EU RISK MANAGEMENT PLAN
FOR
AMVUTTRA (VUTRISIRAN)

RMP version to be assessed as part of this application:

Data-lock point for this RMP	08 May 2024	Version number	2.0
Date of final sign off	23 April 2025		

Rationale for submitting an updated RMP: To update the milestones for the end of data collection and the final report for Study 005, in response to a question from the European Medicines Agency (EMA).

Summary of significant changes in this RMP:

Part	Module	Significant Change in Each Module
Part I **Product Overview**	Product Overview	No Change
Part II **Safety Specification**	Module SI Epidemiology of the Indication and Target Population	No Change
	Module SII Nonclinical Part of the Safety Specification	No Change
	Module SIII Clinical Trial Exposure	No Change
	Module SIV Populations Not Studied in Clinical Trials	No Change
	Module SV Post-Authorisation Experience	No Change
	Module SVI Additional EU Requirements for the Safety Specification	No Change
	Module SVII Identified and Potential Risks	No Change
	Module SVIII Summary of the Safety Concerns	No Change

Part	Module	Significant Change in Each Module
Part III Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)		Removed "or accrual target met, whichever occurs first" from the End of Data Collection milestone, and "or 12 months after end of data collection, whichever occurs first" from the Final Study Report milestone for Study 005, as listed in the Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan table in Part III.2 and in Ongoing and Planned Additional Pharmacovigilance Activities table in Part III.3 per the Agency's request.
Part IV Plans for Post-authorization Efficacy Studies		No Change
Part V Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)		No Change
Part VI Summary of Risk Management Plan		No Change
Part VII Annexes	Annex 1 EudraVigilance Interface	No Change
	Annex 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme	Removed "or 12 months after end of data collection, whichever occurs first" from the Final Study Report milestone for Study 005, as listed in the Planned and Ongoing Studies table in Annex 2 per the Agency's request.
	Annex 3 Protocols for Proposed, on-going and Completed Studies in the Pharmacovigilance Plan	No Change
	Annex 4 Specific Adverse Drug Reaction Follow-up Forms	No Change

Part	Module	Significant Change in Each Module
	Annex 5 Protocols for Proposed and on-going Studies in the RMP Part IV	No Change
	Annex 6 Details of Proposed Additional Risk Minimisation 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 made 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:

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QPPV name: Jana Mlada

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation 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 amyloidosis	hereditary or wild-type Transthyretin amyloidosis
ATTR amyloidosis with cardiomyopathy	wild-type or hereditary Transthyretin amyloidosis with cardiomyopathy
AUC	Area under the curve
CNS	Central nervous system
CHF	congestive heart failure
CYP	Cytochrome P_{450}
DB	Double blinded
EMA	European Medicines Agency
EPAR	European Public Assessment Report
eGFR	Estimated glomerular filtration rate
EU	European Union
GalNAc	*N*-acetylgalactosamine
GD	Gestation day
GLP	Good Laboratory Practice
hATTR amyloidosis	Hereditary transthyretin amyloidosis
hATTR amyloidosis with polyneuropathy	Hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INN	International Nonproprietary Name
INR	International normalised ratio
ISR	Injection site reaction
IV	Intravenous
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
mNIS+7	Modified neuropathy impairment score +7
mRNA	Messenger ribonucleic acid
NOAEL	No observed adverse effect level

Abbreviation	Definition
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NT-proBNP	*N*-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
PAM	Post-authorisation measure
PASS	Post-authorisation safety study
PBRER	Periodic benefit risk evaluation report
PD	Pharmacodynamic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PND	polyneuropathy disability
PT	Preferred Terms
PV	Pharmacovigilance
PSUR	Periodic Safety Update Reports
qM	Once monthly
qw	Once weekly
q3M	Once every 3 months
q3w	Once every 3 weeks
RBP	Retinol binding protein
RMP	Risk Management Plan
RNAi	RNA interference
SC	Subcutaneous
SSA	Senile systemic amyloidosis
siRNA	Small interfering ribonucleic acid
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query.
SOC	System Organ Class
T4	Thyroxine
TBILI	Total bilirubin
THAOS	Transthyretin Amyloidosis Outcomes Survey
TTR	Transthyretin
UK	United Kingdom
ULN	Upper limit of normal
US	United States
V30M	Valine to methionine variant at position 30 in human transthyretin gene
V122I	Valine to isoleucine variant at position 122 in human transthyretin gene
wt	wild type

Abbreviation	Definition
wtATTR amyloidosis	wild-type transthyretin amyloidosis

Part I PRODUCT OVERVIEW

Table 1: Product Overview

Active substance (INN or common name):	vutrisiran
Pharmacotherapeutic group (ATC Code):	N07XX18
Name of Marketing Authorisation Holder or Applicant:	Alnylam Netherlands BV Antonio Vivaldistraat 150 1083 HP Amsterdam Netherlands
Medicinal products to which this RMP refers:	1
Invented name in the European Economic Area (EEA):	Amvuttra
Marketing authorisation procedure:	Centralised Procedure
Brief description of the product:	Chemical class: small interfering ribonucleic acid (siRNA)
	Summary of mode of action: Amvuttra (vutrisiran) is a chemically stabilized double-stranded siRNA that specifically targets variant and wild-type transthyretin *(TTR)* messenger ribonucleic acid (mRNA) and is covalently linked to a ligand containing three *N*-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes. The chemical modification of the oligonucleotide leads to enhanced hepatic stability and prolonged liver residence time and thereby allowing for infrequent dosing. Through a natural process called RNA interference (RNAi), vutrisiran causes the catalytic degradation of *TTR* mRNA in the liver, resulting in the reduction of variant and wild-type serum TTR protein levels and potentially enabling a reduction of TTR amyloid deposits in affected tissues.
	Important information about its composition: The active moiety is vutrisiran, and the active ingredient is vutrisiran sodium. Amvuttra is supplied as a 0.5 mL solution containing 25 mg vutrisiran in a single-use 1 mL pre-filled syringe with a needle shield.
Hyperlink to the Product Information:	Refer to Section 1.3.1 Summary of Product Characteristics (SmPC), Labelling and Patient Information Leaflet (PIL)

Indication in the EEA:	Current: Vutrisiran is indicated for the treatment of hereditary transthyretin amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy (hATTR amyloidosis with polyneuropathy).
	Proposed additional indication: Vutrisiran is proposed for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR amyloidosis with cardiomyopathy).
Dosage in the EEA	Current: The recommended dose of vutrisiran is 25 mg administered via subcutaneous (SC) injection once every 3 months (q3M)
	Proposed: Not applicable.
Pharmaceutical form and strengths	Current: Vutrisiran is supplied as a sterile, preservative-free, clear, colorless-to-yellow solution for SC injection. Each pre-filled syringe contains vutrisiran sodium equivalent to 25 mg vutrisiran in 0.5 mL solution
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC=Anatomical Therapeutic Chemical; ATTR amyloidosis with cardiomyopathy=wild-type or hereditary transthyretin amyloidosis with cardiomyopathy; EEA=European Economic Area; EU=European Union; hATTR=hereditary transthyretin amyloidosis; INN=International Nonproprietary Name; mRNA=messenger ribonucleic acid; PIL=Patient Information Leaflet; q3M=once every 3 months; RMP=Risk Management Plan; RNAi=RNA interference; siRNA=small interfering ribonucleic acid; SC=subcutaneous; SmPC=Summary of Product Characteristics; TTR=transthyretin.

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Treatment of hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy (hATTR amyloidosis with polyneuropathy)

and

Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR amyloidosis with cardiomyopathy)

Transthyretin amyloidosis (ATTR amyloidosis) is a rapidly progressive, multisystemic, debilitating, and ultimately fatal disease encompassing wild-type transthyretin amyloidosis (wtATTR amyloidosis) and hereditary transthyretin amyloidosis (hATTR amyloidosis).[Adams 2021; Gertz 2017; Grodin 2019; Lane 2019; Parman 2016] In hATTR amyloidosis, inherited variants in the *TTR* gene lead to destabilization of the tetrameric protein. There is no known genetic cause of wtATTR amyloidosis, and it is presumed to be the result of age-related mechanisms associated with alteration in TTR physiological processing and clearance.[Dharmarajan 2012; Ruberg 2012] In both wtATTR amyloidosis and hATTR amyloidosis, the tetrameric TTR protein becomes destabilized and disassociates into dimers and monomers, which subsequently misfold and deposit as amyloid fibrils and plaques in the extracellular space of various tissues, including the heart and peripheral nervous system, leading to cellular injury and organ dysfunction.[Hou 2007] Historically, 2 clinical syndromes of hATTR amyloidosis have been described: hATTR amyloidosis with polyneuropathy (previously known as familial amyloidotic polyneuropathy) and hATTR amyloidosis with cardiomyopathy (previously known as familial amyloidotic cardiomyopathy), both of which are characterised by amyloid deposits of both variant and wild type (wt) TTR.[Ando 2013] As hATTR amyloidosis is a systemic disease with amyloid deposition in multiple organs, the majority of patients 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.[Benson 2018; Coelho 2013; Swiecicki 2015] However, historical prevalence data separately describe hATTR amyloidosis with either polyneuropathy or cardiomyopathy, or disease by genotype.[Rapezzi 2013; Schmidt 2018] Nonhereditary, wtATTR amyloidosis was previously known as senile systemic amyloidosis (SSA). In patients with wtATTR amyloidosis, amyloid deposits are typically found primarily in heart tissue. These patients have cardiomyopathy as their primary disease manifestation; however, they also commonly have non-cardiac manifestations as well.[Dharmarajan 2012; Ruberg 2012] The literature offers limited data on the incidence and prevalence of ATTR amyloidosis due to its rarity. The epidemiology of ATTR amyloidosis is summarised in Table 2.

Table 2: Epidemiology of ATTR Amyloidosis

Incidence
Estimates of incidence of ATTR amyloidosis are scarce and are mostly based on analysis of large secondary databases due to the rarity of this condition as well as its subgroups. A population-based study conducted in Italy estimated the annual incidence of wtATTR and hATTR amyloidosis, ranging from 1.4 to 2.7 and 0.1 to 0.3 per 100,000 population, respectively.[Cappelli 2023] An analysis of nationwide French claims from 2011 to 2017 revealed a similar incidence of ATTR amyloidosis with cardiomyopathy, with 1.8 cases per 100,000 annually in 2017, up from 0.5 cases in earlier years. In the US, the annual incidence of ATTR amyloidosis with cardiomyopathy has been estimated to range from 0.6 to 3.8 cases per 100,000 population.[Laires 2024] A recent Japanese study reported an incidence of 3.3 cases per 100,000 population per year in individuals >65 years of age for ATTR amyloidosis with cardiomyopathy in Kumamoto prefecture.[Takashio 2022] In summary, the incidence of wtATTR amyloidosis ranged globally from 1.0 to 4.0 per 100,000 population annually and the incidence of hATTR amyloidosis ranged from 1.0 to 3.0 per million population from non-endemic Europe.
Prevalence
hATTR amyloidosis Until 1990, hATTR amyloidosis was considered to be endemic to northern Portugal, northern Sweden, and 2 regions of Japan. Since the 1990s, new endemic areas have been identified, and the disease has been reported in approximately 40 countries, including many countries in Europe, the United States (US), China, and India.[Adams 2019; Waddington Cruz 2016] 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. For example, the penetrance with the valine to methionine variant at position 30 in the *TTR* gene (V30M) has been reported to be as low as 28% in Cyprus [Dardiotis 2009] and as high as 91% in Portugal.[Planté-Bordeneuve 2003] Although there is increasing evidence that patients develop a mixed phenotype of polyneuropathy and cardiomyopathy, and the terminology has evolved to refer to a single hereditary disease that presents with a spectrum of symptoms [Benson 2018; Coelho 2013; Gentile 2023; Hawkins 2015; Swiecicki 2015], hATTR amyloidosis has traditionally been reported in a genotype-specific manner and has been categorized according to whether the predominant clinical manifestation is neuropathy (hATTR amyloidosis with polyneuropathy) or cardiomyopathy (hATTR amyloidosis with cardiomyopathy).[Rapezzi 2013; Schmidt 2018] 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 The global prevalence of hATTR amyloidosis with polyneuropathy has been estimated to be ~10,186 (range: 5526–38,468) patients, with endemic clusters in Portugal, Sweden, and Japan.[Schmidt 2018] Portugal is known to have the largest cohort of patients with hATTR amyloidosis with polyneuropathy, with 99% of affected families carrying V30M.[Parman 2016] The mean estimated crude prevalence in 2016 was 22.93 cases per 100,000 adults, which accounted for nearly 20% of worldwide patients.[Ines 2018] In certain municipalities of northern Portugal, the prevalence is estimated to be as high as 3.95 cases per 2000 inhabitants (197.5 cases per 100,000 individuals).[Ines 2015] In Sweden, the estimated prevalence of hATTR amyloidosis with polyneuropathy is reported as 250 cases (2.60 cases per 100,000 individuals)[Parman 2016], with certain regions of northern Sweden reporting prevalence rates as high as 104 cases per 100,000 individuals.[Sousa 1993] The prevalence of hATTR amyloidosis with polyneuropathy in other European countries including but not limited to France, Italy, and Germany is lower than that reported in endemic areas, ranging

from 0.06 to 0.93 per 100,000.[Auer-Grumbach 2020; Cappelli 2023; Koutsis 2021; Mazzeo 2015; Parman 2016; Pozsonyi 2021; Reilly 1995]

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 of 6400 patients nationwide [Coelho 2016]).

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]

<u>hATTR amyloidosis with cardiomyopathy</u>

The worldwide prevalence of hATTR amyloidosis with cardiomyopathy is unknown, but certain variants are associated with the condition. The valine to isoleucine variant at position 122 in human transthyretin gene (V122I) is the most common.[Buxbaum 2010; Dharmarajan 2012] The prevalence of hATTR with cardiomyopathy is expected to be variable by region, due to different frequencies of genetic variants.[Gentile 2023] In Europe, across genotypes, the percentage of patients with predominantly cardiac manifestations accounted for 1.4% to 15% and those with a mixed phenotype accounted for 12.9% to 35.7% of all hATTR amyloidosis patients.[Gentile 2023]

In North America, the percentage of patients with predominantly cardiac manifestation ranged from 20% to 34% across the genotypes and of mixed manifestation from 22% to 26%, across the different genotypes.[Gentile 2023] Notably, the frequency of the V122I *TTR* genotype in the African-American population in the US ranges 3.0% to 3.9%.[Jacobson 1990] However, the actual disease burden attributable to the variant in this population has not been reported.

<u>wtATTR amyloidosis</u>

The epidemiology of wtATTR amyloidosis is not well characterized, due in part to factors such as the nonspecificity of symptoms and phenotypic variability seen in affected patients resulting in under-diagnosis of the condition, the historical absence of effective treatments, and low overall awareness of the disease. Nonetheless, a limited number of publications have provided insight into the prevalence of the disease. These publications focus on the prevalence of wtATTR amyloidosis with cardiomyopathy, which is the characteristic clinical manifestation of the disease.

The prevalence of diagnosed wtATTR amyloidosis in Europe in the general population ranges from 3.0 to 9.0 patients per 100,000 population, based on analysis of national registries, nationwide claims, and disease registries in the Nordic countries, France, and Italy.[Cappelli 2023; Damy 2020; Lauppe 2022; Lauppe 2021] Two studies systemically screened for wtATTR amyloidosis to identify undiagnosed cases and reported prevalence estimate of 16.7 per 100,000 population and of 0.13% to 0.46% in the elderly population.[Aimo 2024; Lindmark 2021]

Outside Europe, the prevalence of ATTR amyloidosis with cardiomyopathy in the US has been reported in a recent study. Using different algorithms in the same study, the prevalence was estimated to range from 1.7 to 17.3 per 100,000 population.[Laires 2024] ATTR amyloidosis prevalence in Japan was assessed via an analysis of the Japanese Medical Data Vision, a nationwide electronic health records database.[Winburn 2019] Based on data from 2010 to 2018 (n=20,894,625 patients), 3255 to 3992 patients were identified as having wtATTR amyloidosis, which equates to a prevalence of 15.6 to 19.1 per 100,000. Because the mean age of the study population was 58 years, considerably older than that of a general population, the prevalence estimate is not applicable to the general population.

<u>Summary</u>

The prevalence of hATTR amyloidosis varies significantly by region, ranging from 1.0 to 10.0 in 1000 in the endemic regions of northern Portugal and Sweden and from 1.0 to 10.0 per 1 million in other areas in the EU. The overall prevalence of hATTR amyloidosis can be estimated as approximately 2 in 100,000 in the US, though between 3% to 4% of African Americans have been estimated to have the V122I *TTR* genotype. 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, the US, and Japan, it can be concluded that hATTR amyloidosis is a rare disease worldwide.

The prevalence of wtATTR in the general population ranged from 3.0 to 17.0 per 100,000 population in Europe based on data from Nordic countries, France, and Italy from 1.7 to 17.3 per 100,000 in the US and 15.6 to 19.1 per 100,000 in Japan. As with hATTR amyloidosis, prevalence data are not readily available for other geographic regions.

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

hATTR amyloidosis

Sex and age at disease manifestation 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 to 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 variant 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 demographics and other characteristics of patients with hATTR amyloidosis who were enrolled in the randomised, global, double-blind, placebo-controlled, Phase 3 pivotal study of patisiran (ALNTTR02-004; APOLLO) further illustrate the variability in these characteristics among patients with hATTR amyloidosis: median age at entry was 62 years (range, 24-83 years), median time since diagnosis was 1.37 years (range, 0.0-21.0 years), 74.2% of patients were male, and 57.3% of patients had a non-V30M genotype (39 TTR variants overall). A total of 96 patients (42.7%) had the V30M variant. Similar variability was observed in patients in the ongoing, global, Phase 3, randomised, open-label, study of vutrisiran (ALNTTRSC02-002 [Study 002; HELIOS-A]): median age at entry was 60 years (range, 2685 years), median time since diagnosis was 2.2 years (range, 0.0-15.3 years), 64.6% of patients were male, and 54.9% had non-V30M variant (25 TTR variants overall).

Race/ethnic origin of patients with hATTR amyloidosis:

Hereditary ATTR amyloidosis occurs worldwide in patients of different races and ethnic origins.

The V30M variants occur 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]

Nonetheless, certain genotypes, such as the T60A variant, which is associated with Irish descent, the I68L variant in Italy, and the V122I variant 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]

wtATTR amyloidosis

Sex and age at disease manifestation and diagnosis:

Onset of wtATTR amyloidosis occurs after the age of 60 years in most patients (mean age 72 years), and the disease becomes increasingly common with advancing age.[Gentile 2023] A recent analysis of data from the Transthyretin Amyloidosis Outcomes Survey (THAOS) found that the mean (standard deviation [SD]) age at symptom onset within a global cohort of patients with wtATTR amyloidosis (n=1156) was 72.0 (9.7) years. The mean (SD) interval from symptom onset to diagnosis was 4.7 (6.9) years.[Gentile 2023]

The disease predominantly affects males.[Kroi 2021; Ruberg 2012] A recent systematic review and meta-analysis of 28 studies (combined n=2542) reporting data on the sex distribution of patients with wtATTR amyloidosis found that males accounted for 86.9% of all affected patients.[Kroi 2021]

Individual studies have suggested that the condition, when present, tends to be more severe (as measured by New York Heart Association [NYHA] class, left ventricular ejection fraction, septal thickness, posterior wall thickness, or left ventricular diastolic diameter) and has an earlier onset in male patients than in female patients.[Gonzalez-Lopez 2017; Siepen 2018; Tanskanen 2008]

Race/ethnic origin of patients with wtATTR amyloidosis:

As a sporadic, age-related condition, wtATTR amyloidosis may occur in individuals of any race or ethnic origin.

A THAOS study of US patients with wtATTR (n=189) found that 89.4% were white and 4.2% were of African descent, while globally 94.4% of patients with wtATTR were white, 2.9% were of African descent, 1.5% were Asian, and the remaining 1.2% were of another race/ethnicity.[Dispenzieri 2022; Maurer 2016] The influence of ascertainment bias on these estimates is unclear.[Driggin 2020]

Existing Treatment Options

hATTR amyloidosis with Polyneuropathy

The treatment of hATTR amyloidosis requires a multidisciplinary approach primarily involving neurology, cardiology, and gastroenterology specialties. Historically, the primary approach to treatment has been palliative or symptomatic therapies directed at specific symptoms such as pain, nausea/vomiting, and diarrhea. In some regions, patients now have access to several treatment options, including ribonucleic acid interference (RNAi) therapeutics [eg, patisiran (ONPATTRO®)], antisense oligonucleotides (ASOs) (eg, inotersen and eplontersen), TTR tetramer stabilizers (eg, tafamidis and diflunisal), and orthotopic liver transplant (OLT).

Patisiran , a RNAi therapeutic approved in the European Union (EU), US, Japan, and other regions for treating polyneuropathy in adults with hATTR amyloidosis. Patisiran targets the production of TTR synthesis in the liver by acting on messenger RNA (mRNA) through RNAi. Directly and specifically targeting the underlying pathophysiological basis of disease is critical to halting, and potentially reversing, the progression of disease and for providing highly effective therapy for patients with a broad range of disease severity and disease manifestations. Treatment with patisiran, which directly targets hepatic synthesis of TTR, 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] In the APOLLO study (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 total, 56.1% of patisiran-treated patients demonstrated improvements from baseline in polyneuropathy scores during the study, compared to only 3.9% of placebo-treated patients.

Additional treatment options include *TTR*-targeting antisense oligonucleotides (ASOs), such as inotersen and eplontersen, which work by reducing the production of *TTR* protein.

Inotersen, approved in the EU, US, and other countries for the treatment of the polyneuropathy of hATTR amyloidosis in adults, is an antisense oligonucleotide that targets the production of TTR synthesis in the liver via RNAse H-mediated cleavage of mRNA. Subcutaneous (SC) weekly injection of inotersen has been shown to decrease TTR and result in a significantly smaller increase (ie, worsening) in mNIS+7 and Norfolk QoL-DN than placebo after 66 weeks of treatment.[Benson 2018] However, despite these benefits, the safety profile of inotersen is characterised by the serious risks of thrombocytopenia and glomerulonephritis, which are listed as warnings in product labelling due to the serious and potentially life-threatening nature.[Akcea Therapeutics ; Benson 2017] Both of these risks have been observed with other antisense oligonucleotide treatments. Because of these risks, inotersen treatment requires frequent monitoring of platelet and renal function laboratory parameters. In addition, inotersen is contraindicated in some patients, including patients with a platelet count less than 100×10^9/L and patients with a history of acute glomerulonephritis caused by inotersen.

Eplontersen (Wainua™) was authorized in the United States of America (USA) on 21 December 2023 for the treatment of polyneuropathy of hATTR amyloidosis (hATTR amyloidosis with polyneuropathy) in adults. Data from the clinical development program demonstrated statistically significant improvements in the mNIS+7 and the Norfolk QoL-DN total scores compared to the external placebo control. The most common adverse reactions that occurred in at least 9% of patients treated with eplontersen were vitamin A decreased and vomiting. (Wainua™ prescribing information, December 2023)

Tetramer stabilisers [eg, tafamidis (Vyndaqel®) and diflunisal], which act by binding to the T4-binding site on *TTR* (thus reducing its dissociation into misfolded amyloidogenic monomers), are also used in clinical practice for the treatment of the polyneuropathy of hATTR amyloidosis but are associated with limitations in terms of efficacy and labeling.

Tafamidis has been shown to delay peripheral neurologic impairment in early-stage patients with hATTR amyloidosis with polyneuropathy, but there is no evidence of its impact on clinical activity in patients with more advanced disease. Furthermore, the majority of patients receiving tafamidis continue to experience neuropathy progression with a steady decline in quality of life, ability to walk, and to perform activities of daily living.[Barroso 2017] Tafamidis has been approved in several regions for the treatment of patients with hATTR amyloidosis with polyneuropathy, including the EU (stage 1 polyneuropathy only) and Japan.

Diflunisal, a generic, oral nonsteroidal anti-inflammatory drug, has been demonstrated to bind to and stabilise the TTR tetramer in a manner similar to tafamidis. While used off-label in some countries where available, diflunisal is not an approved treatment for hATTR amyloidosis in any country. In the US, diflunisal carries boxed warnings for cardiovascular thrombotic events and gastrointestinal risk.[Cadila Healthcare Limited 2017]

Orthotopic liver transplantation eliminates variant TTR from the circulation but does not affect the hepatic 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 orthotopic liver transplantation 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]

ATTR amyloidosis (hATTR or wtATTR) with Cardiomyopathy

Historically, the treatment of ATTR amyloidosis with cardiomyopathy has focused on the management of symptoms, such as diuretics for congestive heart failure. Heart or combined heart and liver transplantation is an option for some patients but is seldom performed.

In regions such as the EU, US, and Japan, the only approved product to treat patients with ATTR amyloidosis with cardiomyopathy is the *TTR* tetramer stabilizer

tafamidis.[VYNDAQEL/VYNDAMAX prescribing information, June 2021] The approval of tafamidis was based on results of the 30-month Phase 3 ATTR-ACT trial, in which tafamidis was associated with lower all-cause mortality and a lower rate of cardiovascular-related hospitalization and a slowing of decline in functional capacity (6-minute walk test [6-MWT]) and quality of life (Kansas City Cardiomyopathy Questionnaire - Overall Summary [KCCQ-OS]) compared to placebo in patients with hATTR and wtATTR amyloidosis with cardiomyopathy.[Maurer 2018] In addition, while improvements with tafamidis treatment relative to placebo were observed in 6-MWT and KCCQ-OS, on average, tafamidis-treated patients still showed steady and substantial progression of disease compared to baseline during the course of the study based on these metrics, with a least squares (LS) mean worsening from baseline of approximately 55 m in 6-MWT and approximately 8 points in KCCQ-OS in the pooled tafamidis group at Month 30.[Maurer 2018]

Natural History of ATTR Amyloidosis

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

Polyneuropathy

Polyneuropathy in hATTR amyloidosis 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. 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.[Gertz 1992] The median survival is 4.7 years following diagnosis. [Swiecicki 2015]

Cardiomyopathy

Patients with cardiomyopathy associated with ATTR amyloidosis suffer unrelenting disease progression with rapid, steady declines in functional capacity and quality of life, frequent hospitalizations, and ultimately death. A recent, large natural history study of patients who were diagnosed with wtATTR cardiomyopathy describes substantial worsening, especially among those whose disease progressed in the first 12 months since diagnosis.[Law 2022] In the Phase 3 ATTR-ACT study of tafamidis, declines in functional capacity and quality of life manifest in less than 12 months, based on the substantial worsening in 6-MWT performance and KCCQ-OS observed in placebo-treated patients.[Maurer 2018] These declines were evident across a range of NYHA classes.[Nativi-Nicolau 2021] Natural history studies depict a progression of heart failure resulting in hospitalizations and death 2.5 to 5 years after diagnosis.[Antonopoulos 2022]; [Castano 2015]; [Damy 2015]; [Dungu 2012]; [Hawkins 2015] The Phase 3 studies of patisiran (APOLLO and APOLLO-B) further highlight the rapid progression of cardiac disease manifestation observed in placebo-treated patients.[Adams 2018; Adams 2023] In the APOLLO study, the mean ratio of NT-proBNP at 18 months to baseline was 1.97 in the cardiac subpopulation in the placebo group. In the APOLLO-B study of patients with ATTR cardiomyopathy, the distance walked in the 6-minute test reduced by median of 21 meters among those in the placebo groups. These observations exemplify the rapid progression of the disease over a short period of time.

Important Comorbidities

Polyneuropathy

Patients with hATTR amyloidosis with polyneuropathy often have poor nutritional status and overall wasting due in part to severe gastrointestinal manifestations including frequent episodes of diarrhea.[Antunes 2014] 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 comorbidities. In addition to the ocular symptoms that present as manifestations of hATTR amyloidosis, dry eye has been reported, and decreases in visual acuity are noted as the disease progresses.[Ando 2013] Depression may also be an important comorbidity as a result of this debilitating disease.[Lopes 2015; Rousseau 2013]

Baseline comorbidities reported by APOLLO patients with hATTR amyloidosis with polyneuropathy (N=225) were generally consistent with the underlying disease of hATTR amyloidosis and were similar to baseline comorbidities reported by HELIOS-A patients with hATTR amyloidosis with polyneuropathy (N=164). In APOLLO patients, the most frequently reported (≥50% of patients overall) medical history conditions at baseline were in the System Organ Classes (SOCs) of Nervous system disorders (86.2%), Gastrointestinal disorders (71.1%), Cardiac disorders (66.7%), Surgical and medical procedures (60.0%), and Vascular disorders (56.2%). Eye disorders were reported by 44% of patients at baseline in APOLLO. In HELIOS-A patients, the most frequently reported (≥50% of patients overall) medical history conditions at baseline were in the SOCs of Nervous system disorders (84.8%), Gastrointestinal disorders (70.7%), Cardiac disorders (68.9%), Eye disorders (52.4%), and Vascular disorders (50.0%).

Cardiomyopathy

Patients living with ATTR amyloidosis with cardiomyopathy also share a constellation of comorbidities which may overlap or differ from patients with polyneuropathy. A recent meta-analysis examining 22 studies of musculoskeletal comorbidities of ATTR amyloidosis with cardiomyopathy identified carpal tunnel syndrome (>50%), spinal stenosis (3%-30% depending on type), and brachial biceps tendon rupture (33%-44%) as common comorbidities.[Formiga 2023] Similar comorbidities were identified in a Nordic study evaluating 169 patients in Norway, Sweden, Finland, and Denmark with ATTR amyloidosis with cardiomyopathy, with the addition of diabetes (10.1%) in the latter study.[Eldhagen 2023] In a Korean study of 175 newly diagnosed patients with ATTR amyloidosis with cardiomyopathy [Jang 2022], the most common cardiac manifestation was hypertension (51.3%), with the most common noncardiac manifestations noted as musculoskeletal disease (68%), depression/anxiety/insomnia (44%) and coexistent peripheral neuropathy (33.7%).[Jang 2022]

In the Phase 3 study of patisiran in patients with ATTR amyloidosis with cardiomyopathy (APOLLO-B; N=359), the most frequently reported (≥50% of patients overall) medical history conditions were in the SOCs of Cardiac disorders (94.7%), Eye disorders (63.5%), Vascular disorders (62.1%), and Nervous system disorders (55.4%). The specific medical history terms reported were generally consistent with the underlying disease of ATTR amyloidosis. Within cardiac medical history, atrial fibrillation was reported in 61.3% of patients in the patisiran group and 53.9% of patients in the placebo group, and pacemaker placement was reported in 22.1% of patients in the patisiran group and 27.5% of patients in the placebo group. Overall, 49.3% of patients also had a history of neuropathy/polyneuropathy. Of these, 91.0% reported sensory neuropathy, 13.6% reported motor neuropathy, and 16.4% reported autonomic neuropathy.

In the subgroup of patients not receiving tafamidis at baseline (vutrisiran monotherapy group) in the Phase 3 study of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy (HELIOS-B; N=395), the most frequently reported (≥50% of patients overall) medical history conditions were in the SOCs of Cardiac disorders (99.5%), Nervous system disorders (64.3%), Vascular disorders (62.5%), Metabolism and nutrition disorders (60.3%), Musculoskeletal and connective tissue disorders (54.9%), and Eye disorders (53.4%). The specific medical history terms reported were generally consistent with the underlying disease of ATTR amyloidosis.

Overall, 30.1% of patients also had a history of neuropathy/polyneuropathy. Of these, 93.3% reported sensory neuropathy, 15.1% reported motor neuropathy, and 10.9% reported autonomic neuropathy.

Abbreviations: 6MWT=6-minute walk test; ATTR amyloidosis=hereditary or wild-type transthyretin amyloidosis; EU=European Union; hATTR amyloidosis=hereditary transthyretin amyloidosis; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire - Overall Summary; LS=least squares; mNIS+7=modified neuropathy impairment score +7; mRNA=messenger ribonucleic acid; Norfolk Qol-DN=Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP=N-terminal pro b-type natriuretic peptide; NYHA=New York Heart Association; RNAi=ribonucleic acid interference; SC=subcutaneous; SD=standard deviation; SOC=System Organ Class; THAOS=Transthyretin Amyloidosis Outcomes Survey; TTR=transthyretin; US=United States; V30M=Valine to methionine variant at position 30 in human transthyretin gene; V122I=Valine to isoleucine variant at position 122 in human transthyretin gene; wt=wild type.

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Executive Summary of Important Nonclinical Findings

Vutrisiran binds to a conserved sequence in humans and monkeys, and thus is pharmacologically active in humans and monkeys, but not in rodents or rabbits. There were no target organs of toxicity identified nonclinically when vutrisiran was administered on a once monthly (qM) schedule. Nonadverse vutrisiran-related findings after qM vutrisiran administration were observed in the liver, kidney, injection sites, and inguinal lymph nodes. The liver is the primary site of vutrisiran uptake and accumulation. In mice, vacuolation, enlargement/swelling, degeneration/necrosis, and/or increased hepatocellular glycogen were observed and occasionally correlated with slight alterations in clinical pathology parameters and increases in liver weights. In rats, findings in liver included hepatocellular vacuolation, increased mitotic figures in hepatocytes, increased single cell necrosis, and increased basophilic foci of hepatocellular alteration and hepatocellular karyomegaly. In monkeys, basophilic granules in Kupffer cells and/or hepatocytes were observed and likely represent accumulation of vutrisiran in these cells.[Frazier 2015; Janas 2018] In the kidneys of rats, cytoplasmic basophilic granules, likely representing hematoxylin-stained vutrisiran, were present in the proximal tubules.[Frazier 2015; Janas 2018; Lenz 2018] The incidence and severity of this rat-specific finding did not progress with increased study duration. Transient (≤24 hours) edema and/or erythema was observed at the subcutaneous (SC) injection site in rats. Microscopically, injection site findings included infiltrates of mixed inflammatory cells and/or vacuolated macrophages. Vacuolated macrophages were also present in injection sites in mice (occasionally accompanied by fibroblast vacuolation) and in monkeys; the presence of these macrophages represented a normal phagocytic response. In the lymph nodes of mice, rats, and monkeys, microscopic findings of vacuolated macrophages were not associated with any degenerative changes or clinical pathology correlates, did not progress with chronic dosing, most likely reflected uptake of vutrisiran, and were partially or fully reversed. The no observed adverse effect levels (NOAELs) in the chronic repeat-dose studies were 150 mg/kg/qM in rats and 300 mg/kg/qM in monkeys, the highest doses evaluated.

Serum transthyretin (TTR) is a carrier of retinol binding protein (RBP), which facilitates transport of vitamin A in the blood. TTR also serves as a minor carrier for thyroxine (T4). Studies in monkeys confirmed the secondary pharmacological effects associated with reductions in TTR (up to 99%), namely reductions, relative to baseline, in vitamin A (up to 89%) and T4 (up to 48%). There were no findings in the eye, pituitary, or thyroid in monkeys (further explanation is provided in Table 3).

In the safety pharmacology study in monkeys, there were no observed effects on electrocardiogram or hemodynamic parameters, respiratory rate, or body temperature. Neurological parameters, evaluated during repeat-dose toxicity studies in monkeys, were unaffected by vutrisiran administration at doses ≤300 mg/kg (highest dose tested).

Evaluation of fertility (rats), embryo-foetal (rabbits), and postnatal development (rats) indicated no direct effects associated with exposure to vutrisiran; however, some adverse effects were noted in the rat embryo-foetal development study that were likely secondary to maternal toxicity/stress resulting from the exaggerated once daily dosing schedule during gestation. Vutrisiran was not teratogenic in either rats or rabbits. Vutrisiran was not mutagenic or clastogenic. In a 2-year carcinogenicity study in CD-1 mice in which mice received qM subcutaneous (SC) injections of vutrisiran at 0, 2, 6, or 13 mg/kg (males) or 0, 3, 9, or 18 mg/kg (females), a statistically significant trend for combined hepatocellular

adenomas/carcinomas was noted in females; however, there were no significant differences in the incidence of these neoplasms (ie, significant pairwise comparisons) between vutrisiran-treated females and controls. There were no preneoplastic lesions in liver or other vutrisiran-related neoplasms in females. There were no vutrisiran-related neoplastic findings in male mice at doses up to 13 mg/kg. The area under the curve (AUC)-based exposure margin at 13 mg/kg (qM) in male mice when normalized to the clinical q3M dosing schedule is 26× the human exposure at the maximum recommended human dose (MRHD). In a 2-year carcinogenicity study in Sprague-Dawley rats, rats received once-monthly SC doses of vutrisiran at 0, 4, 7.5, or 15 mg/kg (males) or 0, 6.0, 12.5, or 25 mg/kg (females). In addition, vutrisiran was administered via SC injection once every three months (q3M) to additional groups of males and females at 15 or 25 mg/kg, respectively. Vutrisiran was not carcinogenic in rats at the highest dose levels tested (15 mg/kg qM or 15 mg/kg q3M in males and 25 mg/kg qM or 25 mg/kg q3M in females). The AUC-based exposure margins at 15 mg/kg q3M and at 25 mg/kg q3M for male and female rats, respectively, are 18× and 29× the human exposure at the MRHD. When normalized to the q3M clinical dosing schedule, the AUC-based exposure margins at 15 mg/kg qM and at 25 mg/kg qM for male and female rats, respectively, are 57× and 52× the human exposure at MRHD. Vutrisiran is not considered to have immunostimulatory or immunotoxic potential.

Key safety findings from nonclinical studies and the relevance to human usage are summarised 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: In repeat-dose toxicity studies in mice, vacuolation, enlargement/swelling, degeneration/necrosis, and/or increased hepatocellular glycogen were observed and occasionally correlated with slight alterations in clinical pathology parameters and increases in liver weights. In the 13-week repeat-dose rat toxicity study, vacuolation, increased mitotic figures, necrosis, and basophilic foci were observed. With exception of the basophilic foci, these findings partially or fully reversed after a 12-week recovery. Similar findings were observed in the 6-month repeat-dose rat toxicity study, and in general, findings increased in incidence and/or severity. An exploratory 6-month study in rats evaluating dosing regimen (monthly vs every 3 months) suggests cumulative dose and/or schedule contribute to foci of hepatocellular alteration in rats, a finding not observed in other nonclinical species. In rats, there were no clinical pathology correlates to any of the hepatic findings and they were not considered to be adverse. In the 13-week repeat-dose toxicity study in monkeys, basophilic granules in Kupffer cells were seen at ≥100 mg/kg, which were partially	The liver is the primary site of vutrisiran uptake and accumulation. Nonadverse vutrisiran-related findings were observed in the liver in repeat-dose toxicity studies conducted in rats and monkeys following once-monthly (qM) subcutaneous (SC) dose administration. There was no progression with chronic dosing, and findings showed a trend of reversibility.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
reversed after a 12-week recovery. In the 9-month repeat-dose monkey toxicity study, basophilic granules in Kupffer cells and/or hepatocytes were observed at ≥30 mg/kg (females) or ≥100 mg/kg (males). The basophilic granules in Kupffer cells and/or hepatocytes likely represent accumulation of vutrisiran.[Frazier 2015; Janas 2018] These findings were not associated with any abnormal clinical pathology findings and were not considered to be adverse. In a dose range-finding reproductive study in pregnant rats, clinical pathology changes suggestive of altered liver function, hepatocellular injury, hepatobiliary alteration, and/or cholestasis were observed in females receiving weekly doses at 50 or 150 mg/kg prior to mating followed by daily doses during the period of organogenesis at 10 or 30 mg/kg. A subsequent study in nonpregnant female rats dosed daily for 12 days revealed similar findings. In the pivotal embryo-foetal development study in rats, vacuolation/degeneration, hypertrophy, and individual hepatocyte necrosis were seen at ≥10 mg/kg, with additional findings of focal/multifocal hepatocyte necrosis, infiltrates, and basophilic granules in Kupffer cells at 30 mg/kg. It should be noted that all of these findings in rats were associated with a highly exaggerated dosing schedule (once daily) during gestation relative to the once quarterly clinical dosing schedule. In the pivotal rat embryo-foetal development study, the no observed adverse effect level (NOAEL) for maternal toxicity was 10 mg/kg, which is 323 times the normalised maximum recommended human dose (MRHD) when adjusted for surface area.	
<u>Lymph Nodes:</u> Vacuolated macrophages were observed after once monthly (qM) dosing in mice (≥500 mg/kg), rats (females at ≥12 mg/kg, males at ≥40 mg/kg), and monkeys (≥30 mg/kg), and was reversible following a 12-week recovery period (rats and monkeys). These findings were not associated with any degenerative changes or any clinical or clinical pathology correlates, did not progress with chronic dosing, and most likely reflected uptake of vutrisiran.	Evaluation of AE data from the clinical trials reveals no safety concerns with respect to infections or malignancies related to abnormal lymphoid function.
<u>Adrenal Gland:</u> In a 12-week Tg-rasH2 wt mouse study, subcapsular cell hyperplasia was observed after 3 qM doses at ≥1000 mg/kg. This finding was not seen in any other nonclinical species evaluated. This finding	Clinical trial data revealed no safety concerns related to increased or decreased adrenal cortical function.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
was of unknown significance since it is a common background finding in Tg-rasH2 mice.[Boyle 2018]	
Kidney: Nonadverse, reversible, basophilic granules in the cytoplasm of renal proximal tubular epithelial cells were seen in rats at ≥40 mg/kg/qM, that were occasionally accompanied by vacuolation (≥50 mg/kg). In pregnant rats (30 mg/kg once daily for 12 days), hyaline droplet accumulation, vacuolation, and basophilic granules in the tubule cells and pigment in the tubular lumen were observed. The basophilic granules in the proximal tubules are a rat-specific finding and represent the uptake of vutrisiran.[Frazier 2015; Janas 2018; Lenz 2018]	Clinical trial data revealed no safety concerns related to renal function.
Pancreas: Interstitial edema, adipocyte necrosis, and infiltrates in adipose tissue were observed in pregnant rats that received vutrisiran once daily for 12 days at 30 mg/kg in the pivotal embryo-foetal development study. This finding was not observed in mice, rats, or monkeys receiving vutrisiran monthly. This finding was considered to be related to maternal toxicity/stress associated with the exaggerated once daily dosing schedule and may have been secondary to decreased serum protein/albumin that was observed in a previous 12-day dosing study at 30 mg/kg in female rats.[Duncan 1986]	Clinical trial data revealed no safety concerns related to pancreatic function.
Prostate: In the fertility and early embryonic development study in rats, reduction in absolute and relative prostate weights were observed at ≥30 mg/kg after once weekly (qw) administration. This finding correlated with decreased secretion in the prostate gland, observed microscopically, and reduced body weights. The prostate changes had no effects on fertility or sperm parameters. No prostate findings were observed in mice, rats, or monkeys receiving vutrisiran monthly.	Clinical trial data revealed no safety concerns related to prostate function.
Reproductive and Developmental Toxicity	
Fertility: In toxicity and fertility studies in rats, no effects on male or female fertility were observed. Embryo-Foetal and Developmental Toxicology: Embryo-foetal development studies have been performed in rats and rabbits during organogenesis. In pregnant rats, daily SC administrations of a rat active surrogate throughout organogenesis at	No impact on male or female fertility or embryo-foetal development was detected in animal studies. There are no data on the effects of vutrisiran on human fertility. No data are available on the use of vutrisiran in pregnant women or lactating women. The use of vutrisiran in pregnant or lactating women is considered missing

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
30 mg/kg (qw for 3 weeks prior to mating and once weekly during the period of organogenesis) elicited reductions in serum TTR protein (>95% from baseline), T4 (67% from control on Premating Day 14 and below the detection limits on GD 21), and vitamin A (≥72% from controls). There were no effects on mating, fertility, or embryo-fetal development. In pregnant rats, daily SC doses of vutrisiran at doses of 0, 3, 10, or 30 mg/kg/day during organogenesis resulted in maternal toxicity at ≥10 mg/kg/day which was considered adverse at 30 mg/kg/day and reductions in fetal weight at ≥10 mg/kg. The vutrisiran-related foetal skeletal variations were not considered adverse, and no vutrisiran-related foetal malformations were observed. The NOAEL for maternal toxicity is 10 mg/kg/day and the developmental NOAEL is 3 mg/kg/day. In pregnant rabbits, daily SC administrations of vutrisiran throughout organogenesis at doses up to 30 mg/kg/day resulted in minimum decreases in maternal food consumption and absolute body weights when compared to controls at doses ≥3 mg/kg/day. There were no vutrisiran-related foetal findings. The maternal and developmental NOAEL was concluded to be 30 mg/kg/day. Peri/Postnatal Developmental Toxicity in Rats: There were no effects on gestation, parturition, lactation, or maternal behaviour or on peri/postnatal development in offspring at ≤20 mg/kg (highest dose tested) when vutrisiran administered on GDs 7, 13, and 19 and on lactation days 6, 12, and 18.	information as summarised in Section Part II: Module SVII.
Carcinogenicity and Genotoxicity	
Carcinogenicity: In a 2-year carcinogenicity study in CD-1 mice in which mice received qM SC injections of vutrisiran at 0, 2, 6, or 13 mg/kg (males) or 0, 3, 9, or 18 mg/kg (females), a statistically significant trend for combined hepatocellular adenomas/carcinomas was noted in females; however, there were no significant differences in the incidence of these neoplasms (ie, significant pairwise comparisons) between vutrisiran-treated females and controls. There were no preneoplastic lesions in liver or other vutrisiran-related neoplasms in females. There were no vutrisiran-related neoplastic findings in male mice at doses up to 13 mg/kg. The area under the curve (AUC)-based exposure margin at 13 mg/kg in male mice when normalized to the clinical every	Based on the nonclinical program, there is no evidence to suggest potential for carcinogenicity in humans. Vutrisiran is not carcinogenic in rats or in male mice. In female mice, the vutrisiran-related trend in combined hepatocellular adenoma/carcinoma is considered unlikely to be of relevance to humans given the lack of similar findings in male mice, the absence of preneoplastic findings (ie, foci of cellular alteration), the absence of ongoing liver injury, the lack of genotoxicity, and the absence of reactive metabolites.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
three months (q3M) dosing schedule is 26× the human exposure at the MRHD. Vutrisiran was not carcinogenic in Sprague-Dawley rats administered SC doses once monthly at 0, 4, 7.5, or 15 mg/kg (males) or 0, 6, 12.5, or 25 mg/kg (females) or once every 3 months at 15 or 25 mg/kg (males and females, respectively). The AUC-based exposure margins at 15 mg/kg q3M and at 25 mg/kg q3M for male and female rats, respectively, are 18× and 29× the human exposure at the MRHD. When normalized to the q3M clinical dosing schedule, the AUC-based exposure margins at 15 mg/kg qM and at 25 mg/kg qM for male and female rats, respectively, are 57× and 52× the human exposure at MRHD.	The pharmacologic mode of action of vutrisiran is not considered to pose an increased risk of carcinogenicity.
Genotoxicity: GLP-compliant genotoxicity studies (bacterial reverse mutation, human peripheral blood lymphocyte chromosome aberrations, and rat bone marrow micronucleus) indicated that vutrisiran is neither genotoxic nor clastogenic.	Based on the findings from the nonclinical programme, there is no evidence that vutrisiran has a potential for genotoxicity in humans.
Drug Abuse and Liability Assessment	
No dedicated dependence studies were conducted with vutrisiran. 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, behaviour, or neurological examinations.	There is no evidence that vutrisiran has a potential for abuse in humans, based on findings in both the nonclinical and clinical programmes.
Safety Pharmacology	
Based on its physiochemical properties, vutrisiran has a low likelihood of direct cardiac ion channel interactions or delaying ventricular repolarization. Single SC doses at ≤300 mg/kg (highest dose tested) did not result in QT prolongation or electrocardiogram abnormalities in monkeys. No effects were seen on the respiratory or cardiovascular systems at ≤300 mg/kg. No CNS-related observations were noted in repeat-dose monkey toxicity studies at ≤300 mg/kg/qM (highest dose tested).	There is no evidence that vutrisiran has a potential for neurological, respiratory, or cardiovascular (including QT interval prolongation or delaying ventricular repolarization) effects in humans, based on findings in the nonclinical programme.
Other Toxicity-related Information	
Drug-drug interactions: Vutrisiran is not a substrate of cytochrome P_{450} (CYP) enzymes. Vutrisiran showed no direct or time-dependent inhibition toward any of the CYP isoforms evaluated in vitro. CytochromeP_{450} induction and transporter substrate/inhibition studies have not been conducted with vutrisiran; however, in vitro CYP induction and transporter data for similar siRNA-GalNAc conjugate molecules	No clinical drug-drug interaction studies have been performed. Vutrisiran is not expected to cause interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes, or to modulate the activity of transporters. Therefore, vutrisiran is not expected to have clinically significant interactions with other medicinal products.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
suggest a low potential for drug-drug interaction with vutrisiran.[Ramsden 2019]	
Secondary pharmacology: Repeated administration of vutrisiran to monkeys at ≤300 mg/kg/qM resulted in mean maximum reductions, relative to baseline, in vitamin A (up to 89%) and T4 (up to 48%) as well as mean maximum reductions in the primary pharmacodynamics effect of serum TTR (up to 99%). There were no effects on the eye, pituitary, or thyroid gland.	The risk of development of clinical consequences of vitamin A deficiency, including delayed symptoms, in patients receiving vutrisiran is expected to be low, as transport and tissue uptake of vitamin A can occur in the absence of retinol binding protein (RBP).[Episkopou 1993; van Bennekum 2001] As was done in the clinical studies, patients will be instructed to take the daily recommended amount (2500-3000 IU) of supplemental vitamin A. Because of a theoretical risk, despite the lack of evidence in the clinical development programme, clinical consequences of vitamin A deficiency, including delayed symptoms, is addressed as an important potential risk as summarised in Section Part II: Module SVII.
Immunogenicity: Anti-drug antibodies (ADAs), measured as immunoglobulin G (IgG), immunoglobulin M (IgM), or IgG+IgM directed against vutrisiran were evaluated in rats and monkeys. There were no apparent effects on exposure or any associated clinical signs. In the 6-month study in rats, ADAs were not detected in any samples. In the 9-month study in monkeys, ADAs were detected 8/32 monkeys (1/8 control, 2/8 at 30 mg/kg, 5/8 at 100 mg/kg, 0/8 at 300 mg/kg), with 3 samples positive at baseline (including 1 control) suggesting pre-existing cross-reactive antibodies, and with all titers being ≤100.	Immunogenicity to drugs in nonclinical species is not generally predictive of the potential for immunogenicity in humans. Immunogenicity has been further evaluated in clinical studies. The presence of ADAs had no impact on the safety or efficacy of vutrisiran.
Immunostimulation: Vutrisiran is not considered to have an immunostimulatory potential based on evaluations in vitro in a human whole blood assay and in vivo in monkeys.	There is no evidence from nonclinical studies that vutrisiran has a potential for immunostimulation in humans.

Abbreviations: ADA=Anti-drug antibody; AE=adverse event; AUC=area under the curve; CNS=central nervous system; CYP=cytochrome P_{450}; GD=gestation day; GalNAc=*N*-acetylgalactosamine; GLP=Good Laboratory Practice; IgG=immunoglobulin G; IgM=immunoglobulin M; MRHD=maximum recommended human dose; NOAEL=No observed adverse effect level; qM=once monthly; q3M=once every three months; qw=once weekly; RBP=retinol binding protein; SC=subcutaneous; siRNA=small interfering ribonucleic acid; T4=thyroxine; TTR=transthyretin; wt=wild type.

Nonclinical findings that have relevance to humans are the following:

- Important potential risk:
  - Clinical consequences of vitamin A deficiency, including delayed symptoms

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

In this RMP, data from the following 3 studies in the vutrisiran clinical development programme are considered for the evaluation of the safety profile of vutrisiran:

- **ALN-TTRSC02-001 (Study 001)** is a completed, Phase 1, randomised, single-blind, placebo-controlled, single-ascending dose study to evaluate the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of vutrisiran in healthy adult volunteers.
- **ALN-TTRSC02-002 (Study 002; HELIOS-A)** is an ongoing, global, Phase 3, randomised, open-label study designed to evaluate efficacy, safety, PK, and PD of vutrisiran in adult patients with hATTR amyloidosis with polyneuropathy. Patients were randomised 3:1 to vutrisiran or patisiran, which serves as a reference comparator. Patisiran (ONPATTRO) is a marketed small interfering ribonucleic acid (siRNA) therapeutic that targets *TTR* mRNA.
- **ALN-TTRSC02-003 (Study 003; HELIOS-B)** is an ongoing, global, Phase 3, randomised, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, PK, and PD of vutrisiran in adult patients with ATTR amyloidosis (wtATTR or hATTR) with cardiomyopathy. Patients were randomised 1:1 to vutrisiran or placebo.

Please refer to Table 4 for further details.

External Reference Placebo Group from the APOLLO Study in Patients with hATTR Amyloidosis with Polyneuropathy

The Phase 3 HELIOS-A study included a comparison of vutrisiran data to placebo data from the Phase 3 multicenter, multinational, randomised, double-blind, placebo-controlled study of patisiran in patients with hATTR amyloidosis with polyneuropathy (Study ALN-TTR02-004; APOLLO). The APOLLO placebo group (n=77 patients treated with placebo for a total of 96.1 patient-years of exposure) served as an external reference to reflect the type of disease-related events commonly reported in this population, as APOLLO was conducted in a similar patient population as HELIOS-A. This external reference for safety was utilised for the characterisation of the safety profile of vutrisiran, as described in Section Part II: Module SVII.

Table 4: Clinical Studies with Vutrisiran Considered for the Evaluation of the Safety Profile of Vutrisiran

Study Number Phase Status	Study Description/ Number of Study Centers and Regions	Dose and Duration	Number Dosed		Objective
			Comparator	Vutrisiran	
Healthy Volunteers					
Phase 1 single-ascending dose					
ALN-TTRSC02-001 (Study 001) Complete	Phase 1, randomised, single-blind, placebo-controlled, single-ascending dose study 1 center in the UK	Placebo or SC vutrisiran (5, 25, 50, 100, 200, or 300 mg) Single dose	20 (placebo)	60	To evaluate the safety and tolerability of single doses of vutrisiran
HELIOS-A: Patients with hATTR Amyloidosis with polyneuropathy					
Phase 3					
ALN-TTRSC02-002 (Study 002, HELIOS-A) Ongoing; primary Month 18 analysis complete	Phase 3, randomised (3:1), open-label study in patients with hATTR amyloidosis with a reference comparator patisiran group. For efficacy endpoints, an external placebo control was used from the completed, randomised, double-blind, Phase 3 APOLLO patisiran study in patients with hATTR amyloidosis with polyneuropathy. The study consists of 2 parts: • A completed 18-month Treatment Period (vutrisiran or patisiran); primary analysis at M9 for efficacy • An ongoing Randomised Treatment Extension Period (up to 42 months)[a]; all patients receive vutrisiran 57 centers in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Cyprus, France, Germany, Greece, Italy, Korea, Japan, Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, UK, US	• Vutrisiran 25 mg q3M (SC) or • Patisiran 0.3 mg/kg q3w (IV); plus, premedications 60 min prior to the infusion (ie, corticosteroid, antihistamines, and paracetamol) Total duration: up to 78[a] months	18-month Treatment Period: 42 (patisiran, reference comparator)	18-month Treatment Period: 122 Treatment Extension Periods: 160[b] (including 38 patients initially randomised to patisiran who then switched to vutrisiran during the treatment extension periods)	To determine the efficacy of vutrisiran in patients with hATTR amyloidosis with polyneuropathy by evaluating the effect on neurologic impairment

Study Number Phase Status	Study Description/ Number of Study Centers and Regions	Dose and Duration	Number Dosed		Objective
			Comparator	Vutrisiran	
HELIOS-B: Patients with ATTR Amyloidosis (hATTR or wtATTR) with cardiomyopathy					
Phase 3					
ALN-TTRSC02-003 (Study 003, HELIOS-B) Ongoing; primary analysis (up to 36 months) complete	Phase 3 randomised (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vutrisiran in patients with ATTR amyloidosis (hATTR or wtATTR) with cardiomyopathy. The study consists of 2 periods: • A completed double-blind period: eligible patients randomised 1:1 to receive vutrisiran or placebo for up to 36 months. • An ongoing open-label treatment extension (OLE) period: all patients will receive vutrisiran up to 24 months[c] 87 study centers in 26 countries in North America, South America, Europe, Asia, and Australia	• Vutrisiran or placebo 25 mg q3M (SC) (ratio 1:1) during the DB period (up to 36 months) • OLE period: vutrisiran 25 mg q3M up to 24 months Total duration: up to 60 months [c]	Double-Blind Period: Placebo: 328	Double-Blind Period: 326 Open-Label Extension Period: 547[c] (221 (placebo/vutrisiran)	To determine the efficacy and safety of vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy by evaluating its effect on outcomes and cardiac manifestations.

Abbreviations: ATTR amyloidosis=transthyretin amyloidosis; DB=double blinded; hATTR=hereditary transthyretin amyloidosis; IV=intravenous; min=minutes; OLE=open-label treatment extension period; q3M=once every 3 months; q3w=once every 3 weeks; SC=subcutaneous; UK=United Kingdom; US=United States; wtATTR=wild-type transthyretin amyloidosis.

[a] Upon implementation of Protocol Amendment 4, following the 18-Month Treatment Period, patients were randomised 1:1 to receive vutrisiran at a dose of 25 mg every 3 months or 50 mg every 6 months during the 42-month Randomised Treatment Extension (RTE) Period. Upon implementation of Amendment 6, the vutrisiran 50 mg dose was removed and patients receiving vutrisiran 50 mg every 6 months were transitioned to vutrisiran 25 mg every 3 months at their next scheduled dosing visit in the RTE period.

[b] This includes all patients who received at least 1 dose of vutrisiran, including patients treated with vutrisiran during the 18-month Treatment Period (N=122) and patients initially treated with patisiran during the 18-Month Treatment Period (N=38; data cutoff date 23 February 2024).

[c] Upon implementation of Protocol Amendment 3, following the DB Period, patients were randomised 1:1 to receive vutrisiran at a dose of 25 mg every 3 months or 50 mg every 6 months during the up to 2 year Open-label RTE period. Upon implementation of Amendment 4, the 50 mg dose was removed and patients receiving vutrisiran 50 mg every 6 months were transitioned to receive vutrisiran 25 mg every 3 months at their next scheduled dosing visit in the OLE Period. Upon entering the OLE Period, all patients received 25 mg every 3 months. Study data cutoff date: 08 May 2024.

Exposure in ATTR amyloidosis with cardiomyopathy

A total of 547 patients with ATTR amyloidosis with cardiomyopathy have received at least 1 dose of vutrisiran in HELIOS-B as of 08 May 2024. Of these 547 patients, 326 patients were randomised to receive vutrisiran during the DB Period and an additional 221 patients initially randomised to placebo have received at least 1 dose of vutrisiran in the OLE Period.

Patient exposure to vutrisiran in HELIOS-B (DB Period + OLE Period) by duration, by age categories and sex, and by ethnic or racial origin are presented in Table 5, Table 6, and Table 7, respectively.

Table 5: Duration of Patient Exposure to Vutrisiran in HELIOS-B

Duration of Exposure (N=547)	Patients Number (%)	Patient-years[a]
On vutrisiran for at least:		
≥1 day	547 (100.0)	979.7
≥6 months	357 (65.3)	937.0
≥12 months	294 (53.7)	894.1
≥18 months	278 (50.8)	874.4
≥24 months	267 (48.8)	855.8
≥30 months	257 (47.0)	833.0
≥36 months	183 (33.5)	622.6
≥42 months	57 (10.4)	208.7
≥48 months	4 (0.7)	16.8

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

Source: Study 003 (Data cutoff date: 08 May 2024).

Table 6: Patient Exposure to Vutrisiran by Age Group and Sex in HELIOS-B

Age Group	Male (n=507)		Female (n=40)	
	Patients Number (%)	Patient-years[a]	Patients Number (%)	Patient-years[a]
≥18 to 64 years	25 (4.9)	66.1	5 (12.5)	11.9
≥65 to 74 years	136 (26.8)	274.7	13 (32.5)	22.3
≥75 years	346 (68.2)	560.5	22 (55.0)	44.3
Total	507 (100.0)	901.2	40 (100.0)	78.5

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

Source: Study 003 (Data cutoff date: 08 May 2024).

Table 7: Patient Exposure to Vutrisiran by Racial Origin in HELIOS-B

Racial Origin	Patients Number (%)	Patient-years[a]
Asian	32 (5.9)	53.8
Black or African American	35 (6.4)	62.7
White	465 (85.0)	837.7
Other	4 (0.7)	5.9
Not reported	11 (2.0)	19.6

[a] Patient-years are defined as the sum of the years that patients in the study population have been exposed to vutrisiran.
Source: Study 003 (Data cutoff date: 08 May 2024).

Cumulative Exposure in hATTR amyloidosis with polyneuropathy and ATTR amyloidosis with cardiomyopathy

The safety profile of vutrisiran is evaluated based on the pooled data from the ongoing HELIOS-A and HELIOS-B studies, data cutoff dates 23 February 2024 and 08 May 2024, respectively. The overall cumulative patient exposure to vutrisiran based on the pooled data (N=707) was 1518.9 patient-years.

Pooled Clinical trial exposure to vutrisiran in the ATTR amyloidosis patients in HELIOS-A and HELIOS-B by duration, by age categories and sex, and by racial origin are presented in Table 8, Table 9, and Table 10.

Table 8: Duration of Patient Exposure to Vutrisiran in HELIOS-A and HELIOS-B

Duration of Exposure	HELIOS-A Study[a] N=160		HELIOS-B Study[b] N=547		Total N=707	
	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]
On vutrisiran for at least:						
≥1 day	160 (100.0)	539.2	547 (100.0)	979.7	707 (100.0)	1518.9
≥6 months	156 (97.5)	538.3	357 (65.3)	937.0	513 (72.6)	1475.2
≥12 months	154 (96.3)	536.9	294 (53.7)	894.1	448 (63.4)	1430.9
≥18 months	152 (95.0)	534.4	278 (50.8)	874.4	430 (60.8)	1408.8
≥24 months	138 (86.3)	509.6	267 (48.8)	855.8	405 (57.3)	1365.4
≥30 months	125 (78.1)	480.4	257 (47.0)	833.0	382 (54.0)	1313.4
≥36 months	111 (69.4)	443.1	183 (33.5)	622.6	294 (41.6)	1065.7
≥42 months	94 (58.8)	387.5	57 (10.4)	208.7	151 (21.4)	596.2
≥48 months	62 (38.8)	266.9	4 (0.7)	16.8	66 (9.3)	283.7
≥54 months	8 (5.0)	37.1	0	0	8 (1.1)	37.1

Abbreviations: hATTR amyloidosis=Hereditary transthyretin amyloidosis; wtATTR amyloidosis=wild-type transthyretin amyloidosis.

[a] Includes patients with hATTR amyloidosis with polyneuropathy who received vutrisiran in Study 002.

[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received vutrisiran in Study 003.

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

Source: Study 002 (Data cutoff date: 23 Feb 2024) and Study 003 (Data cutoff date: 08 May 2024).

Table 9: Patient Exposure to Vutrisiran by Age Group and Sex in HELIOS A and HELIOS-B

Age group	HELIOS-A Study[a] N=160				HELIOS-B Study[b] N=547				Total N=707			
	Male (n=102)		Female (n=58)		Male (n=507)		Female (n=40)		Male (n=609)		Female (n=98)	
	Patients Number (%)	Patient-years[c]	Patients Number (%)	Patient-years[c]	Patients Number (%)	Patient-years[c]	Patients Number (%)	Patient-years[c]	Patients Number (%)	Patient-years[c]	Patients Number (%)	Patient-years[c]
≥18 to 64 years	61 (59.8)	221.4	40 (69.0)	134.2	25 (4.9)	66.1	5 (12.5)	11.9	86 (14.1)	287.5	45 (45.9)	146.1
≥65 to 74 years	37 (36.3)	116.2	14 (24.1)	44.8	136 (26.8)	274.7	13 (32.5)	22.3	173 (28.4)	390.8	27 (27.6)	67.2
≥75 years	4 (3.9)	7.9	4 (6.9)	14.6	346 (68.2)	560.5	22 (55.0)	44.3	350 (57.5)	568.4	26 (26.5)	58.9
Total (%)	102 (100.0)	345.5	58 (100.0)	193.7	507 (100.0)	901.2	40 (100.0)	78.5	609 (100.0)	1246.7	98 (100.0)	272.2

Abbreviations: hATTR amyloidosis=Hereditary transthyretin amyloidosis; wtATTR amyloidosis=wild-type transthyretin amyloidosis.

[a] Includes patients with hATTR amyloidosis with polyneuropathy who received vutrisiran in Study 002.

[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received vutrisiran in Study 003.

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

Source: Study 002 (Data cutoff date: 23 Feb 2024) and Study 003 (Data cutoff date: 08 May 2024).

Table 10: Patient Exposure to Vutrisiran by Racial Origin in HELIOS-A and HELIOS-B

Race Origin	HELIOS-A Study[a] N=160		HELIOS-B Study[b] N=547		Total N=707	
	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]
Asian	29 (18.1)	97.0	32 (5.9)	53.8	61 (8.6)	150.8
Black or African American	6 (3.8)	17.1	35 (6.4)	62.7	41 (5.8)	79.8
White	113 (70.6)	380.9	465 (85.0)	837.7	578 (81.8)	1218.5
Other	11 (6.9)	40.1	4 (0.7)	5.9	15 (2.1)	46.0
More than one race	1 (0.6)	4.2	0	0	1 (0.1)	4.2
Not Reported	0	0	11 (2.0)	19.6	11 (1.6)	19.6

Abbreviations: hATTR amyloidosis=Hereditary transthyretin amyloidosis; wtATTR amyloidosis=wild-type transthyretin amyloidosis.
[a] Includes patients with hATTR amyloidosis with polyneuropathy who received vutrisiran in Study 002.
[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received vutrisiran in Study 003.
[c] Patient-years are defined as the sum of the years that patients in the study population have been exposed to vutrisiran.
Source: Study 002 (Data cutoff date: 23 Feb 2024) and Study 003 (Data cutoff date: 08 May 2024).

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

The exclusion criteria used in the pivotal Phase 3 placebo-controlled studies (HELIOS-A in patients with polyneuropathy and HELIOS-B in patients with cardiomyopathy who are representative of the overall population with the disease) were selected primarily to enroll patients able to withstand the rigors of participating in a clinical study, and designed to ensure patient safety where the impact of vutrisiran is unknown (eg, during pregnancy), and to avoid enrolling patients with medical conditions or treatments that could potentially confound the assessment of the safety or efficacy of vutrisiran.

Key exclusion criteria from these studies are presented in Table 11 with a determination of whether the criterion is considered as missing information.

Other important exclusion criteria from HELIOS-A and HELIOS-B that were designed to ensure patients could participate in the study or to avoid confounding efficacy and safety results not presented in Table 11 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 vutrisiran than the overall population.

Both HELIOS-A and HELIOS-B

- Current or future participation in another investigational device or drug study, scheduled to occur during this study, or has received an investigational agent or device within 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to dosing (Day 1).
- Received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR amyloidosis.
- Taking diflunisal, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to dosing (Day 1) (HELIOS-A); or if previously on any of these agents including ursodeoxycholic acid, must have completed a 30-day wash-out prior to dosing (Day 1) (HELIOS-B).
- Acute coronary syndrome or unstable angina within the past 3 months.
- Untreated hypo- or hyperthyroidism.
- Had known human immunodeficiency virus infection; evidence of acute or chronic hepatitis C virus or hepatitis B virus infection; or an active infection requiring systemic antiviral, antiparasitic or antimicrobial therapy that will not be completed prior dosing (Day 1).
- Known history of alcohol abuse within the last 12 months before screening or daily heavy consumption.
- History of intolerance to SC injection(s).

HELIOS-A Only

- Vitamin B_{12} deficiency.
- If currently taking tafamidis, must have completed a 14-day wash-out prior to dosing (Day 1).
- Other known causes of sensorimotor or autonomic neuropathy.
- Uncontrolled clinically significant cardiac arrhythmia or unstable angina.
- Type I diabetes (any length of time).
- Type II diabetes (for ≥5 years).
- An anticipated survival less than 2 years.
- Had (within 3 months) or was planning a major surgery.
- 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).

HELIOS-B Only

- While tafamidis is an allowed concomitant medication in HELIOS-B, the background tafamidis subgroup for whom the Investigator actively planned or anticipated commencing treatment with tafamidis either during the Screening Period or the first 12 months following randomisation, were not eligible for the trial. Note: The background tafamidis subgroup includes patients who have never taken tafamidis and those who have previously been on tafamidis but have not received any tafamidis for at least 30 days before the Screening Visit.
- Required treatment with or is unwilling to avoid any concurrent treatment with diflunisal, non-dihydropyridine calcium channel blockers (eg, verapamil, diltiazem), ursodeoxycholic acid/tauroursodeoxycholate/doxycycline, or TTR lowering agents (eg, patisiran, inotersen).
- Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease (eg, prior myocardial infarction with documented history of cardiac enzymes and ECG changes) that the Investigator feels is a significant contributor or the predominant cause of the patient's heart failure.
- Unstable congestive heart failure (CHF) (including patients who require adjustment of existing diuretics or addition of new diuretics at time of Screening for purposes of achieving optimal management of CHF).
- Had history of sustained ventricular tachycardia or aborted ventricular fibrillation; or atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
- Had persistent elevation of systolic (>170 mmHg) or diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.

Table 11: Key Exclusion Criteria from the Pivotal, Phase 3 HELIOS-A and HELIOS-B Studies

Criteria	Reason for Exclusion	Is It Considered To Be Included As Missing Information?	Rationale If Not Considered Missing Information
HELIOS-A Study (hATTR amyloidosis with polyneuropathy) and HELIOS-B Study (ATTR amyloidosis with cardiomyopathy)			
Known primary amyloidosis (AL amyloidosis), other (non-hATTR) forms of amyloidosis or clinical evidence of leptomeningeal amyloidosis	Because vutrisiran specifically reduces serum TTR, it is unlikely to benefit patients with other non-TTR mediated forms of amyloidosis. Furthermore, vutrisiran is not distributed to the CNS and would not be effective in leptomeningeal amyloidosis. This exclusion criterion aligns with the inclusion criterion defining the qualified population as patients with hATTR amyloidosis.	No	Vutrisiran would not be expected to be effective in these conditions. These conditions are not within the indication for the drug.
Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73m^2 (using MDRD formula)	To avoid confounding the assessment of efficacy and safety of vutrisiran.	No	Vutrisiran would not be expected to have an altered safety profile in patients with severe renal impairment or ESRD based on the observations that mild or moderate renal impairment did not affect the PK/PD of vutrisiran, and the kidneys are not the target organs nor is vutrisiran mainly renally eliminated
Female patients who were pregnant or were considering becoming pregnant during the study	Unknown effect	Yes	Not applicable
Female patients who were breastfeeding	Unknown effect	Yes	Not applicable

Criteria	Reason for Exclusion	Is It Considered To Be Included As Missing Information?	Rationale If Not Considered Missing Information
HELIOS-A Study (hATTR amyloidosis with polyneuropathy)			
Prior liver transplant or is planning to undergo liver transplant during the study period	Due to the comorbidities that are often associated with patients who have received liver transplants and the necessary immunosuppressive therapies, these patients were excluded to avoid confounding the assessment of the safety and efficacy of vutrisiran	No	Vutrisiran would not be expected to have an altered safety profile in patients with prior liver transplant based on the mechanism of lowering variant and wild type TTR as well as documented experience with patisiran in this population.
NYHA heart failure classification >II	To avoid confounding the safety assessment of vutrisiran by including patients with advanced heart failure.	No	In HELIOS-A, an evaluation of cardiac events in patients with a history of cardiac involvement revealed no evidence of a different safety profile vs the overall study population.
Any of the following: • ALT and/or AST >1.5 × ULN • Total bilirubin >ULN (>1.5 ULN with Gilbert's Syndrome) • INR >1.2 (patients on anticoagulant therapy with an INR of ≤3.5 were allowed)	Vutrisiran is targeted to the liver. To avoid confounding the assessment of efficacy and safety of vutrisiran.	Yes	Not applicable
HELIOS-B Study (ATTR amyloidosis with cardiomyopathy)			
Prior or anticipated (during the first 12 months after randomisation) heart, liver or other organ transplant or implantation of left-ventricular assist device.	Due to the comorbidities that are often associated with patients who have received left-ventricular assist devices and organ transplants, as well as the necessary immunosuppressive therapies for transplant recipients, these patients were excluded to	No	Vutrisiran would not be expected to have an altered safety profile in patients with prior organ transplant based on the mechanism of lowering variant and wild type TTR as well as documented

Criteria	Reason for Exclusion	Is It Considered To Be Included As Missing Information?	Rationale If Not Considered Missing Information
	avoid confounding the assessment of the safety and efficacy of vutrisiran		experience with patisiran in this population.
Advanced NYHA Class III heart failure and ATTR Amyloidosis Disease Stage 3 (defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min) or NYHA Class IV	To avoid confounding the safety assessment of vutrisiran by including patients with advanced heart failure.	No	Although patients with advanced NYHA heart failure classification III and NAC ATTR amyloidosis disease stage III (NAC-III) (characterized by NT-proBNP >3000 ng/L and eGFR <45 mL/min) or with NYHA Class IV were excluded from enrollment in the HELIOS-B study, 62 patients (26 randomised to vutrisiran and 36 to placebo) of the 655 total HELIOS-B enrolled patients (9.5%) progressed to NYHA Class IV and/or to NYHA Class III plus NAC-III during the double-blind period. Fewer vutrisiran than placebo patients progressed to NYHA Class IV, 3 vs. 10, or to NYHA Class III/NAC-III, 24 vs. 29. There were no cardiac safety concerns in patients in the HELIOS-B study. Exploratory analyses of prognostic cardiac biomarkers, such as NT-proBNP, along with disease staging (ATTR amyloidosis disease stage), provided additional evidence supporting the disease stabilization effect of vutrisiran and the positive

Criteria	Reason for Exclusion	Is It Considered To Be Included As Missing Information?	Rationale If Not Considered Missing Information
			impact of reducing circulating TTR levels on the pathophysiology of ATTR cardiomyopathy.
Any of the following: 1. AST or ALT levels >2.0 × ULN, 2. Total bilirubin >2.0 × ULN, 3. International normalized ratio (INR) >1.5 (unless patients were on anticoagulant therapy in which case excluded if INR >3.5).	Vutrisiran is targeted at the liver. To avoid confounding the assessment of efficacy and safety of vutrisiran.	Yes	Not applicable

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ATTR=hereditary or wild-type Transthyretin amyloidosis; CNS=central nervous system; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; hATTR=hereditary transthyretin amyloidosis; INR=international normalised ratio; MDRD=Modification of Diet in Renal Disease; NAC=National Amyloidosis Centre; NT-proBNP=*N*-terminal pro b-type natriuretic peptide; NYHA=New York Heart Association; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; ULN=upper limit of normal; TTR=transthyretin.

SIV.2 Limitation to Detect Reactions in Clinical Trial Development Programme

As of the data cutoff dates of 23 February 2024 for HELIOS-A and 08 May 2024 for HELIOS-B, 707 patients with either wtATTR or hATTR amyloidosis were exposed to vutrisiran for approximately 1518.9 person-years Table 8. This pooled clinical safety data set would enable detection of very common (incidence of ≥1/10), common (≥1/100 to <1/10) ADRs, and uncommon ADRs with a frequency as low as 1 in 500 events per patient-years of exposure associated with vutrisiran. The vutrisiran 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 data, 513 patients have been exposed to vutrisiran for ≥6 months, 448 patients for ≥12 months, 430 patients for ≥18 months, 405 patients for ≥24 months, 382 patients for ≥30 months, 294 patients for ≥36 months, 151 patients for ≥42 months, 66 patients for ≥48 months, and 8 patients for ≥54 months Table 8. Based on the available data, there are no known vutrisiran 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 Trial Development Programme

Table 12 presents exposure data in special populations from the vutrisiran pooled data (N=707).

Table 12: Vutrisiran Exposure in Special Patient Populations in HELIOS-A and HELIOS-B

Type of Special Population	HELIOS-A Study[a] N=160		HELIOS-B Study[b] N=547		Total N=707	
	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]
Pregnant women	0	0	0	0	0	0
Breastfeeding women	0	0	0	0	0	0
Patients with relevant comorbidities at baseline:						
Renal impairment[d]						
Mild	45 (28.1)	147.4	210 (38.4)	428.8	255 (36.1)	576.2
Moderate	13 (8.1)	43.4	258 (47.2)	401.9	271 (38.3)	445.3
Severe	2 (1.3)	2.7	10 (1.8)	6.5	12 (1.7)	9.2
Hepatic impairment[e]						
Mild	11 (6.9)	38.4	81 (14.8)	141.9	92 (13.0)	180.3
Moderate	0	0	20 (3.7)	32.3	20 (2.8)	32.3
Severe	0	0	0	0	0	0
Cardiac impairment						
NYHA Classification I	20 (12.5)	59.4	76 (13.9)	158.7	96 (13.6)	218.2

Type of Special Population	HELIOS-A Study[a] N=160		HELIOS-B Study[b] N=547		Total N=707	
	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]	Patient Number (%)	Patient-years[c]
NYHA Classification II	49 (30.6)	173.9	398 (72.8)	729.3	447 (63.2)	903.2
NYHA Classification III	2 (1.3)	0.6	73 (13.3)	91.7	75 (10.6)	92.3
NYHA Classification IV	0	0	0	0	0	0
Subpopulation carrying relevant genetic variants (*TTR* genotype)						
V30M	74 (46.3)	243.5	4 (0.7)	12.2	78 (11.0)	255.7
Non-V30M	86 (53.8)	295.7	50 (9.1)	88.5	136 (19.2)	384.2
PND score ≥3b	16 (10.0)	53.8	6 (1.1)	1.5	22 (3.1)	55.3

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; eGFR=estimated glomerular filtration rate; hATTR=hereditary transthyretin 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 in human transthyretin gene.

Note: Patients who were pregnant or breastfeeding were excluded from HELIOS-A and HELIOS-B studies and there were no reports of pregnancy during the studies.

[a] Includes patients with hATTR amyloidosis with polyneuropathy who received vutrisiran in Study 002.

[b] Includes patients with wtATTR and hATTR amyloidosis with cardiomyopathy who received vutrisiran in Study 003.

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

[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=15 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 and any AST); Moderate: TBILI >1.5×ULN to ≤3.0×ULN and any AST; Severe: TBILI >3×ULN and any AST. Hepatic impairment for patients with Gilbert's syndrome; Mild: AST >ULN.

Source: Study 002 (Data cutoff date: 23 February 2024), and Study 003 (Data cutoff date: 08 May 2024).

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

Vutrisiran is indicated for the treatment of hATTR amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy. Cumulative global patient exposure to vutrisiran from marketing experience was calculated from internal sales data and patient counts collected since the International Birth Date of vutrisiran (13 June 2022) through 12 June 2024 (sales data) and 31 May 2024 (patient counts).

SV.1 Post-Authorisation Exposure

SV.1.1. Method used to calculate exposure

The following methodology for estimating postmarketing patient-years exposure to vutrisiran was used.

Vutrisiran is supplied in prefilled syringes, each containing 0.5 mL solution with 25 mg vutrisiran. The recommended dose of vutrisiran is 25 mg administered by SC injection q3M (quarterly; expected to be equal to 4 prefilled syringes per year).

Therefore, the following formula was used for the calculation of the estimated patient-years exposure to vutrisiran in the postmarketing experience:

$$\textbf{Number of patient-years} = \frac{\textbf{Number of prefilled syringes sold}}{\textbf{4 prefilled syringes per patient per year}}$$

The estimate of the number of patients treated with vutrisiran 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.1.2 Commercial Exposure to Vutrisiran

Cumulatively, as of the 12 June 2024, 13,387 prefilled syringes of vutrisiran had been sold worldwide, corresponding to an estimated 3346.5 patient-years exposure, and cumulatively, as of 31 May 2024, it was estimated that 3034 patients had been treated with vutrisiran.

The cumulative numbers of vutrisiran prefilled syringes sold, estimated patient-years exposure, and estimated number of patients treated are presented by region/country in Table 13.

Table 13: Cumulative Vutrisiran Sales and Estimated Patient Exposure Data From Marketing Experience

Region/Country	Number of Prefilled Syringes Sold	Estimated Patient Exposure (Patient-years)	Estimated Number of Patients Treated
Europe			
Austria	32	8	14
Belgium	17	4.25	12
Cyprus[a]	30	7.5	11
England, Wales & Northern Ireland	783	195.75	198
France[b]	881	220.25	235
Germany	751	187.75	182
Greece[a, c, d]	15	3.75	0
Italy	349	87.25	183
Poland[a, c, e]	1	0.25	0
Portugal	25	6.25	8
Scotland	71	17.75	16
Slovenia[a, c]	2	0.5	0
Spain	518	129.5	209
Sweden	153	38.25	57
Switzerland	41	10.25	15
North America			
USA	7133	1783	1434

Region/Country	Number of Prefilled Syringes Sold	Estimated Patient Exposure (Patient-years)	Estimated Number of Patients Treated
Rest of the World			
Argentina[a]	7	1.75	4
Bolivia[a]	6	1.5	3
Brazil	27	6.75	11
Israel[a]	6	1.5	4
Japan	2539	634.75	438
Total	**13,387**[f]	**3346.5**[g]	**3034**[h]

Abbreviation: USA=United States of America.

[a] Vutrisiran was being supplied via named-patient sales in these countries.

[b] Syringes distributed and patients treated under early access programs in France are reported under commercial exposure, as the product was supplied on a charged-for basis in those programs.

[c] No patients were treated in this country as of the data cutoff of this report.

[d] Prefilled syringes were shipped to Greece but were likely to be internally reallocated by the distributor to Cyprus.

[e] One prefilled syringe was shipped to Poland for a reimbursement dossier and not for a patient.

[f] For Argentina, Bolivia, Brazil, Cyprus, Greece, Israel, Poland, and Slovenia, the vial counts presented are from completed months corresponding to the following period: through May 2024 (cumulative).

[g] 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.

[h] Estimated number of patients treated: Through 31 May 2024 (cumulative).

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

Vutrisiran has low abuse potential based on its physiochemical properties, proposed mechanism of action, and lack of abuse or dependence properties observed in nonclinical and clinical studies. Vutrisiran is a chemically modified double-stranded siRNA that specifically targets variant and wild-type *TTR* mRNA. It is not chemically or pharmacologically similar to other drugs with known abuse potential and does not produce psychoactive effects such as sedation, euphoria, and mood changes.

Vutrisiran is predominantly taken up by the liver, and it is expected that its large molecular weight precludes passive permeation of the blood brain barrier. Nonclinical studies in Sprague-Dawley rats demonstrate that vutrisiran does not cross the blood brain barrier following a single 3 mg/kg dose of [^{3}H]-vutrisiran. There are no known transporters, receptors, or ion-gated channels for active uptake of vutrisiran into neurons. No vutrisiran-related neurobehavioural changes were noted in nonclinical toxicology studies.

Within the clinical development programme, there has been no evidence of abuse potential in patients treated with vutrisiran. In clinical studies, the safety profile of vutrisiran is consistent with the targeted mechanism of action and does not suggest any type of rewarding effects or other abuse-related behaviours. No cases of intentional overdose or drug abuse of vutrisiran have been reported in any clinical study.

Overall, based on the known physiochemical properties, composition, proposed mechanism of action, safety profile, and lack of abuse/dependence properties observed in nonclinical and clinical studies, vutrisiran is not considered a drug with potential for abuse.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

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

The safety profile of vutrisiran has been characterised based on data from the clinical development programme, nonclinical study observations, the patient population, the mechanism of action, and other relevant safety information to identify potential ADRs, risks, and missing information.

Adverse drug reactions for vutrisiran are defined as the most frequently reported adverse events (AEs) in vutrisiran-treated patients in the HELIOS-A study, while accounting for commonly reported AEs in the background disease population using the data from the external reference APOLLO placebo group. Additional considerations included temporal relationship and biologic plausibility. Adverse events were analysed using individual Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) and also grouping by medical concept. The frequency criterion included AEs (individual PT and/or grouped medical concept) reported in >5% of vutrisiran-treated patients in HELIOS-A and >3% higher frequency compared to the APOLLO placebo group (Study 002 CSR2 Table 14.3.1.2.1). Refer to 2.7.4, Section 5.9 and the Vutrisiran ADR Justification Document in Module 1 for details on selection of the following ADRs.

- Arthralgia was reported in 10.7% of vutrisiran-treated patients compared with none in the APOLLO placebo group.
- The medical concept of dyspnoea, which includes the PTs Dyspnoea, Dyspnoea exertional, and Dyspnoea paroxysmal nocturnal, was reported in 6.6% of vutrisiran-treated patients compared with no patients in the APOLLO placebo group.
- Based on the SC mode of vutrisiran administration, injection site reactions (ISRs) are an ADR, which were reported in 4.1% of vutrisiran-treated patients.
- The medical concept of pain in extremity, which includes the PTs Pain in extremity and Limb discomfort, was reported in 14.8% of vutrisiran-treated patients compared with 10.4% of patients in the APOLLO placebo group.
- Based on a gradual increase in mean levels of blood alkaline phosphatase (ALP) over time and a disproportionate incidence of elevations >1.5x upper limit of normal (ULN) in the vutrisiran group of HELIOS-A, ALP increased is an ADR, which was reported in 9.0% of vutrisiran-treated patients.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks that are not considered important for inclusion in the list of safety concerns for vutrisiran are outlined below.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

The adverse reactions outlined below were self-limiting and mostly mild in severity, and none caused treatment discontinuation. Considering the severity of hATTR amyloidosis,

these risks are not included as important safety concerns for management within the risk management plan (RMP).

Arthralgia

Arthralgia was reported in 13 (10.7%) vutrisiran-treated patients in HELIOS-A compared with none in the APOLLO placebo group (Study 002 CSR2 Table 14.3.1.2.1). Adverse events of arthralgia were mostly mild or moderate in severity, with 1 patient having a severe AE; none of the events were serious (Study 002 CSR2 Tables 14.3.1.4.1 and 14.3.1.5). No AEs of arthralgia led to treatment interruption, treatment discontinuation, or study withdrawal (Study 002 CSR2 Tables 14.3.1.6.1, 14.3.1.7.1, and 14.3.1.8.1). Adverse events of arthralgia did not increase over time (Study 002 CSR2 Table 14.3.1.2.3). Therefore, AEs of arthralgia are considered to have minimal clinical impact on patients in the context of the severity of hATTR amyloidosis and are not included as important safety concerns for risk management within the RMP.

Dyspnoea

The medical concept of dyspnoea was reported in 8 (6.6%) vutrisiran-treated patients in HELIOS-A compared with no patients in the APOLLO placebo group (Study 002 CSR2 Table 14.3.1.24). Adverse events within the dyspnoea medical concept were mild or moderate in severity; none of the events were severe or serious (Study 002 CSR2 Tables 14.3.1.4.1 and 14.3.1.5). No AEs of dyspnoea led to treatment interruption, treatment discontinuation, or withdrawal from a clinical study (Study 002 CSR2 Tables 14.3.1.6.1, 14.3.1.7.1, and 14.3.1.8.1). Adverse events of dyspnoea did not increase over time (Study 002 CSR2 Table 14.3.1.2.3). Therefore, AEs of dyspnoea are considered to have minimal clinical impact on patients in the context of the severity of hATTR amyloidosis and are not included as important safety concerns for risk management within the RMP.

Injection site reactions

Based on the SC mode of vutrisiran administration, ISRs are an ADR, which were reported in 5 (4.1%) vutrisiran-treated patients and in 0.6% of the 836 total doses of vutrisiran administered in HELIOS-A (Study 002 CSR2 Table 14.3.1.9.1). Injection Site Reactions were all mild, nonserious, transient, and did not lead to treatment interruption, discontinuation, or withdrawal from the clinical study (Study 002 CSR2 Tables 14.3.1.6.1, 14.3.1.7.1, and 14.3.1.8.1). No patient had more than 1 ISR; thus, there was no increase over time. Symptoms included bruising, erythema, pain, pruritus, and warmth (Study 002 CSR2 Listings 16.2.7.1 and 16.2.7.3). Injection site reactions are considered to have minimal clinical impact on patients in the context of the severity of hATTR amyloidosis and are not included as important safety concerns for risk management within the RMP.

Pain in extremity

The medical concept of pain in extremity was reported in 18 (14.8%) of vutrisiran-treated patients compared with 8 (10.4%) of patients in the APOLLO placebo group (Study 002 CSR2 Table 14.3.1.25). Adverse events within the pain in extremity medical concept were mild or moderate in severity; none of the events were severe or serious (Study 002 CSR2 Tables 14.3.1.4.1 and 14.3.1.5). None of the pain in extremity AEs led to treatment discontinuation (Study 002 CSR2 Listing 16.2.7.1). Adverse events of pain in extremity did not increase over time (Study 002 CSR2 Table 14.3.1.2.3). Therefore, AEs of pain in extremity are considered to have minimal clinical impact on patients in the context of the severity of hATTR amyloidosis and are not included as important safety concerns for risk management within the RMP.

Blood alkaline phosphatase increased

Increases in blood ALP >1.5x ULN were observed in 11 (9.0%) vutrisiran-treated patients in HELIOS-A compared to 1 (2.4%) patisiran-treated patient in HELIOS-A and 1 (1.3%) APOLLO placebo patient (Study 002 CSR2 Table 14.3.5.3.3). Of the 11 vutrisiran-treated patients with increases in ALP >1.5x ULN, 4 patients had confounding factors, such as bone fractures, or no clear increase from the patient's baseline levels. One was reported as a treatment-emergent AE assessed as moderate and related to vutrisiran treatment. Vutrisiran treatment continued uninterrupted, and the patient's ALP levels gradually improved to baseline with ongoing vutrisiran dosing. Of the patients with elevations from baseline and no confounding factors, any concurrent elevations in liver function tests were typically mild and transient with all ALT and AST values <3x ULN and all bilirubin levels <2x ULN. Therefore, an increase in blood ALP is considered to have minimal clinical impact on patients in the context of the severity of hATTR amyloidosis and is not included as an important safety concern for risk management within the RMP.

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

There are no important identified risks pertaining to vutrisiran. The following important potential risk and missing information have been determined based upon detailed review of clinical data, nonclinical findings, and other safety information available at the time of the data-lock for this RMP.

Important Potential Risks:

Clinical Consequences of Vitamin A Deficiency, Including Delayed Symptoms

Because of the mechanism of action of vutrisiran in reducing TTR, there is a theoretical risk of vitamin A deficiency. Serum TTR is a carrier of RBP, which facilitates transport of vitamin A in the blood. Transthyretin knockout mice have little-to-no circulating vitamin A or RBP, but have normal RBP levels and vitamin A stores in the liver and exhibit no signs or symptoms of vitamin A deficiency provided they have access to dietary vitamin A.[Episkopou 1993] In addition, individuals with RBP mutations who have no circulating RBP and very low vitamin A levels exhibit mild clinical symptoms.[Biesalski 1999] Together, these findings indicate that vitamin A transport and tissue uptake can occur in the absence of circulating RBP.

Given the role of TTR as a carrier of RBP and thus vitamin A, there were reductions in circulating TTR (up to 99%) and vitamin A (up to 89%) in the repeat-dose toxicity studies in monkeys, but there were no detectable effects on the eye.

In HELIOS-A, reductions in circulating vitamin A have also been observed in patients during vutrisiran and patisiran treatment. A decrease in serum vitamin A levels is a known PD effect of reducing serum TTR protein, and this PD effect was similar between vutrisiran and patisiran groups in HELIOS-A (Study 002 CSR2 Figure 14.2.5.1). However, no clinically notable trends or changes in ocular AEs were noted or considered attributable to the decrease in serum vitamin A levels.

As a precaution, vitamin A supplementation at the recommended daily amount was advised in the clinical studies and will continue to be recommended to patients undergoing treatment with vutrisiran.

Risk-benefit impact:

There have been no clinical symptoms of vitamin A deficiency detected in the clinical study data. Given the known mechanism of action of vutrisiran in reducing TTR and the decreased serum vitamin A levels seen in clinical studies, there is a potential risk of clinical consequences of vitamin A deficiency, including delayed symptoms. This risk will be characterised further in Study ALN-TTRSC02-005 (Vutrisiran PASS Protocol), hereafter referred to as 'Study 005'. As a precautionary measure, patients are advised to take a vitamin A supplement.

Hypersensitivity Reactions

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

In the vutrisiran group of the HELIOS-A study, 2 patients had a single event of drug hypersensitivity. Neither event was serious nor considered related to study drug.

In addition, 3 (2.5%) patients had a total of 3 treatment-related events (erythema, pruritus, and rash) mapped to the Hypersensitivity SMQ (scope: narrow and broad). None were severe or serious.

One patient experienced 6 severe events (dizziness, dry mouth, hyperhidrosis, hyperthermia, scleral discolouration, and dyspepsia) within 2 days of their first dose of vutrisiran as well as additional mild or moderate events within 2 days of subsequent doses. While the pattern of variable tolerance did not suggest anaphylaxis, a drug hypersensitivity reaction could not be ruled out.

Risk-benefit impact:

In the vutrisiran 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, hypersensitivity reactions are possible. Given a lack of observed serious and severe hypersensitivity in the vutrisiran clinical development program, the impact of this important potential risk on the risk-benefit balance of vutrisiran is expected to be very limited but will be characterised further in Study 005.

Missing information:

Longer-term Safety (>2 years)

In the HELIOS-A study, vutrisiran has been administered to 155 patients. Of these 155 patients, 118 patients completed ≥18 months of treatment, 79 patients completed ≥21 months of treatment, 35 patients completed ≥24 months of treatment, and 5 patients completed ≥27 months of treatment. With limited longer-term safety data, the side effects following chronic treatment with vutrisiran are unknown. Based on the available data, there are no known vutrisiran adverse drug reactions that have a long latency, are due to prolonged exposure, or are due to cumulative effects.

Risk-benefit impact: The effects following longer term treatment (>2 years) with vutrisiran are currently unknown. The collection of safety data during longer term treatment (>2 years) with vutrisiran will occur in the ongoing HELIOS-A study and Study 005.

Use in Patients with Moderate or Severe Hepatic Impairment

In HELIOS-A, a total of 8 patients (6.6%) had mild hepatic impairment (total bilirubin (TBILI) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) >ULN, or TBILI >1.0×ULN to 1.5×ULN and any AST) at baseline (see Table 12). There were no patients who had moderate or severe hepatic impairment. In the study, there were no hepatic safety concerns in patients treated with vutrisiran.

Risk-benefit impact: Vutrisiran has not been studied in patients with moderate or severe hepatic impairment. The effect of this missing information on the risk-benefit balance for patients with moderate or severe hepatic impairment is unknown. These patients will be eligible to enroll in Study 005.

Use in Pregnant Women and Effects on Pregnancy Outcomes

Vutrisiran was noted to be neither genotoxic nor clastogenic in in vitro and in vivo studies, and nonclinical studies indicated there was no direct embryo-foetal toxicity, no detectable level of vutrisiran via foetal transfer noted at any dose, and no developmental effects from exposure during lactation. However, there is a potential concern regarding the possibility of foetal damage due to vitamin A deficiency.

In the clinical studies with vutrisiran, women of child-bearing potential were required to use highly effective methods of contraception, and women who were pregnant were not enrolled in the study. Thus, there are no data on the safety of vutrisiran in this population.

Risk-benefit impact: Vutrisiran is expected to have low risk for reproductive and developmental toxicity in humans based on available data from nonclinical studies. However, given the lack of clinical data in pregnant women, the effect of vutrisiran on pregnancy outcomes and to the foetus and/or infant is currently unknown.

Outcomes in women exposed to vutrisiran during pregnancy or while breastfeeding will be evaluated in Study 005.

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

Not applicable.

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

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

There are no important identified risks pertaining to vutrisiran. Details of the important potential risks are provided in Table 14 and Table 15.

Clinical safety data are summarised from the ongoing Phase 3 studies of vutrisiran: HELIOS-A in patients with hATTR amyloidosis with polyneuropathy and HELIOS-B in patients with ATTR amyloidosis (hATTR or wtATTR) with cardiomyopathy, respectively. The pooled data includes data from 707 patients who have received vutrisiran in both HELIOS-A and HELIOS-B studies as of the data cutoff date of 23 February 2024 and 08 May 2024, respectively.

Further support is provided by results from the completed, randomised, single-blind, placebo-controlled, single-ascending dose, Phase 1 Study 001 to evaluate the safety, tolerability, PD, and PK of vutrisiran in healthy adults.

Table 14: Important Potential Risk: Clinical Consequences of Vitamin A Deficiency, Including Delayed Symptoms

Potential mechanisms	The primary mechanism of action of vutrisiran is to reduce the level of TTR. Serum TTR is a carrier of RBP, which facilitates transport of vitamin A in the blood. Therefore, there is a theoretical risk of vitamin A deficiency when there is a reduction in TTR levels.
Evidence source(s) and strength of evidence	The primary mechanism of action of vutrisiran is to reduce the level of TTR. Serum TTR is a carrier of retinol binding protein (RBP), which helps transport vitamin A in the blood. Therefore, there is a theoretical risk of vitamin A deficiency when TTR levels are reduced. However, there is evidence that vitamin A can be transported to tissues without RBP. [Episkopou 1993] In studies of vutrisiran in monkeys, serum vitamin A was reduced; 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.
Characterisation of the risk	**Pooled Data:** In HELIOS-A, reductions in circulating vitamin A have been observed in vutrisiran and patisiran treatment. A decrease in serum vitamin A levels is a known PD effect of reducing serum TTR protein, and this PD effect was similar between vutrisiran and patisiran groups in HELIOS-A (Study 002 CSR2 Figure 14.2.5.1). Similar effects on serum TTR and vitamin A were observed in vutrisiran treated patients in HELIOS-B (Study 003 CSR 1 Figure 14.2.5.8.1). However, no clinically notable trends or changes in ocular AEs were noted or considered attributable to the decrease in serum vitamin A levels in either study. This risk will be characterised further in the ongoing HELIOS-A RTE and Study 005.
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 ATTR amyloidosis population.
Preventability	Supplementation of vitamin A at the recommended daily amount (2500-3000 IU) is recommended to reduce the potential risk of clinical consequences of vitamin A deficiency, including delayed symptoms, as transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of RBP and because some patients may not get adequate vitamin A from their diet due to ATTR amyloidosis-related gastrointestinal symptoms. During treatment with vutrisiran, vitamin A supplementation should not be adjusted based on serum vitamin A levels since laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body during treatment with vutrisiran.
Impact on the risk-benefit balance of the product	There have been no clinical symptoms of vitamin A deficiency detected in the clinical study data. Given the known mechanism of action of vutrisiran in reducing TTR and the decreased serum vitamin A levels seen in clinical studies, there is a potential risk of clinical consequences of vitamin A deficiency, including delayed symptoms. However, this risk will be characterised further in the ongoing HELIOS-A RTE and Study 005. As a precautionary measure, patients are advised to take a vitamin A supplement.
Public health impact	The public health impact of clinical consequences of vitamin A deficiency, including delayed symptoms, due to vutrisiran is expected to be low.

Abbreviations: AE=adverse event; ATTR amyloidosis=hereditary or wild-type transthyretin amyloidosis; PD=pharmacodynamic; RBP=retinol binding protein; TTR=transthyretin.

Table 15: Important Potential Risk: Hypersensitivity Reactions

Potential mechanisms	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	Hypersensitivity is a theoretical risk for any drug. Possible hypersensitivity reactions were observed in vutrisiran clinical studies. One clinical study patient experienced recurrent adverse events that could suggest a hypersensitivity reaction.
Characterisation of the risk	**Pooled Data:** In the vutrisiran group of the HELIOS-A study, 3 patients had a single event of drug hypersensitivity. None of the events were serious, severe nor considered related to study drug. None led to interruption of dosing and all events resolved. There were no events of drug hypersensitivity in the HELIOS-B study. In addition, 4 (2.5%) patients (2 in HELIOS-A and 2 in HELIOS-B) had a total of 4 treatment-related events (rash [2 events], eczema and rash pruritic) mapped to the Hypersensitivity SMQ (scope: narrow). None were severe or serious. None led to interruption or discontinuation of dosing. One patient in the HELIOS-A study experienced 6 severe events (dizziness, dry mouth, hyperhidrosis, hyperthermia, scleral discolouration, and abdominal discomfort) within 2 days of their first dose of vutrisiran as well as additional mild or moderate events within 2 days of subsequent doses. While the pattern of variable tolerance did not suggest anaphylaxis, a drug hypersensitivity reaction could not be ruled out.
Risk factors and risk groups	Patients with hypersensitivity to vutrisiran or any of the excipients are 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 vutrisiran.
Preventability	As with all drugs, hypersensitivity reactions are possible. Patients should be monitored for signs of hypersensitivity reactions and treated appropriately.
Impact on the risk-benefit balance of the product	In the vutrisiran 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, hypersensitivity reactions are possible. Given a lack of observed serious and severe hypersensitivity in the vutrisiran clinical development program, the impact of this important potential risk on the risk-benefit balance of vutrisiran is expected to be very limited but will be characterised further in Study 005.
Public health impact	The public health impact of hypersensitivity reactions is expected to be low.

Abbreviations: SMQ=standardized MedDRA query.

SVII.3.2 Presentation of the 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 (>2 years)	**Evidence Source:** **Pooled Data:** In the pooled data, 448 patients have been exposed to vutrisiran for ≥12 months, 405 patients for ≥24 months, 294 patients for ≥36 months, 66 patients for ≥48 months and 8 patients for ≥54 months (Table 8). In HELIOS-B, 294 patients were exposed to vutrisiran for ≥12 months, 267 patients for ≥24 months, 183 patients for ≥36 months, 4 patients for ≥48 months and 0 patients for ≥54 months (Table 8). Therefore, the side effects following chronic treatment with vutrisiran are unknown. Based on the available data, there are no known vutrisiran adverse drug reactions that have a long latency, are due to prolonged exposure, or are due to cumulative effects.
	Anticipated risk/consequence of the missing information: The effects following longer term treatment (>2 years) with vutrisiran in patients with hATTR amyloidosis with polyneuropathy was unknown at time of initial marketing authorisation. The collection of safety data during longer term treatment (>2 years) with vutrisiran in patients with hATTR amyloidosis with polyneuropathy is performed in the ongoing HELIOS-A RTE and Study 005. The data from HELIOS-B in patients with ATTR Amyloidosis with Cardiomyopathy provide a solid foundation for assessing the longer-term safety of vutrisiran in this population, particularly for exposures exceeding two years. With a median exposure of ≥24 months (267 patients) and 183 patients treated for ≥36 months, the study suggests that vutrisiran maintains a consistent safety profile over extended periods. The limited number of patients with exposure beyond three years (4 patients exposed for ≥48 months) indicates that while the current data are reassuring, continued monitoring and additional studies will be important to fully establish the safety of vutrisiran for very long-term use in patients with ATTR amyloidosis with cardiomyopathy. Collection of safety data during longer treatment with vutrisiran in this population will be performed in the ongoing Study 005.
Use in patients with moderate or severe hepatic impairment	**Evidence Source:** **Pooled Data:** In the pooled data, a total of 92 (13.0%) patients had mild hepatic impairment (11 (6.9%) in HELIOS-A and 81 (14.8%) in HELIOS-B) and 20 (2.8%) patients had moderate hepatic impairment (0 in HELIOS-A and in 20 (3.7%) patients in HELIOS-B) (TBILI ≤ULN and AST >ULN, or TBILI >1.0×ULN to 1.5×ULN and any AST/ALT or TBILI >1.5×ULN to 3.0×ULN and any AST/ALT) at baseline (Table 12). No patient had severe hepatic impairment in either study. In both studies, there were no hepatic safety concerns in patients treated with vutrisiran.
	Population in need of further characterisation: In HELIOS-A, in patients with hATTR with polyneuropathy, vutrisiran has not been studied in patients with moderate or severe hepatic impairment. These patients are eligible to enroll in Study 005 for further characterisation. In HELIOS-B, in patients with ATTR amyloidosis with cardiomyopathy, the small number of patients with moderate impairment and the lack of data on severe hepatic impairment highlight the need for further characterization. Collection of safety data in patients with moderate or severe hepatic impairment will be performed in the ongoing Study 005.

Missing Information	Details
	The pooled data from HELIOS-A and HELIOS-B indicate that vutrisiran does not raise hepatic safety concerns in patients with mild or moderate hepatic impairment. However, the additional PV activities outlined in this RMP will contribute to address the gaps for a full understanding of the long-term safety of vutrisiran and ensure its safe and effective use across the whole intended patient population.
Use in pregnant women and effects on pregnancy outcomes	**Evidence Source:** Vutrisiran was noted to be neither genotoxic nor clastogenic in in-vitro and in vivo studies, and nonclinical studies indicated there was no direct embryo-foetal toxicity, no detectable level of vutrisiran via foetal transfer noted at any dose, and no developmental effects from exposure during lactation. However, there is a potential concern regarding the possibility of foetal damage due to vitamin A deficiency. In the clinical studies with vutrisiran, women of child-bearing potential were required to use highly effective methods of contraception, and women who were pregnant were not enrolled in the study. Thus, there are no data on the safety of vutrisiran in this population.
	Anticipated risk/consequence of the missing information: Vutrisiran is expected to have low risk for reproductive and developmental toxicity in humans based on available data from nonclinical studies. However, given the lack of clinical data in pregnant women, the effect of vutrisiran on pregnancy outcomes and to the foetus and/or infant is currently unknown. Outcomes in women exposed to vutrisiran during pregnancy are evaluated in Study 005.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ATTR amyloidosis=hereditary or wild-type Transthyretin amyloidosis; hATTR=hereditary transthyretin amyloidosis; RMP=Risk Management Plan; TBILI=total bilirubin; ULN=upper limit of normal.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

A summary of safety concerns is provided in Table 17.

Table 17: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risk	• Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity reactions
Missing information	• Longer-term safety (>2 years) • Use in patients with moderate or severe hepatic impairment • Use in pregnant women and effects on pregnancy outcomes

Part III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance (PV), including AE collection and reporting, signal detection, and signal evaluation, will be conducted as described in the Pharmacovigilance System Master File. Reports of exposure during pregnancy will be routinely collected, reported, and followed up for pregnancy and infant outcomes.

A targeted follow-up questionnaire will be implemented for reports of vitamin A deficiency/ocular toxicity in order to collect additional information on these events; these data will be analysed and presented in the Periodic Safety Update Reports (PSURs) to further characterise this risk (see Annex 4).

III.2 Additional Pharmacovigilance Activities

Additional PV activities include monitoring of safety in the ongoing HELIOS-A Randomised Treatment Extension and Study 005.

- HELIOS-A Randomised Treatment Extension (HELIOS-A RTE):

  The HELIOS-A-RTE study is a Phase 3 global, open-label study to evaluate the safety and efficacy of ALN-TTRSC02 in patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis). The aim of the study is to collect further longer-term safety and efficacy data on vutrisiran in patients with hATTR amyloidosis with polyneuropathy.

- Study ALN-TTRSC02-005 (Study 005):

  Study 005 is a prospective observational study to monitor and assess the safety of Amvuttra® [vutrisiran] in a real-world cohort of ATTR amyloidosis patients. The aim of the study is to characterise the long-term (>2 years) safety of vutrisiran under real-world conditions, including determining the incidence of selected events (eg, hypersensitivity reactions and clinical consequences of vitamin A deficiency, including delayed symptoms) in ATTR amyloidosis patients exposed to vutrisiran, as well as provide comparative safety data from patients including untreated patients and patients treated with other therapies for ATTR amyloidosis excluding patisiran, following local standard of care.

Refer to Table 18 and Table 19 for further study details and milestones for the studies in the Pharmacovigilance Plan.

Details for the studies for the Pharmacovigilance Plans are provided in Annex 2. The HELIOS-A and Study 005 protocols are provided in Annex 3.

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

Study Number and Title	Rationale and Objectives	Study Design	Study Population	Study Status	Milestones
Ongoing long-term interventional study					
HELIOS-A Randomised Treatment Extension The HELIOS-A-RTE study is a Phase 3 global, open-label study to evaluate the safety and efficacy of ALN-TTRSC02 in patients with hATTR amyloidosis.	The aim of the study is to collect further longer-term safety and efficacy data on vutrisiran in patients with hATTR amyloidosis with polyneuropathy.	Phase 3, randomised, open-label study	Adult patients with hATTR amyloidosis with polyneuropathy	Ongoing	LPLV (42-month extension period) (estimated): 31/10/2025 LPLV (End of Study) (estimated): 31/10/2026 Final CSR: 31/10/2027 or 12 months after LPLV whichever occurs earlier.
Planned Prospective Observational Study					
ALN-TTRSC02-005 Study 005: Prospective observational study to monitor and assess the safety of Amvuttra® [vutrisiran] in a real-world cohort of ATTR amyloidosis patients	The primary objective of this study is to characterise the long-term (>2 years) safety of vutrisiran under real-world conditions, including determining the incidence of selected events (eg, hypersensitivity reactions and clinical consequences of vitamin A deficiency, including delayed symptoms) in ATTR amyloidosis patients exposed to vutrisiran, as well as provide comparative safety data from patients including untreated patients and patients treated with other therapies for ATTR	Multinational, Non-interventional, observational study conducted over a period of 10 years, using epidemiological cohort design techniques. Patient data will be collected approximately every 12 months following routine care visits for ATTR amyloidosis.	The study is planned to prospectively follow a cohort of patients with ATTR amyloidosis.	Ongoing	Protocol Submission (Vutrisiran PASS): 13/06/2023 Protocol Amendment Submission: After regulatory approval of type II variation to expand Amvuttra® indication. Interim Report 1: 30/09/2026 Interim Report 2: 30/09/2028 Interim Report 3: 30/09/2030 Interim Report 4: 30/09/2032 Report of Study Results: Study progress reports will

Study Number and Title	Rationale and Objectives	Study Design	Study Population	Study Status	Milestones
	amyloidosis excluding patisiran, following local standard of care. The secondary objectives are to characterise the safety of vutrisiran in sub-populations (eg, patients with moderate or severe hepatic impairment, patients who are pregnant, to describe the epidemiological and clinical characteristics of patients treated with vutrisiran in a real-world setting and to evaluate information from all pregnant or lactating women exposed to vutrisiran, including pregnancy outcomes, and selected infant outcomes.				be provided with each PBRER End of data collection: 31/12/2033
					Final study report: 31/12/2034

Abbreviations: CSR=clinical study report; hATTR amyloidosis=hereditary transthyretin amyloidosis; LPLV=last patient last visit; PASS=post-authorisation safety study; PBRER=periodic benefit-risk evaluation report; Q=quarter; RTE=Randomised Treatment Extension.

III.3 Summary Table of Additional Pharmacovigilance Activities

The summary of ongoing additional PV activities is included in Table 18 and Table 19.

Table 19: Ongoing and Planned Additional Pharmacovigilance Activities

Study Number Short Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones (required by regulators)	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
• Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
• Not applicable				
Category 3 - Required additional pharmacovigilance activities				
HELIOS-A Randomised Treatment Extension The HELIOS-A-RTE[a] study is a Phase 3 global, open-label study to evaluate the safety and efficacy of ALN-TTRSC02 in patients with hATTR Amyloidosis. (Ongoing)	The aim of the study is to collect further longer-term safety and efficacy data on vutrisiran in patients with hATTR amyloidosis with polyneuropathy.	• Longer-term safety (>2 years)[a] • Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity reactions	Final CSR	31/10/2027 or 12 months after LPLV whichever occurs earlier.
ALN-TTRSC02-005 Study 005: Prospective observational study to monitor and assess the safety of Amvuttra® [vutrisiran] in a real-world cohort of ATTR amyloidosis patients (Ongoing)	The primary objective of this study is to characterise the long-term (>2 years) safety of vutrisiran under real-world conditions, including determining the incidence of selected events (eg, hypersensitivity reactions and clinical	• Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity reactions • Longer term safety (>2 years)	Final Protocol	Submitted on 13/06/2023 Protocol Amendment Submission: After regulatory approval of type II variation to expand Amvuttra® indication.

Study Number Short Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones (required by regulators)	Due Dates
	consequences of vitamin A deficiency, including delayed symptoms) in ATTR amyloidosis patients exposed to vutrisiran, as well as provide comparative safety data from patients including untreated patients and patients treated with other therapies for ATTR amyloidosis excluding patisiran, following local standard of care.	• Use in patients with moderate or severe hepatic impairment • Use in pregnancy and pregnancy and infant outcomes	Start of vutrisiran data collection	Actual Start of Data Collection: 10/04/2024
			Interim updates	Interim Report 1: 30/09/2026 Interim Report 2: 30/09/2028 Interim Report 3: 30/09/2030 Interim Report 4: 30/09/2032 Study progress reports will be provided with each PBRER
			Final Report	Final study report: 31/12/2034

Abbreviations: ATTR=hereditary or wild-type Transthyretin amyloidosis; CSR=clinical study report; EC=European Commission; hATTR amyloidosis=hereditary transthyretin amyloidosis; LPLV=last patient last visit; PAM=post-authorisation measure; PBRER=periodic benefit risk evaluation report; RTE=Randomised Treatment Extension.

[a] HELIOS-A Protocol Amendment 3, in place as of 17 July 2020 included an 18-month extension period (for a total study duration of 36 months). Protocol Amendment 4 lengthened the extension period to a maximum of 36 months (for a total study duration of up to 54 months). Protocol Amendment 5 further lengthened the extension period to a maximum of 42 months extension period (for a total study duration of up to 78 months).

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Not applicable. No post-authorisation efficacy studies have been imposed for vutrisiran that are conditions of the marketing authorization.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Careful consideration of the risk-benefit balance for vutrisiran has concluded that routine risk minimisation activities are sufficient to manage the safety concerns of vutrisiran. Routine risk communication through product labeling is considered sufficient to describe the safety profile for the product and to communicate to healthcare professionals the appropriate actions to prevent or mitigate risks, as warranted. Routine risk minimisation activities recommending specific clinical measures to address the risk have been proposed in the label as appropriate to the safety concern.

If, through routine or additional PV activities as summarised in Section Part III, new risks are identified, the risk communication and minimisation measures will be updated as necessary.

An overview of the proposed risk minimisation activities for the important potential risk and missing information for vutrisiran is provided in Table 20.

Table 20: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important potential risk: Clinical consequences of vitamin A deficiency, including delayed symptoms	Routine risk communication: The secondary pharmacologic effect on serum vitamin A levels is described in: • SmPC sections 4.4, 4.6, 5.1, and 5.3 • PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for vitamin A supplementation: • SmPC sections 4.2 and 4.4 • PIL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: Restricted medical prescription
Important potential risk: Hypersensitivity reactions	Routine risk communication: • SmPC Section 4.3 • PIL Section 2 • Legal status: Prescription only

Safety Concern	Routine Risk Minimisation Activities
Missing information: Longer-term safety (>2 years)	Routine risk communication: • SmPC Section 4.8
Missing information: Use in patients with moderate or severe hepatic impairment	Routine risk communication: • SmPC Sections 4.2 and 5.2
Missing information: Use in pregnant women and effects on pregnancy outcomes	Routine risk communication: • SmPC Sections 4.6 and 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Sections 4.4 and 4.6 • PIL Section 2

Abbreviations: PIL=Patient information leaflet; SmPC=Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures are proposed.

V.3 Summary of Risk Minimisation Measures

A summary of PV activities and risk minimisation activities is provided in Table 21.

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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risk:		
Clinical consequences of vitamin A deficiency, including delayed symptoms	Routine risk minimisation measures: • The secondary pharmacologic effect on serum vitamin A levels is described in SmPC sections 4.4, 4.6, 5.1, and 5.3, and PIL Section 2. • Legal status: Prescription-only Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • Specific targeted follow-up of vitamin A deficiency/ocular toxicity Additional PV activities: • Evaluation of data from the HELIOS-A Randomised Treatment Extension (HELIOS-A RTE) • Evaluation of data from Study 005

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hypersensitivity reactions	Routine risk minimisation measures: • SmPC Section 4.3 and PIL Section 2 • Legal status: Prescription-only Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the HELIOS-A RTE • Evaluation of data from Study 005
Missing Information:		
Longer-term safety (>2 years)	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the HELIOS-A RTE • Evaluation of data from Study 005
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: • SmPC sections 4.2 and 5.2 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from Study 005
Use in pregnant women and effects on pregnancy outcomes	Routine risk minimisation measures: • SmPC sections 4.4, 4.6, and 5.3, and PIL Section 2 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from Study 005

Abbreviations: PIL=Patient Information Leaflet; PV=Pharmacovigilance; RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics.

Part VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR AMVUTTRA

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

Amvuttra's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Amvuttra should be used.

This summary of the RMP for Amvuttra 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 Amvuttra's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Amvuttra is authorised for the treatment of hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy (hATTR amyloidosis with polyneuropathy) and proposed for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR amyloidosis with cardiomyopathy). It contains vutrisiran as the active substance and it is given by SC injection.

Further information about the evaluation of Amvuttra’s benefits can be found in Amvuttra’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage link to the EPAR summary landing page.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PIL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including in the Periodic Safety Update Report 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 Amvuttra is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Amvuttra are risks that need special risk management activities to further investigate or minimise 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 Amvuttra. 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 risks	• None
Important potential risk	• Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity reactions
Missing information	• Longer-term safety (>2 years) • Use in patients with moderate or severe hepatic impairment • Use in pregnant women and effects on pregnancy outcomes

II.B Summary of Important Risks

Important Potential Risk: Clinical Consequences of Vitamin A Deficiency, Including Delayed Symptoms	
Evidence for linking the risk to the medicine	The primary mechanism of action of Amvuttra is to reduce the level of transthyretin (TTR). Serum TTR is a carrier of retinol binding protein (RBP), which helps transport vitamin A in the blood. Therefore, there is a theoretical risk of vitamin A deficiency when TTR levels are reduced. However, there is evidence that vitamin A can be transported to tissues without RBP.[Episkopou 1993] In studies of Amvuttra in monkeys, serum vitamin A was reduced; 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.
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 ATTR amyloidosis population.

Important Potential Risk: Clinical Consequences of Vitamin A Deficiency, Including Delayed Symptoms	
Risk minimisation measures	Routine risk minimisation measures: • The secondary pharmacologic effect on serum vitamin A levels is described in SmPC Sections 4.4, 4.6, 5.1, and 5.3, and PIL Section 2. • Legal status: Prescription-only Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **Study ALN-TTRSC02-002, HELIOS-A: Randomised Treatment Extension (Ongoing):** • Evaluation of data from HELIOS-A RTE **Study ALN-TTRSC02-005, Study 005: Prospective, Observational Study (Ongoing)** • Evaluation of data from Study 005

Abbreviations: hATTR=Hereditary transthyretin amyloidosis; PIL=patient information leaflet; RBP=Retinol binding protein; RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics.
Source: [Episkopou 1993].

Important Potential Risk: Hypersensitivity Reactions	
Evidence for linking the risk to the medicine	Hypersensitivity is a theoretical risk for any drug. **Pooled Data:** In the vutrisiran group of the HELIOS-A study, 3 patients had a single event of drug hypersensitivity. None of the events were serious, severe nor considered related to study drug. None led to interruption of dosing and all events resolved. There were no events of drug hypersensitivity in the HELIOS-B study. In addition, 4 (2.5%) patients (2 in HELIOS-A and 2 in HELIOS-B) had a total of 4 treatment-related events (rash [2 events], eczema and rash pruritic) mapped to the Hypersensitivity SMQ (scope: narrow). None were severe or serious. None led to interruption or discontinuation of dosing. One patient in the HELIOS-A study experienced 6 severe events (dizziness, dry mouth, hyperhidrosis, hyperthermia, scleral discolouration, and dyspepsia) within 2 days of their first dose of vutrisiran as well as additional mild or moderate events within 2 days of subsequent doses. While the pattern of variable tolerance did not suggest anaphylaxis, a drug hypersensitivity reaction could not be ruled out.
Risk factors and risk groups	Patients with hypersensitivity to vutrisiran or any of the excipients are 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 vutrisiran.

Important Potential Risk: Hypersensitivity Reactions	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 and PIL Section 2 • Legal status: Prescription-only Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **Study ALN-TTRSC02-002, HELIOS-A: Randomised Treatment Extension (Ongoing):** • Evaluation of data from HELIOS-A RTE **Study ALN-TTRSC02-005, Study 005: Prospective, Observational Study (Ongoing)** • Evaluation of data from Study 005

Abbreviations: PIL=patient information leaflet; RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics; SMQ=standardized MedDRA query.

Missing Information: Longer-term safety (>2 years)	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **Study ALN-TTRSC02-002, HELIOS-A: Randomised Treatment Extension (Ongoing)** • Evaluation of data from HELIOS-A RTE **Study ALN-TTRSC02-005, Study 005: Prospective, Observational Study (Ongoing)** • Evaluation of data from Study 005

Abbreviation: RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics.

Missing Information: Use in patients with moderate or severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 5.2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	**Study ALN-TTRSC02-005, Study 005: Prospective, Observational Study (Ongoing)** • Evaluation of data from Study 005

Abbreviation: SmPC=Summary of Product Characteristics.

Missing Information: Use in pregnant women and effects on pregnancy outcomes	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4, 4.6, and 5.3, and PIL Section 2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	**Study ALN-TTRSC02-005, Study 005: Prospective, Observational Study (Ongoing)** • Evaluation of data from Study 005

Abbreviations: PIL=Patient information leaflet; SmPC=Summary of Product Characteristics.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation There are no studies which are conditions of the marketing authorisation of Amvuttra.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study: HELIOS-A Randomised Treatment Extension (Ongoing)

Purpose of the study: The HELIOS-A-RTE study is a Phase 3 global, open-label study to evaluate the safety and efficacy of ALN-TTRSC02 in patients with hATTR Amyloidosis. The aim of the study is to collect further longer-term safety and efficacy data on vutrisiran in patients with hATTR amyloidosis with polyneuropathy.

Study ALN-TTRSC02-005, Study 005: Prospective, Observational Study (Ongoing)

Purpose of the study: This is a prospective, observational study to monitor and assess the safety of Amvuttra® [vutrisiran] in a real-world cohort of ATTR amyloidosis patients. The aim of the study is to characterise the long-term (>2 years) safety of vutrisiran under real-world conditions, including determining the incidence of selected events (eg, hypersensitivity reactions and clinical consequences of vitamin A deficiency, including delayed symptoms) in ATTR amyloidosis patients exposed to vutrisiran, as well as provide comparative safety data from patients including untreated patients and patients treated with other therapies for ATTR amyloidosis excluding patisiran, following local standard of care. The secondary objectives are to characterise the safety of vutrisiran in sub-populations (eg, patients with moderate or severe hepatic impairment, patients who are pregnant, to describe the epidemiological and clinical characteristics of patients treated with vutrisiran in a real-world setting and to evaluate information from all pregnant or lactating women exposed to vutrisiran, including pregnancy outcomes, and selected infant outcomes.

PART VII ANNEXES

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Refer to Vutrisiran: Targeted Follow-up Questionnaire for Reports of Ocular Events

Vutrisiran: Targeted Follow-up Questionnaire for Reports of Ocular Events

This form is to be used for reports from health care providers as well as from patients/caregivers as far as applicable.

1. Manufacturer Control Number (MCN): (MCN to be assigned by Alnylam)					
Patient Initials:		Patient Date of Birth: (DD/MMM/YYYY)		Patient Age: (Years)	
Patient Sex:	☐ M ☐ F	Patient Weight:	☐ kg ☐ lb		
Race or origin:	Please select all that apply: ☐White ☐Hispanic, Latino or Spanish origin ☐Black or African American ☐Asian ☐American Indian or Alaska Native ☐Native Hawaiian or Other Pacific Islander ☐Aboriginal ☐Torres Strait Islander ☐Other ☐Data not available				

2. Description of the Adverse Event

Please select any of the following symptoms of the ocular event(s) followed by the pertinent details.

☐ Night blindness

Date symptoms began: _____

Duration of vutrisiran treatment before start of symptoms: _____

Event outcome (choose one):

☐ Recovered (date of resolution of symptoms) _____

☐ Recovered with sequelae (describe sequelae) _____

☐ Ongoing

☐ Fatal

☐ Unknown

Action taken with vutrisiran in response to the event (choose one):

☐ Dose not changed

☐ Drug interrupted

Did symptoms improve with interruption? _____

Date treatment was resumed _____

2. Description of the Adverse Event

Did symptoms recur with resuming treatment? _____

If yes, date symptoms recurred _____

☐ Drug withdrawn

Did symptoms improve with drug withdrawal? _____

☐ Xerophthalmia (pathologic dryness of the conjunctiva and cornea)

Date symptoms began: _____

Duration of vutrisiran treatment before start of symptoms: _____

Event outcome (choose one):

☐ Recovered (date of resolution of symptoms) _____

☐ Recovered with sequelae (describe sequelae) _____

☐ Ongoing

☐ Fatal

☐ Unknown

Action taken with vutrisiran in response to the event (choose one):

☐ Dose not changed

☐ Drug interrupted

Did symptoms improve with interruption? _____

Date treatment was resumed _____

Did symptoms recur with resuming treatment? _____

If yes, date symptoms recurred _____

☐ Drug withdrawn

Did symptoms improve with drug withdrawal? _____

☐ Keratomalacia (softening of the cornea)

Date symptoms began: _____

Duration of vutrisiran treatment before start of symptoms: _____

Event outcome (choose one):

☐ Recovered (date of resolution of symptoms) _____

☐ Recovered with sequelae (describe sequelae) _____

☐ Ongoing

☐ Fatal

2. Description of the Adverse Event

☐ Unknown

Action taken with vutrisiran in response to the event (choose one):

☐ Dose not changed

☐ Drug interrupted

Did symptoms improve with interruption? _____

Date treatment was resumed _____

Did symptoms recur with resuming treatment? _____

If yes, date symptoms recurred _____

☐ Drug withdrawn

Did symptoms improve with drug withdrawal? _____

☐ Retinopathy

Date symptoms began: _____

Duration of vutrisiran treatment before start of symptoms: _____

Event outcome (choose one):

☐ Recovered (date of resolution of symptoms) _____

☐ Recovered with sequelae (describe sequelae) _____

☐ Ongoing

☐ Fatal

☐ Unknown

Action taken with vutrisiran in response to the event (choose one):

☐ Dose not changed

☐ Drug interrupted

Did symptoms improve with interruption? _____

Date treatment was resumed _____

Did symptoms recur with resuming treatment? _____

If yes, date symptoms recurred _____

☐ Drug withdrawn

Did symptoms improve with drug withdrawal? _____

☐ Other (describe) _____

2. Description of the Adverse Event

Date symptoms began: _____

Duration of vutrisiran treatment before start of symptoms: _____

Event outcome (choose one):

☐ Recovered (date of resolution of symptoms) _____

☐ Recovered with sequelae (describe sequelae) _____

☐ Ongoing

☐ Fatal

☐ Unknown

Action taken with vutrisiran in response to the event (choose one):

☐ Dose not changed

☐ Drug interrupted

Did symptoms improve with interruption? _____

Date treatment was resumed _____

Did symptoms recur with resuming treatment? _____

If yes, date symptoms recurred _____

☐ Drug withdrawn

Did symptoms improve with drug withdrawal? _____

3. Disease Progression

Is this adverse event considered to be a manifestation of hATTR amyloidosis disease progression?
Yes ☐ No ☐

4. Vutrisiran Therapy Details

Provide dates for:		Date (DD/MMM/YYYY)	
The first vutrisiran injection			
The injection before the most recent injection			
The most recent (current) injection			
Vutrisiran	**Dose:**	**Route:**	**Frequency:**

How many vutrisiran injections (including this one) has the patient received?
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ More than 5

Please provide number if more than 5:

5. Details of Vitamin A Supplementation

Is the patient taking supplemental vitamin A? Yes ☐ No ☐					
If yes:	Dose:	Route:	Frequency:	Start date:	Stop date (if applicable):

6. Treatment for Ocular Event(s) Please describe the treatment given for the ocular event(s)					
Medication	Dose	Route	Frequency	Start date	Stop date (if applicable)
Other Treatment (Please specify):					

7. Diagnostic Evaluation Please indicate if any tests or consultations 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) or Findings:	Reference Range (if applicable)
Serum vitamin A or retinol levels			
Opthalmology consultation			
Other - Please specify:			
Other - Please specify:			

8. Risk Factors		
Medical Condition	**Yes No**	If yes, please describe the details of the medical condition including if it is current, of recent onset (within past 3 months), or in the past (date of occurrence) as well as symptoms and treatment(s) involved:
Amyloid eye deposits	☐ ☐	
Diabetic retinopathy	☐ ☐	
Macular degeneration	☐ ☐	

8. Risk Factors			
Medical Condition	**Yes**	**No**	If yes, please describe the details of the medical condition including if it is current, of recent onset (within past 3 months), or in the past (date of occurrence) as well as symptoms and treatment(s) involved:
Cataract	☐	☐	
Glaucoma	☐	☐	
Dry eye	☐	☐	
Eye pain	☐	☐	
Vision changes	☐	☐	
Night blindness	☐	☐	
Alcoholism	☐	☐	
Others (specify):	☐	☐	

9. Concomitant Medications
Please list concomitant medications taken by the patient at the time of the event.

Medication	Dose	Route	Frequency	Start date

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 MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.