRR.

Observed Adverse Drug Reactions:

In addition to the groupings above, which allow for identification of possible safety concerns by evaluating the occurrence of similar AEs, an imbalance between treatment arms of individual treatment-emergent AEs can indicate that they might be related to the treatment.

Adverse drug reactions (ADRs) identified in Study 004 are listed below. These are treatment-emergent AEs that occurred more frequently in patients in the patisiran-LNP group compared to patients in the placebo group by at least 3 percentage points, and they include IRRs, listed above.

- Infusion-related reactions (IRRs: 18.9% vs 9.1%)
- Oedema peripheral (29.7% vs 22.1%)
- Vertigo (5.4% vs 1.3%)
- Dyspnoea (6.8% vs 0)
- Muscle spasms (8.1% vs 1.3%)

- Dyspepsia (8.1% vs 3.9%)
- Arthralgia (7.4% vs 0)
- Erythema (6.8% vs 2.6%)
- Bronchitis (6.1% vs 2.6%)
- Sinusitis (4.1% vs 0)
- Rhinitis (4.1% vs 0)

In addition, extravasation can occur with any medicinal product administered by intravenous (IV) infusion. Extravasation was observed in <0.5% of infusions. Signs and symptoms included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema, or injection site redness, burning sensation, or injection site pain.

SVII.1.1 Adverse Drug Reactions Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The identified ADRs above that are not considered important for inclusion in the list of safety concerns for patisiran-LNP are outlined below.

Reason for Not Including an Identified ADR in the List of Safety Concerns in the RMP:

- ADRs with minimal clinical impact on patients (in relation to the severity of the indication treated): muscle spasms, dyspepsia, arthralgia, erythema, bronchitis, sinusitis, and rhinitis. None of these AEs caused discontinuation and with the exception of 1 case of severe dyspepsia, all events were mild or moderate in severity. Events of extravasation were mild or moderate in severity. There have been no reports of tissue injury or damage and all events resolved. Considering the severe, progressive, and ultimately fatal nature of hATTR amyloidosis, these risks are considered to have minimal clinical impact.
- Risks evaluated in further detail and also determined not to represent important identified risks:
  - Oedema peripheral: In Study 004, oedema peripheral was reported in 29.7% of patients in the patisiran-LNP group and 22.1% of patients in the placebo group. In this study, 56.0% of patients overall met predefined criteria for cardiac involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history), and in this cardiac subpopulation, oedema peripheral was reported in 32.2% of patients in patisiran-LNP group vs 25.0% in the placebo group. In the overall population, the proportion of patients who experienced oedema peripheral in the patisiran-LNP group decreased over the course of the study: during the first 9 months, the percentage of patients with oedema peripheral during each 3-month interval had a range of 7.6% to 10.8%; during the second 9 months, the percentage during each 3-month interval had a range of 2.1% to 6.5%. In contrast, in the placebo group, the proportion of patients with reports of oedema peripheral showed an increasing trend. During

the first 9 months oedema peripheral reports had a range of 4.0% to 7.5%, and during the second 9 months had a range of 5.9% to 12.5%. All the AEs of oedema peripheral were mild or moderate in severity. Oedema peripheral was considered related to study drug in only 1 patient in the patisiran-LNP group and in 5 patients in the placebo group. No patients discontinued treatment due to oedema peripheral; 1 patient in the placebo group had an infusion cycle delay. Data from the pooled analysis of the 218 patients treated with patisiran-LNP in completed Study 003, completed Study 004, and interim data (14 July 2017) from Study 006 are consistent with the placebo-controlled data with respect to reported events of oedema peripheral; there were no discontinuations due to oedema peripheral. Refer to 2.7.4, Section 2.1.1.2 Adverse Events.

- Vertigo: In Study 004, vertigo was reported for 8 patients in the patisiran-LNP group (5.4% of patients) and 1 in the placebo group (1.3% of patients). A review of individual patient profiles revealed that in the patisiran-LNP group, 7 of 8 patients who reported vertigo had symptoms in the context of orthostatic hypotension, systemic cardiovascular disorders, fatigue, and asthenia, all related to hATTR amyloidosis. These events reported as vertigo did not lead to specific investigations to validate a true vertigo diagnosis as they were mild, transient, and assessed by the investigator as not related to study drug. One patient who had an ongoing medical history of dizziness due to nervous disorders related to amyloidosis, cardiomyopathy, heart failure, heart conduction disorders, and episodes of syncope experienced 2 episodes of vertigo on study, 1 severe and 1 mild. Both events were transient, and no specific investigations were conducted to validate a diagnosis of vertigo. Both reported events for this patient were deemed not related to study drug, but rather related to orthostatic hypotension due to amyloidosis. These events did not result in any change of dose or study drug administration process. Data from the pooled analysis of 218 patients who received patisiran-LNP in completed Study 003, completed Study 004, and interim data (14 July 2017) from Study 006 are consistent with the placebo-controlled data with respect to reported events of vertigo. Vertigo did not cause discontinuation in this larger group of patients exposed to patisiran-LNP for a longer time. Overall, it is not clear that most of these events were true vertigo, but rather may have been dizziness related to underlying disease manifestations. Refer to 2.7.4, Section 2.1.1.2 Adverse Events.
- Dyspnoea: In Study 004, 10 patients (6.8%, 14 events) in the patisiran-LNP group reported dyspnoea, compared with no patients in the placebo group. All of the events were considered by the investigators to be not related or unlikely related to study drug. The majority of the patients had a medical history of cardiac disorders, with dyspnoea reported by 6 patients (6.7%, 8 events) in the patisiran-LNP group in the predefined cardiac subpopulation. When dyspnoea was analyzed over time, the proportion of patients and number of events decreased over time (first 9 months: 2.0-2.1%, 10 events; second 9 months: 0.7-1.4%, 4 events). Most of the events were mild or moderate in severity, none caused discontinuation, and none were deemed related to study treatment. Two patients in the patisiran-LNP group had single events of dyspnoea that were

considered severe. Neither of the events was considered an IRR, and no action was taken with the study drug (ie, dose not changed). One patient who had been having worsening dyspnoea due to congestive heart failure and associated chest discomfort was admitted to the hospital (thus meeting a criterion for a serious adverse event [SAE]) for evaluation and treatment of worsening orthostatic hypotension. The patient's medications were adjusted, and the event resolved. The event was considered not related to study drug. These data suggest that during patisiran-LNP study treatment, dyspnoea was often indicative of underlying cardiac disease. Refer to 2.7.4, Section 2.1.1.2 Adverse Events.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following important identified risks, important potential risks, and missing information have been determined after a detailed analysis of the double-blind, randomized, placebo-controlled pivotal Phase 3 study (Study 004), the pooled safety data across the patisiran-LNP studies in patients with hATTR amyloidosis (218 patients from completed Studies 003 and 004 and from an interim data cut [14 July 2017] of ongoing open-label extension Study 006 who received patisiran-LNP), and findings from the nonclinical studies.

Important Identified Risks

Infusion-related Reactions

Infusion-related reactions (IRRs) have been observed in a higher proportion of patisiran-LNP-treated patients compared with placebo-treated patients. IRRs have been reported during IV administration of lipid-containing products,[Doessegger 2015; Salvador-Morales 2009] suggesting that one or more of the lipid excipients of patisiran-LNP could be responsible for these reactions.

Risk-benefit impact:

IRRs can be mitigated by treating patients with premedication (corticosteroid, antihistamines, and paracetamol) on the day of infusion; other suggested management practices include adjusting the rate of infusion.[Doessegger 2015; Szebeni 2014] All patients receiving patisiran-LNP (as well as patients receiving placebo) received premedication regimens. In the pooled dataset of 218 patients treated with patisiran-LNP, IRRs were mild or moderate in severity and resolved. There were no severe IRRs or serious adverse events (SAEs). The proportions of patients reporting IRRs and number of symptoms associated with IRRs decreased over time. Among a total of 6954 doses given to the 218 patients; 25 doses were interrupted for 13 patients, with most interruptions coming early in treatment, and with only 2 incomplete doses given. One patient discontinued treatment due to an IRR. Given the significance of the disease and the benefit of patisiran-LNP treatment, the benefit of treatment outweighs the risk posed by IRRs that can be managed in clinical practice.

IRRs observed in the patisiran-LNP clinical program are further characterized in Table 12.

Important Potential Risks

Consequences of Vitamin A Deficiency

Because of the mechanism of action of patisiran-LNP, there is a theoretical risk of vitamin A deficiency. Given the role of TTR as a carrier of RBP and thus vitamin A,[van Bennekum 2001] studies in monkeys with patisiran-LNP confirmed the secondary pharmacological effects associated with reductions in TTR, namely reductions, relative to baseline, in circulating RBP and vitamin A. There were no sequelae due to the reductions of vitamin A in monkeys after chronic administration of patisiran-LNP. In the clinical studies, reductions in circulating vitamin A have also been observed but without any manifestations of vitamin A deficiency. Vitamin A transport and tissue uptake can occur in the absence of RBP.[Biesalski 1999; van Bennekum 2001] As a precaution, vitamin A supplementation at the usual daily recommended amount was advised in the clinical studies and will continue to be recommended to patients undergoing treatment with patisiran-LNP.

Risk-benefit impact:

The impact of this important potential risk on the risk-benefit balance of patisiran-LNP is expected to be negligible. There is no safety concern relative to vitamin A deficiency in the clinical study data. As a precaution, patients will be advised to take vitamin A supplementation of approximately 2500 IU per day.

If a patient develops ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness), referral to an ophthalmologist is recommended.

Vitamin A levels that are too high or too low may be associated with an increased risk of foetal malformation. Information regarding recommended action for vitamin A supplementation and monitoring of vitamin A levels in the event of pregnancy, both planned and unplanned, are provided in the Product Information.

Observations regarding vitamin A deficiency are described in Table 13.

Severe Hypersensitivity

Severe hypersensitivity reactions can occur due to a variety of immune mediated (eg, antibody mediated or T cell) and non-immune mediated (eg, pseudoallergy) responses that are often drug specific.[Dezsi 2014; Pichler 2007; Szebeni 2014]

Risk-benefit impact:

In the patisiran-LNP clinical studies, an increased risk of serious or severe hypersensitivity reactions has not been observed, and no specific risk factors have been identified. However, as with all drugs, severe hypersensitivity reactions are possible. Therefore, patisiran-LNP is contraindicated in patients with severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients. Given a lack of observed serious and severe hypersensitivity in the patisiran-LNP clinical development program and the contraindication for patients with severe hypersensitivity to the active substance or any of the excipients, the impact of this important potential risk on the risk-benefit balance of patisiran-LNP is expected to be negligible.

Observations related to severe hypersensitivity are described in Table 14.

Hepatic Disorders

In the nonclinical studies in rodents and monkey, patisiran-LNP revealed changes in serum liver markers and liver histopathology. In the patisiran-LNP clinical studies, an increased risk of hepatic adverse events (AEs) has not been observed; the frequency of hepatic AEs has been low with no imbalances noted between the treatment groups in the placebo-controlled Study 004 and across the overall pooled experience. In Study 004, a small increase (≤4.1 U/L) from baseline in mean absolute values of alanine transaminase (ALT) and aspartate aminotransferase (AST) was observed in the patisiran-LNP group compared with placebo that remained stable over the 18-month treatment period. The mean change from baseline in ALT and AST was not associated with mean changes from baseline in alkaline phosphatase (ALP) or total bilirubin. Similar results were observed in Studies 003 and 006. Across the 3 studies, ALT and AST have continued to remain stable over time for periods up to 49.5 months. Given the significance of the disease and the benefit of patisiran-LNP treatment, the impact of this important potential risk on the benefit-risk balance of patisiran-LNP is expected to be negligible.

Observations related to hepatic disorders are described in Table 15.

Missing Information

All missing information is summarized in Table 16.

Longer-term Safety (>3 years)

In clinical studies, patisiran-LNP has been administered to 218 patients with hATTR amyloidosis for periods up to 3.74 years. There is limited information regarding the safety of patisiran-LNP for periods longer than 3 years. Patisiran is indicated for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis), a chronic disease with high morbidity and mortality. As such, it is expected that patients would require long-term or perhaps life-long treatment for their disease.

Risk-benefit impact: Although the side effects following chronic treatment with patisiran-LNP are unknown, based on the current clinical experience, additional safety concerns with long term treatment are not anticipated. Patisiran-LNP is indicated to treat hATTR amyloidosis, a progressive and ultimately fatal disease. Therefore, the impact of a lack of longer-term safety data on the risk-benefit balance, while unknown, is not expected to significantly affect the known safety profile of patisiran-LNP.

Use in Patients with Moderate or Severe Hepatic Impairment

Patients were excluded from patisiran-LNP studies if they had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >2.5 × upper limit of normal (ULN), total bilirubin (TBILI) >ULN (with a higher level allowed for Gilbert's syndrome), and international normalized ratio ≤2.0 (≤3.5 allowed if on anticoagulant therapy). In the pooled population (N=218), 13 patients (6.0%) had mild (TBILI=ULN and AST/ALT >ULN **or** TBILI >1.0×ULN to ≤1.5×ULN and any AST/ALT) and 2 patients (0.9%) had moderate (TBILI >1.5×ULN to ≤3.0×ULN and any AST/ALT) hepatic impairment at baseline. Therefore, data on patisiran-LNP in patients with moderate hepatic impairment are limited, and patisiran-LNP has not been studied in patients with severe hepatic impairment.

Risk-benefit impact: There have been no reports of Hy's law cases (ALT or AST >3×ULN concurrent with TBILI >×2ULN). The frequency of hepatic AEs was low and balanced between treatment groups, and no significant changes in liver function tests were reported in patients treated for up to 3.74 years. Based on these results, there were no hepatic safety concerns in the population studied, and no specific monitoring of liver function tests beyond routine standard of care have been proposed. Patisiran-LNP has not been studied in patients with severe hepatic impairment, and in very few patients with moderate hepatic impairment. The effect of this missing information on the risk-benefit balance for patients with moderate or severe hepatic impairment is unknown but is not expected to significantly affect the known safety profile of patisiran-LNP.

Use in Patients with Severe Renal Impairment or End-stage Renal Disease

In the pooled patient population (N=218), 68 patients (31.2%) had mild (estimated glomerular filtration rate [eGFR] ≥60 to <90 mL/min/1.73 m^2) to moderate (eGFR ≥30 to <60 mL/min/1.73 m^2) renal impairment, and only 1 patient had severe renal impairment. Therefore, the effect of patisiran-LNP on patients with severe renal impairment or end-stage renal disease (ESRD) has not been studied.

Risk-benefit impact: Patients with hATTR amyloidosis may have amyloid deposition in the kidney, and severe renal impairment that can progress to ESRD has been reported.[Lobato 2012] Clinical pharmacology data have shown that urinary excretion is a minor clearance pathway for patisiran and its components. Therefore, exposure to patisiran-LNP is not expected to be greatly affected by reduced renal function. Patients with mild or moderate renal impairment did not require dose adjustments. The effect of this missing information on the risk-benefit balance for patients with severe renal impairment or ESRD, while unknown, is not expected to be significantly different from that for the overall population.

Use in Patients with Prior Liver Transplant

Patients who had undergone a liver transplant or who were planning to undergo this procedure were excluded from participation in patisiran-LNP clinical studies to avoid confounding the assessment of efficacy and safety.

Risk-benefit impact: Patisiran-LNP targets the liver and has not been studied in patients after liver transplantation. The effect of this missing information on the risk-benefit balance for patients with prior liver transplant is unknown, but is not expected to significantly affect the overall known safety profile of patisiran-LNP.

Use in Pregnancy and Lactation

In the clinical studies with patisiran-LNP, women of child-bearing potential were required to use contraception, and women who were pregnant or lactating were excluded from participation. Thus, there are no data on the safety of patisiran-LNP in this population.

Risk-benefit impact: While patisiran-LNP is expected to have low risk for reproductive and developmental toxicity based on available data from nonclinical studies, the effects of maternal serum TTR reduction or serum vitamin A reduction on a fetus are unknown. Vitamin A levels that are too high or too low may be associated with foetal malformations. The effect of possible risks of patisiran-LNP on the risk-benefit balance during pregnancy is unknown, and contraception is recommended for women of child-bearing potential.

In lactating rats, while patisiran itself was not present in milk, small amounts of the lipid components were present. Negligible transfer of patisiran-LNP to human milk is expected, and it would be digested upon consumption. Therefore, the risk of systemic exposure in a breastfeeding child is likely to be low. The impact of this missing information on the risk-benefit balance of patisiran-LNP is unknown; however, consideration of the development and health benefits of breast-feeding should be considered along with the mother's clinical need of patisiran-LNP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

None

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Clinical safety data are summarized from the completed double-blind, randomized, placebo-controlled pivotal Phase 3 study ALN-TTR02-004 (referred to as Study 004) and a pooled dataset (referred to as the pooled population) from Studies 003, 004, 006, 008, 011, and the patisiran arm of the vutrisiran study, ALN-TTRSC02-002. The pooled population includes data from 636 patients who have received patisiran for up to 88.6 months (as of the final database lock for Study 006 of 07 December 2022 and the interim data cut for Study 011 of 09 August 2023).

SVII.3.1 Presentation of Important Identified Risk and Important Potential Risks

Details of the important identified risk are provided in Table 12.

Details of the important potential risks are provided in Table 13 and Table 14.

Table 12: Important Identified Risk: Infusion-related Reactions (IRRs)

Potential mechanisms	Infusion-related reactions (IRRs) can occur during IV administration of lipid-containing products,[Doessegger 2015; Salvador-Morales 2009] suggesting that 1 or more of the lipid excipients of patisiran could be responsible for these reactions.
Evidence source(s) and strength of evidence	Infusion-related reactions (IRRs) were reported in clinical studies of patisiran and included such signs and symptoms as back pain, flushing, nausea, and headache. This group of symptoms was reported more frequently in patients receiving patisiran than in patients receiving placebo in a double-blind, randomized, placebo-controlled pivotal Phase 3 clinical study. IRRs were noted in other clinical studies of patisiran. Patients received premedications (corticosteroid, antihistamines, and paracetamol) to reduce the risk of IRRs. IRRs were mostly mild in severity and decreased in frequency over time. Few infusions had to be interrupted, and among those that were, most were resumed, and the full dose was administered.

Characterization of the risk	**Study 004:** In the double-blind, randomized, placebo-controlled pivotal Phase 3 study (N=225; 148 patisiran and 77 placebo), 18.9% of patients in the patisiran group and 9.1% of patients in the placebo group reported at least 1 IRR. In the patisiran group, signs and symptoms of IRRs reported in ≥2% of patients were back pain (6.1%), flushing (4.1%), nausea (3.4%), headache (2.7%), arthralgia and dyspnoea (2.0% each). Flushing was reported in 7.8% of patients in the placebo group as well, indicating that this AE is most likely due to the premedication regimen or causes other than patisiran. None of the IRRs in the patisiran group were severe; all IRRs were mild or moderate in severity. None were reported as SAEs. One patient reported an IRR that led to discontinuation of study treatment. All reported IRRs in the patisiran treatment group resolved without sequelae. Among patients in the patisiran treatment group who experienced IRRs, 78.6% of patients had their first IRR within the first 2 doses. There was little evidence that symptoms increased in frequency with repeated doses. The overall proportion of patients reporting IRRs and number of symptoms associated with IRRs decreased over time. The number of infusion interruptions due to IRRs was low (17 infusions in 8 patients in the patisiran group out of a total of 3740 infusion interruptions in 148 patients). Most patients with an interruption were able to receive a complete dose, with only 2 incomplete doses due to IRRs. **Pooled population:** The pattern of IRRs in the pooled patisiran population (N=636) is consistent with that seen in the placebo-controlled studies. IRRs were reported in 20.4% of patients and were mostly (14.0%) mild in severity, with 39 patients (6.1%) reporting moderate IRRs, and 2 patients (0.3%) reporting a severe IRR. Among a total of 32,009 doses given to the 636 patients, 94 infusions were interrupted due to IRRs for 35 patients. Most infusions (92.6%) that were interrupted were completed and the full dose was administered. A total of 4 (0.6%) patients in the Pooled Population discontinued treatment due to an IRR that was either mild or moderate in severity. As with the placebo-controlled study, the number of patients experiencing IRRs and the number of IRRs decreased over time. Refer to 2.7.4, Section 2.7.1 Infusion-Related Reactions and 2.5, Section 5.7.1 Infusion-Related Reactions.
Risk factors and risk groups	In general, it is difficult to predict which patients in a population may be more susceptible to IRRs. However, it is known that the IRRs may be prevented or the symptoms made less severe by the administration of premedication.[Doessegger 2015; Szebeni 2014] Controlling how fast the drug is infused is also important to help decrease the number and severity of IRRs.

Preventability	Premedicating patients with a corticosteroid and/or antihistamines, or slowing of the infusion rate, are approaches that have been taken to reduce the incidence and/or severity of IRRs of lipid-containing drugs.[Doessegger 2015; Szebeni 2014] The incidence and severity of patisiran can be prospectively mitigated via administration of premedications and also by adjusting the rate of infusion. Therefore, all patients should receive premedication prior to patisiran administration to reduce the risk of IRRs. Premedications (corticosteroid, paracetamol, H1/H2 blockers) should be given on the day of patisiran infusion at least 60 minutes prior to the start of infusion. Patisiran should be infused intravenously over approximately 80 minutes at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, then increasing to approximately 3 mL/min for the remainder of infusion. If an IRR occurs, slowing or temporarily stopping the infusion should be considered. Additional medical management (eg, corticosteroids or other symptomatic treatment) should be provided as medically indicated by the patient's symptoms and status. Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of 1 or more of the premedications with subsequent infusions to reduce the risk of IRRs.
Impact on the risk-benefit balance of the product	The IRRs observed with patisiran were manageable with premedications and infusion-rate adjustments. There has been no evidence that IRRs worsen over time or with subsequent infusions. Given the significance of the disease and the benefit of patisiran treatment, the benefit of treatment outweighs the risk posed by IRRs.
Public health impact	The public health impact of IRRs due to patisiran is considered negligible.

Table 13: Important Potential Risk: Consequences of Vitamin A Deficiency

Potential mechanisms	Because of the mechanism of action of patisiran, there is a theoretical risk of vitamin A deficiency. Given the role of TTR as a carrier of RBP and thus vitamin A,[van Bennekum 2001] studies in monkeys with patisiran confirmed the secondary pharmacological effects associated with reductions in TTR, namely reductions, relative to baseline, in circulating RBP and vitamin A. There were no sequelae due to the reductions of vitamin A in monkeys after chronic administration of patisiran. In the clinical studies, reductions in circulating vitamin A have also been observed but without any manifestations of vitamin A deficiency. Vitamin A transport and tissue uptake can occur in the absence of RBP.[Biesalski 1999; van Bennekum 2001]

Evidence source(s) and strength of evidence	The primary mechanism of action of patisiran is to reduce the level of TTR in the serum and reduction of amyloid deposits in the tissues. One function of TTR is to carry retinol binding protein (RBP), which distributes vitamin A in serum. There is, therefore, a theoretical risk of vitamin A deficiency. However, vitamin A can be distributed into tissues without RBP.[Biesalski 1999; van Bennekum 2001] RBP and serum vitamin A were reduced in studies of patisiran in monkeys; however, no evidence of vitamin A deficiency was observed. Patients in the clinical studies were advised to take vitamin A supplementation at the usual recommended daily amount. No symptoms of vitamin A deficiency such as night blindness or other eye conditions were seen in patients receiving patisiran.
Characterization of the risk	In the placebo-controlled study (Study 004) at 18 months, a mean percent reduction from baseline of serum RBP of 45.3±22.4% (range 7.3 to 78.6%) was observed in the patisiran group, compared with a mean reduction of 0.5±14.3% (range: 36.8 to 30.5%) in the placebo group. The mean percent reductions of serum vitamin A at 18 months were 62.4±14.4% (range: 9 to 84%) in the patisiran group and 0.1±15.7% (range: 53 to 29%) in the placebo group. Refer to CSR Study 004 Table 14.2.3.6, Table 14.2.3.7. <u>Patients experiencing selected ocular AEs:</u> Because ocular abnormalities are commonly observed in patients with vitamin A deficiency, particular attention was paid to the AEs in the Eye Disorders SOC. Patients with hATTR amyloidosis also report eye disorders due to their underlying disease or consistent with their advanced age.[Conceicao 2016; Martins 2015] In Study 004, treatment-emergent AEs in this SOC occurred in similar proportions of both treatment groups (27.7% in the patisiran group and 26.0% in the placebo group), with night blindness experienced by 1 (1.3%) patient in the placebo group. In the pooled population of patients treated with patisiran (N=636), 199 (31.3%) patients experienced treatment-emergent eye disorders, with night blindness reported in 3 (0.5%) patients. None of the cases of reported night blindness were confirmed by the ophthalmological evaluation. All cases reporting the preferred term of night blindness were nonserious, mild, reported limited information regarding the event and did not lead to change in dosing. Therefore, an analysis of AEs in the Eye Disorders SOC did not suggest an effect from vitamin A deficiency. Serial ophthalmology examinations performed in Study 004, including electroretinography, did not suggest changes related to vitamin A deficiency. Overall, the examination findings remained stable throughout treatment. Refer to 2.7.4, Section 2.7.8 Ocular Events.
Risk factors and risk groups	Prolonged dietary deficiency and other conditions such as gastrointestinal malabsorption due to a variety of causes can lead to vitamin A deficiency in the hATTR amyloidosis population.

Preventability	As transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of RBP,[Biesalski 1999; Episkopou 1993; van Bennekum 2001] and because some patients may not get adequate vitamin A from their diet due to hATTR amyloidosis-related gastrointestinal symptoms, supplementation at the recommended daily amount of vitamin A is recommended. Laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body during treatment with patisiran and should not be used to guide vitamin A supplementation.
Impact on the risk-benefit balance of the product	The impact of this important potential risk on the risk-benefit balance of patisiran is expected to be negligible. There is no safety concern relative to vitamin A deficiency in the clinical study data. As a precaution, patients are advised to take vitamin A supplementation at the usual recommended daily amount. If a patient develops ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness), referral to an ophthalmologist is recommended.
Public health impact	The public health impact of vitamin A deficiency due to patisiran is considered negligible.

Table 14: Important Potential Risk: Severe Hypersensitivity

Potential mechanisms	Severe hypersensitivity reactions can occur due to a variety of immune mediated (eg, antibody mediated) and non-immune mediated (eg, pseudoallergy) responses that are often drug specific.[Dezsi 2014; Pichler 2007; Szebeni 2014]
Evidence source(s) and strength of evidence	Severe hypersensitivity is a theoretical risk for any drug but has not been observed in patients taking patisiran.
Characterization of the risk	There were 10 (1.6%) patients with 12 severe events mapped to the Hypersensitivity SMQ (scope: narrow and broad) among patients in the pooled population (N=636). Hypersensitivity AEs categorized as severe were acute respiratory failure (2 [0.3%] patients with 3 events), IRR (2 [0.3%] patients with 2 events), shock, respiratory arrest, generalised oedema, skin necrosis, dermatitis, respiratory failure, and circulatory collapse (1 [0.2%] patient each). All were considered not related to patisiran, with the exception of the 2 IRRs.
Risk factors and risk groups	Patients with severe hypersensitivity to the active substance or any of the excipients are clearly at higher risk. Patients with a personal history of atopy may be at higher risk in general; however, there are no specific data to suggest that these patients would be at higher risk of a reaction to patisiran.
Preventability	As with all drugs, severe hypersensitivity reactions are possible. Therefore, patisiran is contraindicated in patients with severe hypersensitivity (e.g., anaphylaxis) to the active substance or any of the excipients, as described in the SmPC (*Section 4.3*).

Impact on the risk-benefit balance of the product	In the patisiran clinical development program, no reports of severe hypersensitivity to patisiran have been observed. Patisiran is administered by healthcare professionals, allowing for intervention if an immediate hypersensitivity reaction should occur. Given a lack of observed hypersensitivity in the patisiran clinical development program and the contraindication for patients with severe hypersensitivity, the impact of this important potential risk on the risk-benefit balance of patisiran is expected to be negligible.
Public health impact	Severe hypersensitivity reactions to patisiran have not been observed. Therefore, the public health impact is expected to be low.

Table 15: Important Potential Risk: Hepatic Disorders

Potential mechanisms	Patisiran is an siRNA that uses RNAi to inhibit the synthesis of wt and variant TTR protein in hepatocytes. Patisiran is formulated as lipid nanoparticles for delivery to the liver.
Evidence sources and strength of evidence	Hepatoxicity was observed in the nonclinical studies in rat and monkey (see Table 3 for details). In Study 004, a small increase (≤4.1 U/L) from baseline in mean absolute values of ALT and AST was observed in the patisiran group compared to the placebo group that remained stable over the 18-month treatment period. The mean change from baseline in ALT and AST was not associated with mean changes from baseline in ALP or TBILI. Similar results were observed in Studies 003 and 006. Across the 3 studies, ALT and AST levels remained stable over time for periods up to 84.9 months.
Characterization of the risk	**Study 004:** In Study 004. the mean change from baseline in absolute values of ALT in the patisiran group ranged from 1.8 to 3.8 U/L and for AST ranged from 2.3 to 4.1 U/L across the visits over the 18-month duration of the study. The majority of patients had ALT and AST values <ULN in Study 004. Overall, 12 (15.6%) patients in the placebo group and 47 (31.8%) patients in the patisiran group had at least 1 ALT or AST value >ULN. All of the elevations were ≤3×ULN, except for 1 (0.7%) patient in the patisiran group who had a transient elevation of ALT of 4.2×ULN on Day 84 without changes in AST, ALP, and TBILI. There have been no patients with ALT or AST values >3×ULN with concurrent elevation of TBILI >2×ULN at any time in any of the studies. The proportion of patients with hepatic events mapping to the Drug related hepatic disorders - comprehensive search SMQ was 5.4% in the patisiran group and 9.1% in the placebo group. Within the SMQ, the frequency of AEs in the Hepatobiliary disorders SOC (1.4% patisiran, 1.3% placebo) and Investigations SOC (3.4% patisiran, 3.9% placebo) were similar across the 2 treatment groups. Most of the hepatic AEs were mild or moderate in severity, and considered not related or unlikely related to study drug. Hepatic AEs considered possibly related to study drug were hepatic enzyme increased and blood ALP increased in the patisiran group (1 patient [0.7%] each) and hypoalbuminemia in the placebo group (1 patient [1.3%]), all of which

	were mild in severity. Hepatic SAEs were reported in 3 patients in the placebo group (LFTs abnormal, hypoalbuminemia, and liver transplant; 1 patient each) and in 1 patient in the patisiran group (ascites). All hepatic SAEs were considered unlikely or not related to study drug. **Pooled population:** There were 66 (10.4%) patients with hepatic events mapped to the Drug related hepatic disorders - comprehensive search SMQ among patients in the pooled population (N=636). Most hepatic events reported were laboratory elevations within the investigations SOC, which occurred in 6.1% of subjects. A total of 7 patients in the Pooled Population had hepatic events that were serious. One patient in Study 011 had a severe SAE of hepatic enzyme increased that was considered related to study drug. Another patient in Study 011 had an AE of hepatic enzyme increased that led to discontinuation of study drug. Hepatic events reported in ≥1% of patients were transaminases increased (1.7%), blood ALP increased (1.4%), ALT increased (1.3%), hepatic enzyme increased (1.3%), ascites (1.3%), and blood AST increased (1.1%); most AEs were mild or moderate in severity and not considered related to study treatment.
Risk factors and risk groups	In general, people with alcoholism, autoimmune diseases, bile duct disorders, exposure to hepatotoxins or hepatotoxic materials, hepatitis viruses, hereditary traits, obesity are considered to be risk factors for developing hepatic disorders. No risk factors have been identified in the clinical trials.
Preventability	Clinically significant changes in liver function tests or hepatic disorders attributable to patisiran have not been observed in clinical studies to date.
Impact on the risk-benefit balance of the product	Given the significance of the disease and the benefit of patisiran treatment, the benefit of treatment outweighs the risk posed by hepatic AEs; the impact of this important potential risk on the benefit-risk balance of patisiran is expected to be negligible.
Public health impact	The public health impact is expected to be low.

SVII.3.2 Presentation of Missing Information

The areas of missing information selected to be part of the list of safety concerns are presented in Table 16 .

Table 16: Missing Information

Missing Information	Details
Longer-term safety (>3 years)	**Evidence Source:** In the pooled patient population, 580 patients have been exposed to patisiran for ≥12 months, 366 patients for ≥24 months, 195 patients for ≥36 months, 167 patients for ≥48 months, 144 patients for ≥60 months, 125 patients for ≥72 months, and 24 patients for ≥84 months (Table 5). Based on the available data, there are no known patisiran adverse drug reactions that have a long latency, are due to prolonged exposure, or are due to cumulative effects.
	Population in Need of Further Characterization: The recently completed open-label extension study (Study 006) gathered safety data in patients exposed up to 5 years to characterize the longer-term safety profile of patisiran.
Use in patients with moderate or severe hepatic impairment	**Evidence Source:** Among the 636 patients who received patisiran in the pooled population, 71 (11.2%) had mild, 14 (2.2%) had moderate, and 1 (0.2%) had severe hepatic impairment at baseline. Therefore, data on patisiran in patients with moderate or severe hepatic impairment are limited. There have been no Hy's law cases (ALT or AST >3×ULN concurrent with TBILI >2×ULN) in clinical studies of patisiran. The frequency of hepatic AEs was low and balanced between treatment groups, and no clinically significant changes in liver function tests were reported in patients. Refer to 2.5, Section 5.7.4 Hepatic Events and to Table 15.
	Anticipated risk/consequence of the missing information: There have been no hepatic safety concerns in the population studied, and no specific monitoring of liver function tests beyond routine standard of care have been proposed. Patisiran has been studied in very few patients with moderate or severe hepatic impairment; the risk of its use in these patients is unknown.
Use in patients with severe renal impairment or end-stage renal disease	**Evidence Source:** Clinical pharmacology data have shown that urinary excretion is a minor clearance pathway for the siRNA (ALN-18328) and the lipid DLin-MC3-DMA components of patisiran. In the pooled population of patients treated with patisiran (N=636), 219 (34.4%) patients had mild renal impairment, 171 (26.9%) patients had moderate renal impairment, and 8 (1.3%) patients had severe renal impairment at baseline. No increased risk was associated with administration of patisiran to patients with renal impairment, and no dose adjustments were necessary.
	Anticipated risk/consequence of the missing information: There have been no renal safety concerns in the patisiran clinical studies. Patisiran has been studied in very few patients with severe renal impairment or end-stage renal disease; therefore, the risk of its use in these patients is unknown.

Missing Information	Details
Use in patients with prior liver transplantation	**Evidence Source:** Patients who had previously undergone a liver transplant for treatment of hATTR amyloidosis or who were planning to undergo this procedure were excluded from participation in the patisiran clinical studies, with the exception of the completed Study ALN-TTR02-008, which was a Phase 3b, open-label study to evaluate the safety, efficacy, and pharmacokinetics of patisiran in patients with hATTR amyloidosis with disease progression post-OLT. In Study 008, a total of 23 patients received at least 1 dose of patisiran, 22 of whom completed the study, with 1 patient having discontinued the study after receiving 1 dose of patisiran, due to patient decision.
	Population in Need of Further Characterization: The final data from Study 008 indicate that patisiran has an acceptable safety profile in the treatment of hATTR amyloidosis with disease progression post-OLT, and results were consistent with the established safety profile of patisiran in patients with hATTR amyloidosis and polyneuropathy without a history of OLT. However, the data on the use of patisiran in this patient population are limited and therefore the risk of the use of patisiran in this patient population requires further characterization.
Use in pregnancy and lactation	**Evidence Source:** In the clinical studies with patisiran, women of child-bearing potential were required to use contraception, and women who were pregnant or lactating were excluded from participation. Thus, there are no data on the safety of patisiran in this population. In nonclinical studies, patisiran had no adverse effects on male or female fertility, pregnancy, or embryo-fetal development at doses that did not result in maternal toxicity. While patisiran is expected to have low risk for reproductive and developmental toxicity based on available data from nonclinical studies, the effects of maternal serum TTR reduction or serum vitamin A reduction on a fetus are unknown. Vitamin A levels that are too high or too low may be associated with an increased risk of fetal malformation. In lactating rats, while patisiran itself was not present in milk, small amounts of the lipid components were present.
	Anticipated risk/consequence of the missing information: The risk to pregnancy outcomes and to the fetus and infant are unknown. Patisiran is not recommended for use in pregnancy and contraception is recommended for women of child-bearing potential. It is unknown whether patisiran is excreted in human milk.

Part II: Module SVIII Summary of the Safety Concerns

A summary of the safety concerns is provided in Table 17.

Table 17: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risk	• Infusion-related reactions (IRRs)
Important potential risks	• Consequences of vitamin A deficiency • Severe hypersensitivity • Hepatic disorders
Missing information	• Longer-term safety (>3 years) • Use in patients with moderate or severe hepatic impairment • Use in patients with severe renal impairment or end-stage renal disease • Use in patients with prior liver transplantation • Use in pregnancy and lactation

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance, including AE collection and reporting, signal detection, and signal evaluation will be conducted as described in the Pharmacovigilance System Master File. Specific targeted follow-up of questionnaires for IRRs and severe hypersensitivity will be analyzed and presented in the periodic safety update reports (PSURs) to inform further risk management (see Annex 4). Reports of exposure during pregnancy will be routinely collected, reported, and followed up for pregnancy and infant outcomes.

III.2 Additional Pharmacovigilance Activities

Additional Pharmacovigilance activities include an ongoing global pregnancy surveillance program Study 010, and a planned prospective observational cohort Study 009:

- ALN-TTR02-010 (Study 010) is a global pregnancy surveillance program being conducted as part of an FDA postmarketing requirement to collect and evaluate information on exposure during pregnancy and infant outcomes in hATTR amyloidosis patients exposed to patisiran. As of the data lock point of this risk management plan (RMP), no patients have enrolled in Study ALN-TTR02-010 (see Table 19).
- Study ALN-TTR02-009 (Study 009) is a non-interventional observational cohort study that is being conducted over a period of 10 years and will provide real-world safety experience from patisiran use, as well as provide comparative safety data from other treatments, or no treatment, that can be used to further assess the findings and any association with patisiran. The study cohort will include all patients with hATTR amyloidosis under care at the participating clinics, as no exclusion criteria are intended with this observational cohort. Patients treated at home, as well as patients with hepatic or renal impairment, and patients with prior liver transplantation will be observed as part of the cohort. The planned size of the total hATTR amyloidosis study cohort is 300 patients and will include 150 patients exposed to patisiran over a period of up to 10 years from the time the first patient is treated with patisiran post-authorization. The study is targeting to evaluate at least 900 patient-years of patient experience on patisiran.

Studies 010, and 009 are described in Table 18. Annex 2 provides additional details for the completed Study 006, and Ongoing Studies 010, and 009, and Annex 3 provides a copy of the Study 010, and Study 009 protocols.

Table 18: Ongoing and Planned Studies in the Post-authorization Pharmacovigilance Development Plan

Study Number and Title	Rationale and Objectives	Study Design	Study population	Study Status	Milestones
Ongoing Prospective Observational Cohort Study					
Study Number: ALN-TTR02-009 (Study 009) Title: Prospective Observational Study to Monitor and Assess the Safety of Patisiran-LNP in a Real-world Cohort of hATTR Amyloidosis Patients	The primary objective of this study is to characterize the safety of patisiran under real-world conditions, including determining and comparing the incidence of selected AEs (eg, cardiovascular, hepatic) in hATTR amyloidosis patients exposed to patisiran. An appropriate control group within the study cohort will be created to serve for comparative risk analyses.	Non-interventional, observational, using epidemiological cohort design techniques. Patient data will be derived from medical charts obtained during routine clinical care.	The study is planned to prospectively follow a cohort of hATTR amyloidosis patients, including both prevalent and newly diagnosed patients.	Ongoing	Start of data collection: 25 March 2021 Basic interim report 1: 18 October 2022 Basic interim report 2: 18 October 2023 Full interim analysis report 1 (Year 3): 18 October 2024 Basic interim report 3: 18 October 2025 Basic interim report 4: 18 October 2026 Full interim analysis report 2 (Year 6): 18 October 2027 Basic interim report 5: 18 October 2028 Basic interim report 6: 18 October 2029 Basic interim report 7: 18 October 2030 Final report of study results: 25 March 2032

Study Number and Title	Rationale and Objectives	Study Design	Study population	Study Status	Milestones
Ongoing Global Pregnancy Surveillance Program					
Study Number: ALN-TTR02-010 (Study 010) Title: Patisiran-LNP Pregnancy Surveillance Program	The primary objective of this program is to collect and evaluate data on exposure during pregnancy and infant outcomes in hATTR amyloidosis patients exposed to patisiran.	A pregnancy surveillance program that will collect primary data from patisiran-exposed pregnant women and their healthcare providers, as well as their infant's healthcare providers.	Women who have been exposed to patisiran during at any point starting from 12 weeks before last menstrual period or at any point during pregnancy	Ongoing	Study start: 30 July 2020 (first site activated) Annual interim reports: Submitted by 31 October each year Estimated completion: 31 December 2030 Final program report planned: 31 December 2031

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 19: Ongoing and Planned Additional Pharmacovigilance Activities

Study Number Short Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
• Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
• Not applicable				
Category 3 - Required additional pharmacovigilance activities				
ALN-TTR02-009 (Study 009) Non-interventional Observational Cohort Study Ongoing	The primary objective of this study is to characterize the safety of patisiran in real-world conditions, including determining and comparing the incidence of selected AEs (eg, cardiac hepatic) in hATTR amyloidosis patients exposed to patisiran. An appropriate control group within the study cohort will be created to serve for comparative risk analyses.	Hepatic disorders Longer-term safety (>3 years) Use in patients with moderate or severe hepatic impairment Use in patients with severe renal impairment or end-stage renal disease Use in patients with prior liver transplantation	Start of data collection: Basic interim report 1: Basic interim report 2: Full interim analysis report 1 (Year 3): Basic interim report 3: Basic interim report 4: Full interim analysis report 2 (Year 6): Basic interim report 5: Basic interim report 6: Basic interim report 7: Final report of study results:	25 March 2021 18 October 2022 18 October 2023 18 October 2024 18 October 2025 18 October 2026 18 October 2027 18 October 2028 18 October 2029 18 October 2030 25 March 2032

Study Number **Short Name** **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
ALN-TTR02-010 (Study 010) Global Pregnancy Surveillance Program Ongoing	The primary objective of this program is to collect and evaluate data on exposure during pregnancy and infant outcomes in hATTR amyloidosis patients exposed to patisiran	Use in pregnancy and lactation	Study start:	30 July 2020 (first site activated)
			Annual interim reports:	submitted by 31 October each year
			Estimated completion:	31 December 2030
			Final program report planned:	31 December 2031

PART IV. PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No post-authorization efficacy studies have been imposed for patisiran that are conditions of the marketing authorization or that are specific obligations.

PART V. RISK MINIMIZATION MEASURES

V.1 Routine Risk Minimization Measures

Careful consideration of the benefit-risk balance for patisiran leads to the conclusion that routine risk minimization activities are sufficient to manage the majority of the safety concerns associated with patisiran. Routine risk communication through product labeling describes the safety profile for the product and communicates to healthcare professionals the appropriate actions to prevent or mitigate risks, where those recommendations exist. In addition to the routine risk minimization measures, Educational Materials will be provided to health care professionals and patients to support the home administration of patisiran (Section V.2).

Routine pharmacovigilance activities as summarized in Section III.1 , and if through routine pharmacovigilance new risks are identified, the risk communication and minimization measures will be updated as necessary.

An overview of the proposed risk minimization activities for the important identified risk, important potential risks, and missing information for patisiran are provided in Table 20.

Table 20: Risk Minimization Measures by Safety Concern

Safety Concern	Risk Minimization Activities
Important identified risk: Infusion-related reactions (IRRs)	Routine risk communication: • Description of the proportion of patients with, frequency, nature and severity of IRRs is provided in *Section 4.4* and *Section 4.8* of the SmPC • Description of IRRs is provided in *Section 2* and *Section 4* of the Package Leaflet Routine risk minimization activities recommending specific clinical measures to address the risk: • Onpattro therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis (*Section 4.2* of the SmPC) • Premedication is required, and recommended medications, dosages, and timing are described in *Section 4.2* of the SmPC and *Section 3* of the Package Leaflet • Instructions on the recommended rate of infusion are provided in *Section 4.2* of the SmPC • Recommendations for medical management of an IRR, if it occurs, including interruption or slowing of the Onpattro infusion rate and/or instituting medical management as clinically indicated (*Section 4.4* of the SmPC) • Information that some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs (*Section 4.4* of the SmPC) • Instructions that the decision for whether a patient can receive infusions at home should be made by the treating physician and may

Safety Concern	Risk Minimization Activities
	be considered for patients who have tolerated at least 3 infusions well in the clinic (*Section 4.2* of the SmPC). Home infusion should be performed by a healthcare professional Other routine risk minimization measures beyond the Product Information: • Legal status: restricted medical prescription Additional risk minimization measures: • Educational Materials for HCPs and patients to ensure the safe and sustainable administration of Onpattro in the home
Important potential risk: Consequences of vitamin A deficiency	Routine risk communication: • The secondary pharmacologic effect of Onpattro on serum vitamin A levels is described in *Section 4.4, Section 4.5, Section 4.6,* and *Section 5.1* of the SmPC, and in *Section 2* of the Package Leaflet Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that serum vitamin A levels below lower limit of normal should be corrected and any ocular symptoms due to vitamin A deficiency be evaluated prior to initiation of treatment (*Section 4.4* of the SmPC and *Section 2* of the Package Leaflet) • Recommendation for vitamin A supplementation of approximately 2500 IU per day (*Section 4.2* and *Section 4.4* of the SmPC and guidance for patients in *Section 2* of the Package Leaflet) • Recommendation not to use serum vitamin A levels to guide vitamin A supplementation (*Section 4.4 and 4.5* of the SmPC) • If a patient develops ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness), referral to an ophthalmologist is recommended (*Section 4.4* of the SmPC) and patients are advised to talk to their doctor if they notice symptoms suggestive of vitamin A deficiency (*Section 2* of the Package Leaflet) • A statement that vitamin A levels that are too high or too low may be associated with an increased risk of foetal malformation has been added in *Section 4.4 and 4.6* of the SmPC and *Section 2* of the Package Leaflet, and recommendation that pregnancy should be excluded before treatment initiation. Women of childbearing potential should practise effective contraception during Onpattro treatment (*Section 4.4 and 4.6* of the SmPC and *Section 2* of the Package Leaflet). Recommendation to monitor vitamin A levels, to modify vitamin A supplementation for pregnancy (planned and unplanned), and monitoring of the foetus have been added to *Section 4.4* and *Section 4.6* of the SmPC. Other routine risk minimization measures beyond the Product Information: • Legal status: restricted medical prescription

Safety Concern	Risk Minimization Activities
Important potential risk: Severe hypersensitivity	Routine risk communication: • Statement that Onpattro is contraindicated in patients with severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients in *Section 4.3* of the SmPC and *Section 2* of the Package Leaflet Other routine risk minimization measures beyond the Product Information: • Legal status: restricted medical prescription
Important potential risk: Hepatic disorders	Routine risk communication: • None Other routine risk minimization measures beyond the Product Information: • Legal status: restricted medical prescription
Missing information: Longer-term safety (>3 years)	Routine risk communication: • A summary of the safety profile of Onpattro in the clinical development program is provided in *Section 4.8* of the SmPC
Missing information: Use in patients with moderate or severe hepatic impairment	Routine risk communication: • Information on the absence of data in patients with moderate and severe hepatic impairment is included in *Section 4.2* of the SmPC. A statement that Onpattro should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in *Section 4.2* of the SmPC. This section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild hepatic impairment in *Section 5.2* of the SmPC.
Missing information: Use in patients with severe renal impairment or end-stage renal disease	Routine risk communication: • Information on the absence of data in patients with severe renal impairment or end-stage renal disease is included in *Section 4.2* of the SmPC. A statement that Onpattro should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in *Section 4.2* of the SmPC. This section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild or moderate renal impairment in *Section 5.2* of the SmPC
Missing information: Use in patients with prior liver transplantation	Routine risk communication: • *Section 4.8* of the SmPC states that in an open-label study in 23 hATTR amyloidosis patients with polyneuropathy progression post liver transplant, the safety profile of patisiran was consistent with previous clinical studies. • *Section 5.1* of the SmPC states that in an open-label study, 23 patients with hATTR amyloidosis and polyneuropathy progression after receiving a liver transplant were treated with patisiran at a dose of 300 micrograms per kg via IV infusion once every 3 weeks. Median time from transplant to first patisiran dose was 9.4 years and median duration of patisiran treatment was 13.1 months. All patients received concomitant immunosuppressants.

Safety Concern	Risk Minimization Activities
	• *Section 5.2* of the SmPC states that in a clinical study in hATTR amyloidosis patients who had undergone prior liver transplant, steady state pharmacokinetic parameters and TTR reduction were comparable to those observed in patients without a liver transplant.
Missing information: Use in pregnancy and lactation	Routine risk communication: • Information on the absence of clinical data in pregnant and lactating women is included in *Section 4.6* of the SmPC, with a cross-reference to nonclinical data on embryo-fetal development, lactation, and fertility in *Section 5.3* of the SmPC Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for use of effective contraception in women of childbearing potential is provided in *Section 4.4* and *Section 4.6* of the SmPC and *Section 2* of the Package Leaflet

V.2 Additional Risk Minimization Measures

Additional risk minimization measures (aRMMs) as described in Section V.1 include Educational Materials for health care providers and patients to ensure safe and sustainable administration of patisiran in the home.

V.3 Summary of Risk Minimization Measures

A summary of pharmacovigilance activities and risk minimization activities is provided in Table 21.

Table 21: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risk:		
Infusion-related reactions (IRRs)	Routine risk minimization measures: • Description of the proportion of patients with, frequency, nature, and severity of IRRs is provided in Section 4.4 and Section 4.8 of the SmPC • Description of IRRs is provided in Section 2 and Section 4 of the Package Leaflet • Onpattro therapy should be initiated under the supervision of a physician	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific targeted follow-up of IRRs Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	knowledgeable in the management of amyloidosis (Section 4.2 of the SmPC) • Premedication is required, and recommended medications, dosages, and timing are described in (Section 4.2 of the SmPC and Section 3 of the Package Leaflet) • Instructions on the recommended rate of infusion are provided in Section 4.2 of the SmPC • Recommendations for medical management of an IRR, if it occurs, including interruption or slowing of the Onpattro infusion rate and/or instituting medical management as clinically indicated (Section 4.4 of the SmPC) • Information that some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs (Section 4.4 of the SmPC) • Instructions that the decision for whether a patient can receive infusions at home should be made by the treating physician and may be considered for patients who have tolerated at least 3 infusions well in the clinic (Section 4.2 of the SmPC). Home infusion should be	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	performed by a healthcare professional. • Legal status: restricted medical prescription <u>Additional risk minimization measures:</u> • Educational Materials for HCPs and patients to ensure the safe and sustainable administration of patisiran in the home	
Important Potential Risk:		
Consequences of vitamin A deficiency	<u>Routine risk minimization measures</u>: • The secondary pharmacologic effect of patisiran on serum vitamin A levels is described in Section 4.4, Section 4.5, Section 4.6, and Section 5.1 of the SmPC and in Section 2 of the Package Leaflet • Recommendation that serum vitamin A levels below lower limit of normal should be corrected and any ocular symptoms due to vitamin A deficiency be evaluated prior to initiation of treatment (Section 4.4 of the SmPC and Section 2 of the Package Leaflet) • Recommendation for vitamin A supplementation of approximately 2500 IU per day (Section 4.2 and Section 4.4 of the SmPC and guidance for patients in Section 2 of the Package Leaflet) • Recommendation not to use serum vitamin A levels to guide vitamin A supplementation (Section 4.4 and 4.5 of the SmPC) • If a patient develops ocular symptoms suggestive of	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • None <u>Additional pharmacovigilance activities</u>: • Evaluation of data from the non-interventional observational cohort Study 009 Final Study Report: 25 March 2032

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	vitamin A deficiency (e.g., night blindness), referral to an ophthalmologist is recommended (Section 4.4 of the SmPC) and patients are advised to talk to their doctor if they notice a change in their vision (Section 2 of the Package Leaflet) • A statement that vitamin A levels that are too high or too low may be associated with an increased risk of foetal malformation has been added in Section 4.4 and 4.6 of the SmPC and Section 2 of the Package Leaflet, and recommendation that pregnancy should be excluded before treatment initiation. Women of childbearing potential should practise effective contraception during patisiran treatment (Section 4.4 and 4.6 of the SmPC and Section 2 of the Package Leaflet). Recommendation to monitor vitamin A levels, to modify vitamin A supplementation for pregnancy (planned and unplanned), and monitoring of the foetus have been added to Section 4.4 and 4.6 of the SmPC. • Legal status: restricted medical prescription <u>Additional risk minimization measures:</u> • None	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Severe hypersensitivity	Routine risk minimization measures: • Statement that patisiran is contraindicated in patients with severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients in Section 4.3 of the SmPC and Section 2 of the Package Leaflet • Legal status: restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific targeted follow-up of severe and serious events of severe hypersensitivity Additional pharmacovigilance activities: • None
Hepatic disorders	Routine risk minimization measures: • None Legal status: • Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Evaluation of data from the non-interventional observational cohort Study 009 Final Study Report: 25 March 2032
Missing Information:		
Longer-term safety (>3 years)	Routine risk minimization measures: • A summary of the safety profile of patisiran in the clinical development program is provided in Section 4.8 of the SmPC. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Evaluation of data from the non-interventional observational cohort Study 009 Final Study Report: 25 March 2032

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with moderate or severe hepatic impairment	Routine risk minimization measures: • Information on the absence of data in patients with moderate and severe hepatic impairment is included in Section 4.2 of the SmPC; this section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild hepatic impairment in Section 5.2 of the SmPC. • A statement that patisiran should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in Section 4.2 of the SmPC. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Evaluation of data from the non-interventional observational cohort Study 009 Final Study Report: 25 March 2032
Use in patients with severe renal impairment or end-stage renal disease	Routine risk minimization measures: • Information on the absence of data in patients with severe renal impairment or end-stage renal disease is included in Section 4.2 of the SmPC; this section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild or moderate renal impairment in Section 5.2 of the SmPC. • A statement that patisiran should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in Section 4.2 of the SmPC. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Evaluation of data from the non-interventional observational cohort Study 009 Final Study Report: 25 March 2032

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with prior liver transplantation	Routine risk minimization measures: • Section 4.8 of the SmPC states that in an open-label study in 23 hATTR amyloidosis patients with polyneuropathy progression post liver transplant, the safety profile of patisiran was consistent with previous clinical studies. • Section 5.1 of the SmPC states that in an open-label study, 23 patients with hATTR amyloidosis and polyneuropathy progression after receiving a liver transplant were treated with patisiran at a dose of 300 micrograms per kg via IV infusion once every 3 weeks. Median time from transplant to first patisiran dose was 9.4 years and median duration of patisiran treatment was 13.1 months. All patients received concomitant immunosuppressants. • Section 5.2 of the SmPC states that in a clinical study in hATTR amyloidosis patients who had undergone prior liver transplant, steady state pharmacokinetic parameters and TTR reduction were comparable to those observed in patients without a liver transplant. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Evaluation of data from the non-interventional observational cohort Study 009 Final Study Report: 25 March 2032
Use in pregnancy and lactation	Routine risk minimization measures: • Information on the absence of clinical data in pregnant and lactating women is included in	Routine pharmacovigilance activities beyond adverse

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Section 4.6 of the SmPC, with a cross-reference to nonclinical data on embryo-fetal development, lactation, and fertility in Section 5.3 of the SmPC. • Recommendation for use of effective contraception in women of childbearing potential is provided in Section 4.4 and Section 4.6 of the SmPC and Section 2 of the Package Leaflet. <u>Additional risk minimization measures:</u> • None	<u>reactions reporting and signal detection:</u> • None <u>Additional pharmacovigilance activities</u>: • Evaluation of data from the Global Pregnancy Surveillance Program Study 010 to collect and evaluate data on pregnancy exposure and infant outcomes Final Program Report: 31 December 2031

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN FOR ONPATTRO (PATISIRAN)

This is a summary of the RMP for Onpattro. The RMP details important risks of Onpattro, how these risks can be minimized, and how more information will be obtained about Onpattro's risks and uncertainties (missing information).

Onpattro's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Onpattro should be used.

This summary of the RMP for Onpattro should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Onpattro's RMP.

I. The medicine and what it is used for

Onpattro is authorized for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. It contains patisiran as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Onpattro's benefits can be found in Onpattro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/onpattro*.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Onpattro, together with measures to minimize such risks and the proposed studies for learning more about Onpattro's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Onpattro, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Onpattro is not yet available, it is listed under 'missing information'.

II.A List of important risks and missing information

Important risks of Onpattro are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Onpattro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risk	• Infusion-related reactions
Important potential risks	• Consequences of vitamin A deficiency • Severe hypersensitivity • Hepatic disorders
Missing information	• Longer-term safety (>3 years) • Use in patients with moderate or severe hepatic impairment • Use in patients with severe renal impairment or end-stage renal disease • Use in patients with prior liver transplantation • Use in pregnancy and lactation

II.B Summary of important risks

Important Identified Risk: Infusion-Related Reactions (IRRs)	
Evidence for linking the risk to the medicine	Infusion-related reactions (IRRs) were reported in clinical studies of Onpattro and included such signs and symptoms as back pain, flushing, nausea, and headache. This group of symptoms was reported more frequently in patients receiving Onpattro than in patients receiving placebo in a double-blind, randomized, placebo-controlled pivotal Phase 3 clinical study. IRRs were noted in other clinical studies of Onpattro. Patients received premedications (corticosteroid, antihistamines, and paracetamol) to reduce the risk of IRRs. IRRs were mostly mild in severity and decreased in frequency over time. Few infusions had to be interrupted, and among those that were, most continued until the full dose was administered.
Risk factors and risk groups	In general, it is difficult to predict which patients in a population may be more susceptible to IRRs. However, it is known that IRRs may be prevented or the symptoms made less severe by the administration of

Important Identified Risk: Infusion-Related Reactions (IRRs)	
	premedication.[a,b] Controlling how fast the drug is infused is also important to help decrease the number and severity of IRRs.
Risk minimization measures	Routine risk minimization measures: • Description of the proportion of patients with, frequency, nature and severity of IRRs is provided in Section 4.4 and Section 4.8 of the SmPC • Description of IRRs is provided in Section 2 and Section 4 of the Package Leaflet • Onpattro therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis (Section 4.2 of the SmPC) • Premedication is required, and recommended medications, dosages, and timing are described in Section 4.2 of the SmPC and Section 3 of the Package Leaflet • Instructions on the recommended rate of infusion are provided in Section 4.2 of the SmPC • Recommendations for medical management of an IRR, if it occurs, including interruption or slowing of the Onpattro infusion rate and/or instituting medical management as clinically indicated (Section 4.4 of the SmPC) • Information that some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs (Section 4.4 of the SmPC) • Instructions that the decision for whether a patient can receive infusions at home should be made by the treating physician and may be considered for patients who have tolerated well at least 3 infusions well in the clinic (Section 4.2 of the SmPC). Home infusion should be performed by a healthcare professional • Legal status: restricted medical prescription Additional risk minimization measures: • Educational Materials for HCPs and patients to optimize the safe administration of patisiran in the home

[a] Doessegger and Banholzer, Clin Tranl Immunology, 2015 Jul;4(7):e39.
[b] Szebeni, Mol Immunol, 2014 Oct;61(2):163-73.

Important Potential Risk: Consequences of Vitamin A Deficiency	
Evidence for linking the risk to the medicine	The primary mechanism of action of Onpattro is to reduce the level of TTR. One function of TTR is to carry retinol binding protein, which distributes vitamin A in serum. There is, therefore, a theoretical risk of vitamin A deficiency. However, vitamin A can distribute into tissues by TTR-independent mechanisms. Retinol binding protein and serum

Important Potential Risk: Consequences of Vitamin A Deficiency	
	vitamin A were reduced in studies of Onpattro in monkeys; however, no evidence of vitamin A deficiency was observed. Patients in the clinical studies were advised to take vitamin A supplementation at the usual recommended daily dose. No symptoms of vitamin A deficiency such as night blindness or other eye conditions were seen in patients receiving Onpattro.
Risk factors and risk groups	Prolonged dietary deficiency and other conditions such as gastrointestinal malabsorption due to a variety of causes can lead to vitamin A deficiency in the hATTR amyloidosis population.
Risk minimization measures	<u>Routine risk minimization measures:</u> • The secondary pharmacologic effect of Onpattro on serum vitamin A levels is described in Section 4.4, Section 4.5, Section 4.6, and Section 5.1 of the SmPC • Recommendation that serum vitamin A levels below lower limit of normal should be corrected and any ocular symptoms due to vitamin A deficiency be evaluated prior to initiation of treatment (Section 4.4 of the SmPC and Section 2 of the Package Leaflet) • Recommendation for vitamin A supplementation of approximately 2500 IU per day (Section 4.2 and Section 4.4 of the SmPC and guidance for patients in Section 2 of the Package Leaflet • Recommendation not to use serum vitamin A levels to guide vitamin A supplementation (Section 4.4 and 4.5 of the SmPC) • If a patient develops ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness), referral to an ophthalmologist is recommended (Section 4.4 of the SmPC) and patients are advised to talk to their doctor if they notice a change in their vision (Section 2 of the Package Leaflet) • A statement that vitamin A levels that are too high or too low may be associated with an increased risk of foetal malformation has been added in Section 4.4 and 4.6 of the SmPC and Section 2 of the Package Leaflet, and recommendation that pregnancy should be excluded before treatment initiation. Women of childbearing potential should practise effective contraception during patisiran treatment (Section 4.4 and 4.6 of the SmPC and Section 2 of the Package Leaflet). Recommendation to monitor vitamin A levels, to modify vitamin A supplementation for pregnancy (planned and unplanned), and monitoring of the foetus have been added to Section 4.4 and 4.6 of the SmPC. • Legal status: restricted medical prescription
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Important Potential Risk: Severe Hypersensitivity	
Evidence for linking the risk to the medicine	Severe hypersensitivity is a theoretical risk for any drug, but has not been observed in patients taking Onpattro.
Risk factors and risk groups	Patients with a history of severe hypersensitivity to patisiran or any of the excipients are clearly at higher risk. Patients with a personal history of atopy may be at higher risk in general; however, there are no specific data to suggest that these patients would be at higher risk of a reaction to Onpattro.
Risk minimization measures	Routine risk minimization measures: • Statement that Onpattro is contraindicated in patients with severe hypersensitivity (e.g., anaphylaxis) to the active substance or any of the excipients in Section 4.3 of the SmPC and Section 2 of the Package Leaflet • Legal status: restricted medical prescription

Important Potential Risk: Hepatic disorders	
Evidence for linking the risk to the medicine	Hepatoxicity was observed in the nonclinical studies in rodents and monkey. In the placebo-controlled Phase 3 study, there was no increase in hepatic AEs in patients treated with patisiran compared to patients treated with placebo. A small increase of ALT and AST from baseline was observed in the patisiran group compared with placebo that remained stable for the 18-month treatment period. The changes in ALT and AST were not associated with changes in ALP or TBILI. Similar results were observed in the open-label extension studies. Across the 3 studies, ALT and AST levels remained stable over time for periods up to 84.9 months.
Risk factors and risk groups	Patients with hepatic impairment or liver transplants may be at higher risk for hepatic disorders.
Risk minimization measures	Routine risk minimization measures: • Legal status: restricted medical prescription
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Longer-term Safety (>3 years)	
Risk minimization measures	Routine risk minimization measures: • A summary of the safety profile of Onpattro and duration of exposure in the clinical development program is provided in Section 4.8 of the SmPC
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment	
Risk minimization measures	Routine risk minimization measures: • Information on the absence of data in patients with moderate and severe hepatic impairment is included in Section 4.2 of the SmPC. A statement that patisiran should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in Section 4.2 of the SmPC. This section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild hepatic impairment in Section 5.2 of the SmPC
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Patients with Severe Renal Impairment or End-stage Renal Disease	
Risk minimization measures	Routine risk minimization measures: • Information on the absence of data in patients with severe renal impairment or end-stage renal disease is included in Section 4.2 of the SmPC. A statement that patisiran should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in Section 4.2 of the SmPC. This section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild or moderate renal impairment in Section 5.2 of the SmPC
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Patients with Prior Liver Transplantation	
Risk minimization measures	Routine risk minimization measures: • Section 4.8 of the SmPC states that in an open-label study in 23 hATTR amyloidosis patients with polyneuropathy progression post liver transplant, the safety profile of patisiran was consistent with previous clinical studies. • Section 5.1 of the SmPC states that in an open-label study, 23 patients with hATTR amyloidosis and polyneuropathy progression after receiving a liver transplant were treated with patisiran at a dose of 300 micrograms per kg via IV infusion once every 3 weeks. Median time from transplant to first patisiran dose was 9.4 years and median duration of patisiran treatment was 13.1 months. All patients received concomitant immunosuppressants. • Section 5.*2* of the SmPC states that in a clinical study in hATTR amyloidosis patients who had undergone prior liver transplant, steady state pharmacokinetic parameters and TTR reduction were comparable to those observed in patients without a liver transplant.
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Pregnancy and Lactation	
Risk minimization measures	Routine risk minimization measures: • Information on the absence of clinical data in pregnant and lactating women is included in Section 4.6 of the SmPC, with a cross-reference to nonclinical data on embryo-fetal development, lactation, and fertility in Section 5.3 of the SmPC • Recommendation for use of effective contraception in women of childbearing potential is provided in Section 4.4 and Section 4.6 of the SmPC and Section 2 of the Package Leaflet
Additional pharmacovigilance activities	• Evaluation of data from the Global Pregnancy Surveillance Program Study 010 to collect and evaluate data on pregnancy exposure and infant outcomes

II.C Post-authorization Development Plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Onpattro.

II.C.2 Other studies in post-authorization development plan

Study ALN-TTR02-009, Prospective Observational Cohort Study

This non-interventional observational cohort study will provide real-world experience from patisiran use, as well as provide comparative safety data from other treatments, or no treatment, that can be used to further assess the findings and any association with patisiran. The study cohort will include all patients with hATTR amyloidosis under care at the participating clinics, as no exclusion criteria are intended with this observational cohort. Patients treated at home, as well as patients with hepatic or renal impairment, and patients with prior liver transplantation will be observed as part of the cohort. The planned size of the total hATTR amyloidosis study cohort is 300 patients and will include 150 patients exposed to patisiran over a period of up to 10 years from the time the first patient is treated with patisiran post-authorization. The study is targeting to evaluate at least 900 patient-years of patient experience on patisiran.

Study ALN-TTR02-010, Global Pregnancy Surveillance Program

This global pregnancy surveillance program will collect and evaluate information on exposure during pregnancy and infant outcomes in patients with hATTR amyloidosis who are exposed to patisiran. As of the data lock point of this RMP, no patients have enrolled in Study ALN-TTR02-010.

PART VII. ANNEXES

ANNEXES TABLE OF CONTENTS

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Onpattro™ (patisiran): Targeted Follow up Questionnaire for Reports of Infusion Related Reaction (IRR)

1. Manufacturer Control Number (MCN): (MCN to be assigned by Alnylam)			
Patient Initials:		**Patient Date of Birth: (DD/MMM/YYYY)**	
Patient Gender:	☐ M ☐ F	**Patient Weight:**	☐ kg ☐ lb
Is the reported event considered an IRR?	☐ Yes ☐ No		

2. IRR Description

Please provide a detailed description of the IRR, including when the IRR started, the type of symptoms, how long the symptoms lasted, and what treatment was given (if applicable).

Please mark the signs and symptoms of the IRR (select all those apply):

- ☐ Abdominal pain
- ☐ Back pain
- ☐ Chest discomfort
- ☐ Chest pain
- ☐ Itching (pruritus)
- ☐ Chills
- ☐ Cough
- ☐ Dizziness
- ☐ Facial oedema
- ☐ Fatigue
- ☐ Flushing
- ☐ Headache
- ☐ Hypertension
- ☐ Hypotension
- ☐ Joint Pain (Arthralgia)
- ☐ Musculoskeletal pain (Myalgia)
- ☐ Nausea
- ☐ Neck Pain
- ☐ Palpitations
- ☐ Rash
- ☐ Fainting (syncope)
- ☐ Increased heart rate (tachycardia)
- ☐ Shortness of breath (Dyspnoea)

☐ OTHER: Please write down below

Date of IRR:
(DD/MMM/YYY):

The IRR began:

☐ During the infusion
How long did the symptoms start after the start of the infusion (minutes)

_____

☐ After the completion of the infusion
How long did the symptoms start after the completion of the infusion (hours/minutes)

_____

3. Pre-Medications Given Prior to Onpattro Infusion

Were the pre-medications given at least 60 minutes before the Onpattro infusion:

☐ **Yes** ☐ **No**

For each pre-medication given, please check the box and provide the name, dose, and route.

	Brand Name of the Pre-Medication	**Dose**	**Route**
☐ Corticosteroid			
☐ Antihistamines (H1 blockers)			
☐ Antihistamines (H2 blockers)			
☐ Antipyretics			
☐ Other			
☐ Other			

4. Onpattro Therapy Details

Provide dates for:	Date (DD/MMM/YYYY)
The first Onpattro infusion	
The infusion before the most recent infusion	
The most recent (current) infusion	

	Dose:	**Route:**	**Frequency:**
Onpattro			

How many Onpattro infusions (including this one) has the patient received?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ More than 5

Please provide number if more than 5:

Please provide information on the current Onpattro infusion below:

4. Onpattro Therapy Details

The infusion was given at: ☐ A clinic setting ☐ Home

The total duration of the Onpattro infusion (including any the time for interruptions, but not including the time for pre-medication administration) was:

☐ Less than an hour ☐ 1 to 2 hours ☐ More than 2 hours

Please describe what action was taken with the infusion:	The infusion rate was:
☐ Continued ☐ Interrupted and restarted ☐ Discontinued If interrupted, please describe for how long (minutes):	☐ Not changed ☐ Slowed down

5. Treatment for IRR

Please describe the treatment given for the IRR

Medication	Dose	Route	Frequency

Other Treatment (Please specify):

6. Laboratory tests / Imaging

Please indicate if any tests have been performed, and their results:

Please list relevant lab tests / imaging performed	Date and time of the test (DD/MMM/YYYY, HH:MM):	Test Results (include units)	Reference Range (if applicable)

7. Please provide information on the <u>previous</u> infusions below:
Has this patient received reduced doses of corticosteroid pre-medications (less than 10 mg dexamethasone or equivalent)? ☐Yes ☐No If yes, please describe
Has any infusion been missed? ☐Yes ☐No If yes, please describe which infusion(s) were missed, the reason(s), the anticipated date(s) of the missed dose(s), and the date of the next dose
Has the patient had IRR with previous infusions? ☐Yes ☐No If yes, please describe

Thank you for completing this form.			
This form was completed by:			
Name:		Position:	
Signature:		Date:	
E-mail:			
Telephone number:			

Onpattro™ (patisiran): Targeted Follow-up Questionnaire for Reports of Severe Hypersensitivity (sHS) / Anaphylaxis

1. Manufacturer Control Number (MCN): (MCN to be assigned by Alnylam)			
Patient Initials:		**Patient Date of Birth: (DD/MMM/YYYY)**	
Patient Gender:	☐ M ☐ F	**Patient Weight:**	☐ kg ☐ lb
Is the reported event considered a severe hypersensitivity reaction?		☐ Yes	☐ No

2. Description of the adverse event

Please provide a detailed description of the hypersensitivity reaction, including the timing of the event, what the symptoms were, when they occurred, how long the symptoms lasted, and what treatment was given (if applicable).

Date of hypersensitivity reaction:

(DD/MMM/YYY):

The hypersensitivity reaction began:

☐ During the infusion

How long did the symptoms start after the start of the infusion (minutes)

_____

☐ After the completion of the infusion

How long did the symptoms start after the completion of the infusion (hours/minutes)

_____

3. Pre-Medications Given Prior to Onpattro Infusion

Were the pre-medications given at least 60 minutes before the Onpattro infusion:

☐ Yes ☐ No

For each pre-medication given, please check the box and provide the name, dose, and route.

	Brand Name of the Pre-Medication	**Dose**	**Route**
☐ Corticosteroid			

☐ Antihistamines (H1 blockers)			
☐ Antihistamines (H2 blockers)			
☐ Antipyretics			
☐ Other			
☐ Other			

4. Onpattro Therapy Details

Provide dates for:	Date (DD/MMM/YYYY)
The first Onpattro infusion	
The infusion before the most recent infusion	
The most recent (current) infusion	

	Dose:	Route:	Frequency:
Onpattro			

How many Onpattro infusions (including this one) has the patient received?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ More than 5

Please provide number if more than 5:

Please provide information on the current Onpattro infusion below:

The infusion was given at: ☐ A clinic setting ☐ Home

The total duration of the Onpattro infusion (including any the time for interruptions, but not including the time for pre-medication administration) was:

☐ Less than an hour ☐ 1 to 2 hours ☐ More than 2 hours

Please describe what action was taken with the infusion:	The infusion rate was:
☐ Continued ☐ Interrupted and restarted ☐ Discontinued If interrupted, please describe for how long (minutes):	☐ Not changed ☐ Slowed down

5. Treatment for hypersensitivity

Please describe the treatment given for the hypersensitivity reaction

Medication	Dose	Route	Frequency

Other Treatment (Please specify):

6. Laboratory tests / Imaging
Please indicate if any tests have been performed, and their results:

Please list relevant lab tests / imaging performed	Date and time of the test (DD/MMM/YYYY, HH:MM):	Test Results (include units)	Reference Range (if applicable)
Serum tryptase			
Serum histamine			
Other - Please specify:			
Other - Please specify:			

7. Risk Factors

Any previous hypersensitivity reaction to **pre-medications** given prior to Onpattro ☐ Yes ☐ No
Please describe the detail of the event(s) including symptoms and drug(s) involved:

Any previous hypersensitivity reaction to **Onpattro infusion** ☐ Yes ☐ No
Please describe the detail of the event(s) including symptoms and drug(s) involved:

Any previous hypersensitivity reaction to **other drugs**: ☐ Yes ☐ No
If yes, please describe the detail of the event(s) including symptoms and drug(s) involved:

Allergens: Please indicate if the patient currently has or had in the past any of the following **allergies**.

Allergen	**Yes** **No**	If yes, please describe the detail of the hypersensitivity reaction including symptoms and allergen involved:

Antibiotics	☐ ☐	
Environmental	☐ ☐	
Food	☐ ☐	
Insect bite	☐ ☐	
Intravenous radiocontrast media	☐ ☐	
Latex	☐ ☐	
Others (specify):	☐ ☐	

Medical Conditions: Please indicate if the patient currently has, or had in the <u>past three months</u> any of the following **medical conditions** that are known to be risk factors for developing hypersensitivity reactions

Medical Condition	**Yes**	**No**	If yes, please describe the detail of the hypersensitivity reaction including symptoms and drug(s) involved:
Asthma	☐	☐	
Atopy	☐	☐	
Heavy alcohol use (≥14 units/week)	☐	☐	
Transfusion of blood or blood products	☐	☐	
Others (specify):	☐	☐	

Any previous use of epinephrine/adrenaline (i.e. Epi-Pen)? ☐ Yes ☐ No

If yes, please specify (including the reason for use):

8. Please provide information on the previous infusions below:			
Has this patient received reduced doses of corticosteroid pre-medications (less than 10 mg dexamethasone or equivalent)? ☐Yes ☐No If yes, please describe			
Has any infusion been missed? ☐Yes ☐No If yes, please describe which infusion(s) were missed, the reasons, the anticipated date(s) of the missed dose(s), and the date of the next dose			
Did the patient experience hypersensitivity reaction with previous infusions? ☐Yes ☐No If yes, please describe			

Thank you for completing this form.			
This form was completed by:			
Name:		Position:	
Signature:		Date:	
E-mail:			
Telephone number:			

Annex 6 Details of Proposed Additional Risk Minimization Activities

Educational Materials for healthcare providers and patients to ensure the safe and sustainable administration of patisiran in the home in the post-marketing setting will be submitted to the national competent authorities. The Educational Materials are intended to supplement the information provided in the SmPC and the Package Leaflet and will convey the important key concepts outlined below.

The Educational Materials for HCPs should include information about:

- Suitability of the patient for home infusion;
- Requirements for home infusion, including availability and timely administration of the appropriate premedication;
- The appropriate infusion rate;
- Signs and symptoms of IRRs;
- Action to take in the event of an IRR and in case of emergency;
- Steps to consider to prevent further IRRs;
- Reasons triggering HCPs to consider whether the patient should stop home infusions and return to the clinic to have their infusions.

The Educational Materials for patients (a home infusion guide detailing the steps to undertake during home infusion) should include information about:

- How the infusion is given;
- The potential for IRRs to occur;
- Signs and symptoms of IRRs;
- Patients to inform immediately the HCP if they experience any of the signs and symptoms of IRRs.