Alnylam®

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

ALNYLAM PHARMACEUTICALS BRIEFING DOCUMENT

PATISIRAN FOR THE TREATMENT OF CARDIOMYOPATHY OF WILD-TYPE OR HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS IN ADULTS TO SLOW THE DECLINE IN FUNCTIONAL CAPACITY AND REDUCE SYMPTOMS

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
6MWT	6-minute walk test
ACE	Angiotensin-converting enzyme
ADA	Anti-drug antibody
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AL	Amyloid light chain
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocks
AST	Aspartate aminotransferase
ATTR	Transthyretin-mediated amyloidosis
ATTR-CM	Transthyretin-mediated amyloidosis with cardiomyopathy
ATTR-PN	Transthyretin-mediated amyloidosis with polyneuropathy
AV	Atrioventricular
CD	Change Difference
CV	Cardiovascular
DILI	Drug Induced Liver Injury
DB	Double-blind
EAP	Expanded Access Program
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FMQ(s)	Food and Drug Administration Medical Query(ies)
GI	Gastrointestinal
hATTR	Hereditary transthyretin-mediated amyloidosis
hATTR-PN	Hereditary transthyretin-mediated amyloidosis with polyneuropathy
HF	Heart failure
HL	Hodges-Lehmann
IQR	Interquartile range
IRR(s)	Infusion-related reaction(s)
IV	Intravenous(ly)
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire-Overall Summary
KCCQ-PLS	Kansas City Cardiomyopathy Questionnaire-Physical Limitation Score
LNP(s)	Lipid nanoparticle(s)

LS	Least-squares
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MAR	Missing at random
mBMI	Modified body mass index
MCID	Minimal clinically important difference
mITT	Modified Intent-to-Treat
MMRM	Mixed-effect repeated measures
mNIS+7	Neuropathy Impairment Score+7
Norfolk-QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PND	Polyneuropathy disability
q3W	Once every 3 weeks
QoL	Quality of life
R-ODS	Rasch-built Overall Disability Scale
RBP	Retinol binding protein
RNAi	Ribonucleic acid interference
SAE(s)	Serious adverse event(s)
SGLT2	Sodium-glucose cotransporter-2
siRNA	Small interfering ribonucleic acid
SMQs	Standardized Medical Dictionary for Regulatory Activities Query(ies)
sNDA	Supplemental New Drug Application
SOC	System Organ Class
TTR	Transthyretin
ULN	Upper limit of normal
US	United States
vTTR	Variant transthyretin
wt	Wild-type
wtATTR	Wild-type transthyretin-mediated amyloidosis
wtATTR-CM	Wild-type transthyretin-mediated amyloidosis with cardiomyopathy

1 EXECUTIVE SUMMARY

1.1 Introduction

Alnylam Pharmaceuticals seeks approval of a supplemental New Drug Application (sNDA) for patisiran for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (wt or hATTR amyloidosis, collectively referred to as ATTR amyloidosis) in adults to slow the decline in functional capacity and reduce symptoms. Patisiran was approved in the United States (US) in 2018 for the treatment of the polyneuropathy of hATTR amyloidosis (hATTR-PN).

ATTR amyloidosis is a rare, serious, and life-threatening disease. The unrelenting disease progression that characterizes both wtATTR and hATTR amyloidosis is driven by the ongoing deposition of hepatically-synthesized TTR as amyloid. Deposition of TTR amyloid in the peripheral nerves or heart causes polyneuropathy, cardiomyopathy, or both. While there are multiple manifestations of ATTR amyloidosis, the field has come to understand that this is one disease with the most serious presentations being polyneuropathy and cardiomyopathy (Adams et al 2019; Ruberg et al 2019). The latter is characterized by an inexorable progression of heart failure (HF), irreversible loss of functional capacity, worsening health and quality of life (QoL), and high mortality (Lane et al 2019).

Patisiran is comprised of a small interfering ribonucleic acid (siRNA) formulated in lipid nanoparticles (LNPs) that specifically targets the production of TTR, the pathogenic substrate for amyloid deposition, at its source of production. It utilizes ribonucleic acid interference (RNAi), an endogenous cellular mechanism for regulating mRNA levels, to selectively degrade all forms of TTR mRNA in hepatocytes, resulting in ≥85% reduction of serum levels of wt and variant TTR (vTTR).

Patisiran is a first-line therapy for the treatment of hATTR-PN (Kittelson et al 2020; Alcantara et al 2021; Iannazzo 2021; Ando et al 2022). The APOLLO study, which formed the basis of the initial approval of patisiran in 2018, was a global, randomized, double-blind (DB), placebo-controlled Phase 3 trial designed to evaluate the efficacy (primary endpoint, Neuropathy Impairment Score+7 [mNIS+7]; secondary endpoint, Norfolk Quality of Life-Diabetic Neuropathy [Norfolk-QoL-DN]) and safety of patisiran in patients with hATTR-PN. In contrast to the rapid disease progression observed in the placebo arm of APOLLO, patisiran-treated patients showed stabilization or improvement of their polyneuropathy. In addition, pre-specified analyses of patients with evidence of ATTR cardiomyopathy demonstrated improvements in exploratory measures of cardiac structure and function, and post-hoc analyses of safety data in all patients provided evidence of a reduction in the risk of death and cardiac hospitalization (Adams et al 2018; Adams et al 2021; Solomon et al 2019). APOLLO thus validated the hypothesis that by markedly reducing production of TTR amyloid, patisiran can effectively and safely treat the signs and symptoms of ATTR amyloidosis. To date, patisiran has been approved in over 35 countries for the treatment of hATTR-PN. There are over 8,500 patient-years of experience with patisiran in clinical trials and the post-marketing setting, with some patients treated for over 7 years.

To formally establish the benefits of patisiran on the cardiac manifestations of ATTR amyloidosis that were first observed in APOLLO, the APOLLO-B study evaluated patisiran in an ATTR population with predominant cardiomyopathy (ATTR-CM). Specifically, the study was designed to assess the effects of patisiran on functional capacity (primary endpoint, 6-minute walk test [6MWT]) and health status and QoL (first secondary endpoint, Kansas City Cardiomyopathy Questionnaire-Overall Summary [KCCQ-OS]) at 12 months. The study design, endpoints, and objectives incorporated input from the Food and Drug Administration (FDA) and are consistent with FDA's 2019 Draft Guidance for Industry Treatment for Heart Failure: Endpoints for Drug Development (FDA 2019a).

In APOLLO-B, compared with placebo, patisiran-treated patients showed statistically significant and clinically meaningful differences in functional capacity (6MWT) and health status and QoL (KCCQ-OS) at Month 12. These results were further supported by improvements compared with placebo on clinically important laboratory parameters (N-terminal pro-brain natriuretic peptide [NT-proBNP] and troponin I), echocardiographic assessments of cardiac structure and function, and trends favoring patisiran on both New York Heart Association (NYHA) class, and ATTR amyloidosis disease stage (an established laboratory-based staging system; Gillmore et al 2018). While the study was not powered and was not of a duration intended to show treatment differences in composite endpoints of morbidity and mortality, the results in these endpoints numerically favored patisiran with no evidence of harmful effects. No new safety signals emerged in this study and the overall safety profile was consistent with what has been established in clinical trials and post-marketing use for patisiran in hATTR-PN.

The results from APOLLO-B and the totality of evidence from the patisiran development program, including confirmatory data from APOLLO, and a strong biologic rationale, support a favorable benefit-risk profile for patients with cardiomyopathy due to wtATTR or hATTR amyloidosis. Taken together, these data support the expansion of the approved indication for patisiran to include treatment of ATTR-CM to slow the decline in functional capacity and reduce symptoms.

1.2 Background and Unmet Need in ATTR Amyloidosis with Cardiomyopathy

In ATTR amyloidosis, destabilized tetrameric TTR protein dissociates into monomers and oligomers, which then misfold and deposit as amyloid in various tissues, causing the multiple manifestations of this disease (Ruberg et al 2019). Wild-type ATTR amyloidosis is associated with aging and presents with predominant cardiomyopathy, although there is increasing evidence of concurrent polyneuropathy in these patients. Inherited mutations that destabilize the TTR protein cause hATTR amyloidosis, which can present with polyneuropathy, cardiomyopathy, or both. ATTR-CM typically presents at age >65 years old; wtATTR amyloidosis, which is associated with aging, is typically diagnosed after age 70 years (Connors et al 2016; Dispenzieri et al 2022). Approximately 80–90% of patients are male (Kroi et al 2021). The predominant form (~80%) is wtATTR amyloidosis and is rising with growing disease awareness and diagnosis (Lane et al 2019; Ruberg et al 2019). The US prevalence of ATTR-CM is estimated to be <200,000 (Jacobson et al 2015; Lindmark et al 2021; Quarta et al 2014).

Amyloid infiltration of the ventricular and atrial myocardium causes chamber wall thickening and disrupts conduction pathways. The typical presentation of ATTR-CM is HF with preserved ejection fraction. Atrial fibrillation and atrioventricular (AV) block are also common (Ruberg et al 2019). A dramatic loss of strength and stamina along with fatigue and shortness of breath severely impact QoL (Rintell et al 2021). Ongoing amyloid deposition directly drives the rapid progression of HF that leads to recurrent hospitalizations and death (Fontana et al 2015; Martinez-Naharro et al 2019; Chacko et al 2020). Median survival is approximately 2.5–5.5 years, depending on the stage of disease at diagnosis (Antonopoulos et al 2022; Castano et al 2015; Damy et al 2016; Dungu et al 2012; Hawkins et al 2015).

Tafamidis, a small molecule that binds and stabilizes the TTR tetramer, was approved in 2019, and is the only therapy approved for the treatment of ATTR-CM in the US. The ATTR-ACT trial in patients with ATTR-CM demonstrated improvements with tafamidis vs placebo in a composite of cardiovascular (CV) events and all-cause mortality after 30 months with differences in the treatment arms only emerging after 18 months for death. Tafamidis also showed a reduction in decline in 6MWT and KCCQ-OS vs placebo at earlier timepoints. However, disease progression continued, albeit at a slower rate than placebo (Maurer et al 2018). Recent real-world evidence has also shown that exercise capacity declines substantially in a subset of tafamidis-treated patients who have signs of ongoing cardiac amyloid deposition (Badr Eslam et al 2022; Dalia et al 2021; Nakaya et al 2023). Tafamidis is not approved to treat the polyneuropathy of ATTR amyloidosis in the US.

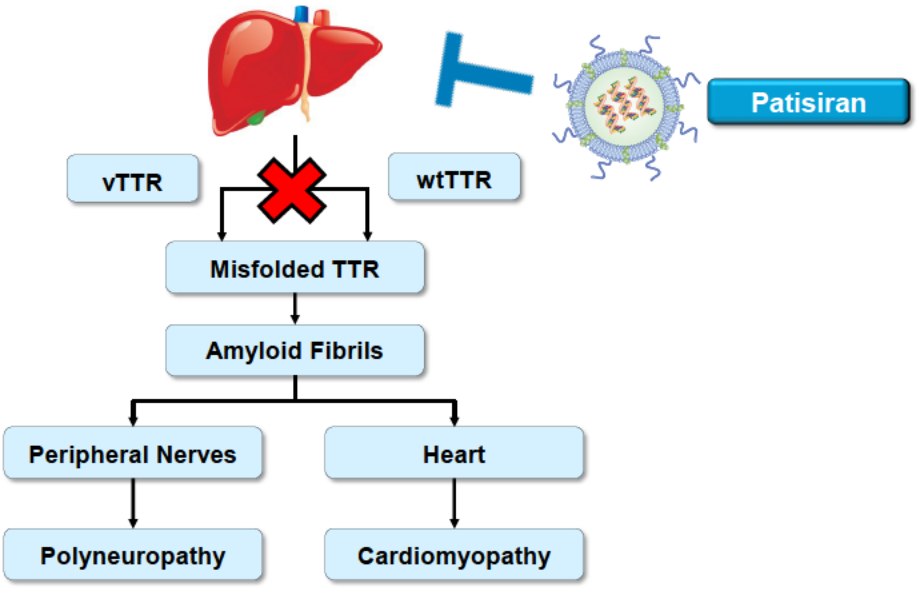
A high unmet need exists for additional treatment options to address disease progression, especially for therapies with a differentiated mechanism of action. The need for treatment options for ATTR-CM is highlighted by the rapid enrollment of 200 patients whose ATTR-CM has progressed on tafamidis into the patisiran Expanded Access Program (EAP; Section 8). The incidence of progression is substantial: 22% of patients in APOLLO-B who were on tafamidis alone showed worsening of heart failure by NYHA class after 12 months. Therapies that can suppress amyloid deposition before there is substantial loss of functional capacity and health would be ideal (Maurer et al 2022). This sentiment was echoed in the Amyloidosis Forum, a June 2023 meeting held by the Amyloidosis Research Consortium and FDA where ATTR patients expressed a strong interest in the development of new treatments that preserve functional capacity, health status, and QoL (Amyloidosis Research Consortium 2023).

1.3 Overview of Patisiran

*1.3.1 **Therapeutic Hypothesis***

The liver produces >95% of TTR in the circulation (Felding and Fex 1982). Patisiran is comprised of an siRNA formulated for targeted delivery to hepatocytes where it degrades TTR mRNA by the mechanism of RNAi, inhibiting the synthesis of both wt and variant TTR protein with equal potency. The therapeutic hypothesis is that a rapid and substantial reduction in TTR protein synthesis will inhibit subsequent amyloid formation and deposition in the heart and other tissues, thereby stabilizing or slowing the rate of disease progression (Figure 1).

Figure 1: Patisiran Therapeutic Hypothesis



vTTR=variant transthyretin; wtTTR=wild-type transthyretin.

1.3.2 Proposed Indication and Dosing Regimen

The proposed indication of patisiran is for *the treatment of cardiomyopathy of wt or hATTR amyloidosis in adults to slow the decline in functional capacity and reduce symptoms*.

The recommended dose of patisiran is 0.3 mg/kg (up to 30 mg) administered via intravenous (IV) infusion once every 3 weeks (q3W) with pre-medication to mitigate the risk of infusion-related reactions (IRRs). This dose and regimen were selected given the potent and near maximal reduction in TTR observed across several studies (Section 5.1.1). The same dosing regimen is approved for use in patients with hATTR-PN.

1.4 Clinical Development Program for Patisiran

The patisiran clinical development program consists of 8 clinical trials across the spectrum of ATTR amyloidosis (Table 3). The pivotal results demonstrating the efficacy and safety of patisiran in patients with wtATTR or hATTR amyloidosis with cardiomyopathy are from the global, randomized, DB, placebo-controlled, Phase 3 APOLLO-B study as well as the open-label extension (OLE period; Sections 6.2 and 7) supported by existing confirmatory evidence from the global, randomized, DB, placebo-controlled, Phase 3 APOLLO study that led to patisiran's approval in 2018 for the treatment hATTR-PN (Section 6.1).

1.5 Phase 3 APOLLO Study of the Polyneuropathy of hATTR Amyloidosis

APOLLO was a global, randomized, DB, placebo-controlled trial designed to evaluate the efficacy and safety of patisiran in patients with hATTR-PN (Adams et al 2018) (additional details provided in Section 3.4). Patients with 39 different variant mutations in the TTR gene

were enrolled in this study. The primary endpoint was the change from baseline at Month 18 in the composite measure of neuropathy impairment, mNIS+7. Secondary endpoints included neuropathy symptom specific QoL (Norfolk-Qol-DN), disability (Rasch-built Overall Disability Scale [R-ODS]), gait speed (10-meter walk test), nutritional status (modified body mass index [mBMI]) and autonomic symptoms (COMPASS 31). Patisiran demonstrated rapid and sustained reductions in serum TTR resulting in improvement in neuropathy impairment and QoL as early as Month 9 (Figure 10). Patisiran-treated patients showed clinically meaningful and statistically significant improvements compared with placebo ($p<0.001$ for both mNIS+7 and Norfolk QoL). The results were consistent and significant across all other secondary endpoints (Adams et al 2018) and a long-term follow-up study has shown that the treatment benefits observed in APOLLO are sustained (Adams et al 2021).

Approximately 56% of patients in APOLLO were part of a pre-specified cardiac subgroup based on criteria for evidence of cardiac amyloid involvement, and the effects of patisiran on cardiomyopathy manifestations were assessed in this subgroup. Pre-specified exploratory analyses included echocardiographic assessment of left ventricular (LV) structure and function and the cardiac biomarker NT-proBNP. Compared with placebo, patisiran reduced NT-proBNP by 37% and 55%, respectively at Months 9 and 18 in the cardiac subpopulation (Month 9 ratio of fold change patisiran/placebo: 0.63; 95% confidence interval [CI]: 0.50–0.80; Month 18: 0.45; 95% CI: 0.34–0.59; $p<0.001$) (Solomon et al 2019). At Month 18, echocardiographic assessments demonstrated significant improvements with patisiran compared with placebo in LV wall thickness and end-diastolic volume, signs consistent with the suppression of ongoing amyloid deposition in the heart, and associated improvements compared to placebo in cardiac output and global longitudinal strain, the latter being a measure of systolic function (Figure 12) (Solomon et al 2019).

Additionally, a post-hoc analysis of safety data that included all patients in APOLLO regardless of cardiac status showed a reduction in the composite endpoints of all-cause hospitalizations and all-cause deaths as well as cardiac hospitalizations and all-cause death (additional details provided in Section 6.1.4) (Solomon et al 2019). APOLLO formed the basis for further evaluation of patisiran in ATTR-CM in APOLLO-B.

1.6 Pivotal Phase 3 APOLLO-B Study of the Cardiomyopathy of ATTR Amyloidosis

APOLLO-B was designed with input from the FDA, including the study population, selection of the primary and first secondary endpoints of 6MWT and KCCQ-OS, and study duration. Given that ATTR amyloidosis is a rare and serious disease, FDA endorsed APOLLO-B as a single trial to support approval consistent with 2019 Draft Guidance for the Industry Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (FDA 2019b). The objectives and features of the APOLLO-B study are also reflected in FDA's subsequent Draft Guidance for Industry Treatment for Heart Failure: Endpoints for Drug Development (FDA 2019a) (additional details provided in Section 4.3).

1.6.1 ***Study Design***

APOLLO-B is a global trial designed to assess the efficacy and safety of patisiran in adults with the cardiomyopathy of wtATTR or hATTR amyloidosis to evaluate the efficacy of patisiran relative to placebo on functional capacity (6MWT) and health status and QoL (KCCQ-OS) at 12 months (Figure 16). The study is comprised of a completed, 12-month, DB, placebo-controlled period, and an ongoing, 36-month, OLE period, in which all patients receive patisiran. The duration of the placebo-controlled portion of the study was selected based on the APOLLO and ATTR-ACT studies where differences in functional endpoints were observed within 12 months with patisiran and tafamidis (Adams et al 2018, Maurer et al 2018). APOLLO-B was anticipated to enroll approximately 80% of the study population with wtATTR amyloidosis patients because of its predominant prevalence among the ATTR-CM population. Eligible patients were required to have a diagnosis of ATTR-CM confirmed by either biopsy or technetium scintigraphy; the latter was allowed because of the rapid, widespread adoption of non-invasive diagnosis in the few years prior to the start of APOLLO-B. The study was designed to include patients with a range of disease severity, including patients in an early disease stage where the potential for slowing of disease progression could be most beneficial. The patients at highest risk (i.e., in NYHA class IV or in both NYHA class III and amyloidosis disease stage 3 [NT-proBNP >3000 ng/L and estimated glomerular infiltration rate (eGFR) <45 ml/min/1.73m^2]; Gillmore et al 2018) were excluded, to ensure that the patients enrolled were more likely to complete assessments at end of the 12-month DB period of the study.

At the time of study initiation in 2019, tafamidis had just been approved in the US and was under review in other countries for the treatment of ATTR-CM. Therefore, the use of tafamidis in APOLLO-B was permitted where it was approved and commercially available and only in patients who had received treatment for ≥6 months and experienced disease progression in the opinion of the Investigator. The proportion of patients on background tafamidis was capped at 30% of total enrollment to avoid potential confounding effects, with the option for any patient to initiate tafamidis treatment during the study.

A full list of enrollment criteria is provided in Appendix 12.1.

The primary endpoint was the change from baseline at Month 12 in the 6MWT. The 6MWT measures the distance walked over 6 minutes using highly standardized procedures and provides a clinically relevant assessment of functional capacity. The test is commonly employed to quantify functional capacity in HF, including clinical studies in ATTR-CM (Bittner et al 1993; Flynn et al 2009; Flynn et al 2012; Forman et al 2012; Mangla et al 2013; Masoudi et al 2004; Maurer et al 2018). The first secondary endpoint was the change from baseline at Month 12 in KCCQ-OS score . KCCQ-OS is a reliable, sensitive, and validated clinical outcome assessment that has been used extensively in trials of HF therapeutics. The KCCQ-OS measures patients' perception of health status, which encompasses HF symptoms and the impact of HF on physical and social function, and QoL.

Additional secondary endpoints included a composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits) and change from baseline in 6MWT over the 12-month DB period. There were also composite endpoints of all-cause mortality and

frequency of all-cause hospitalizations and urgent HF visits over the 12-month DB period. Exploratory endpoints included change from baseline at Month 12 in NT-proBNP, troponin I, NYHA class, and ATTR amyloidosis disease stage as well as change from baseline in serum TTR levels through Month 12. APOLLO-B also included an exploratory imaging sub-study evaluating technetium-labeled cardiac scintigraphy using an established diagnostic scale (Hutt et al 2017; Perugini et al 2005).

Definitions of the analysis populations for APOLLO-B are provided in Section 6.2.1.3.1.

1.6.2 Patient Demographic and Baseline Disease Characteristics

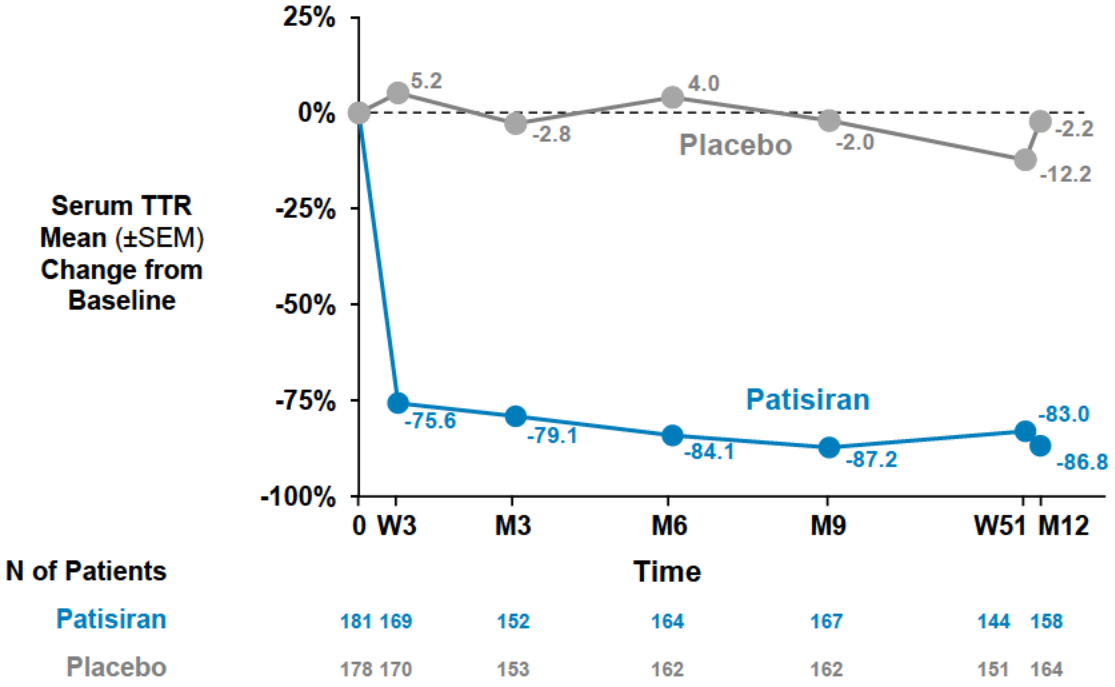
A total of 360 patients were randomized (1:1) to patisiran (0.3 mg/kg up to 30 mg) or placebo. As expected, the median age at screening was 76.0 years, 89.4% were male, and 80.2% of patients enrolled were wt ATTR-CM. Baseline demographics and disease characteristics were generally similar between the patisiran and placebo groups as well as patients who were and were not on background tafamidis (see Sections 6.2.2.2 and 6.2.2.3 for details). Additional details for US baseline demographics and disease characteristics are provided in Appendix 12.2. For the overall study population, most patients were diagnosed within a year of enrolling in the study. The majority of patients had NYHA class II HF (85.2%) and were in ATTR amyloidosis disease stage 1 (68.0%; NT-proBNP <3000 ng/L and eGFR >45 ml/min/1.73 m^2) or stage 2 (25.3%; NT-proBNP <3000 ng/L or eGFR >45 ml/min/1.73 m^2). Approximately 25% of patients were on background tafamidis, and most of these patients (77/91, 85%) were from the US.

1.6.3 Double-Blind Period Efficacy Findings

1.6.3.1 Pharmacodynamics: TTR Reduction

Patisiran administration resulted in marked, rapid, and sustained reduction in circulating TTR (variant and wt forms; Figure 2). The decrease was evident as early as Week 3, and levels remained consistently reduced through Month 12. At Month 12, the mean (standard error of the mean [SEM]) decrease in serum TTR was 86.8% (1.1%) from baseline.

Figure 2: Change from Baseline in Serum TTR During 12-Month DB Period in APOLLO-B (Full Analysis Set)



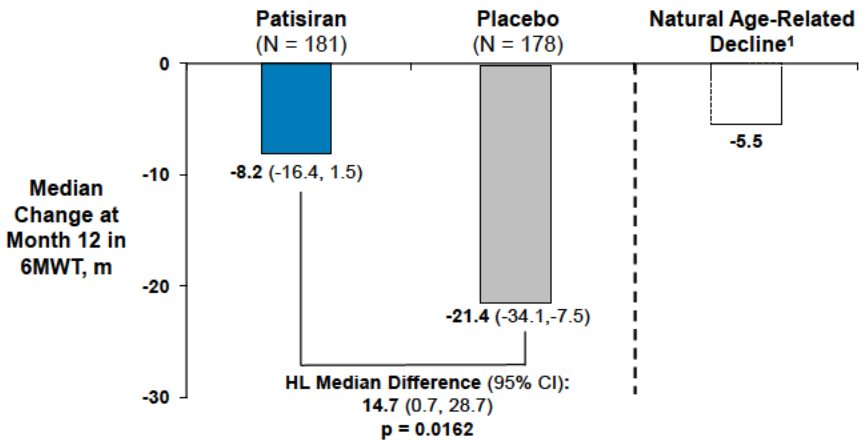
DB=double-blind; M=month; TTR=transthyretin; W=week.

1.6.3.2 Primary Endpoint: 6-Minute Walk Test

APOLLO-B met its primary endpoint of functional capacity as measured by change from baseline in 6MWT distance at Month 12, compared with placebo (Hodges-Lehmann [HL] estimate of the median difference, 14.7 meters; p=0.0162; Figure 3).

In relative terms, over 12 months, patisiran treatment slowed the decline in functional capacity by 62% compared with placebo. The change seen in the patisiran arm is comparable to the age-related decline of 5–6 meters a year reported in healthy adults (Enright and Sherrill 1998). Across a broad range of thresholds of deterioration (e.g., change <0 meters), a consistently greater percentage of placebo-than patisiran-treated patients showed a decline (Figure 18). Likewise, a consistently greater percentage of patisiran- than placebo-treated patients showed an improvement at thresholds of change >0 meters (Figure 19; Figure 43). The treatment effect was consistent across multiple sensitivity analyses (Table 11). 6MWT data for all time points are presented in Figure 31.

Figure 3: Change from Baseline in 6MWT at Month 12 in the DB Period of APOLLO-B (Full Analysis Set)

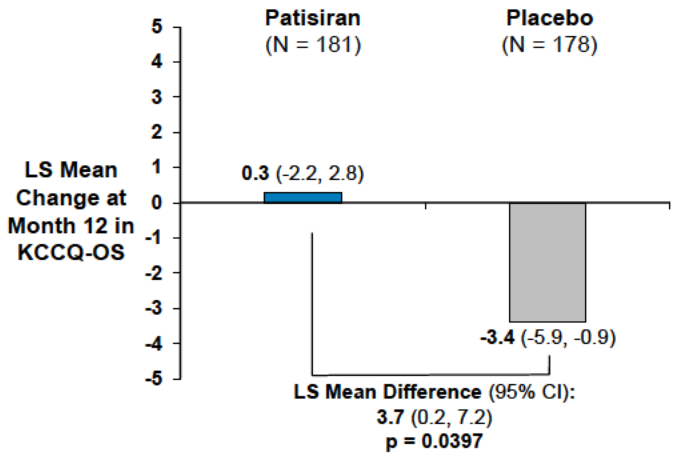


1. Enright and Sherrill 1998 reporting decline in 6MWT in healthy subjects of similar age
6MWT=6-minute walk test; DB=double-blind; Note: Analysis includes patients not on background tafamidis (patisiran monotherapy, 75% of patients) and patients on background tafamidis (concomitant tafamidis).

1.6.3.3 *First Secondary Endpoint: Kansas City Cardiomyopathy Questionnaire-Overall Summary*

In APOLLO-B, patisiran had a significant impact on health status and QoL, as assessed in the first secondary endpoint, change in KCCQ-OS at Month 12. The least-squares [LS] mean difference was 3.7 points compared with placebo (p=0.0397; Figure 4). The LS mean change in KCCQ-OS score increased in the patisiran group by +0.3 points indicating stabilization of health status and QoL, compared with a decrease in the placebo group by −3.4 points (additional details in Section 6.2.1.2.2).

Figure 4: Change from Baseline in KCCQ-OS Score at Month 12 in DB Period of APOLLO-B (Full Analysis Set; MMRM)



DB=double-blind; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; MMRM=mixed-effect model repeated measures.
Note: Analysis includes patients not on background tafamidis (patisiran monotherapy, 75% of patients) and patients on background tafamidis (concomitant tafamidis).

The results consistently favored patisiran across all domains of the KCCQ including physical limitation, total symptoms, QoL, and social limitation (Figure 22), with greater treatment effects observed in activities of daily living that require higher cardiac output (e.g., walking, ascending stairs) and symptoms that commonly affect ATTR patients with cardiomyopathy (e.g., dyspnea, orthopnea) (Figure 38).

A treatment effect favoring patisiran was consistently observed across response thresholds (Figure 44). KCCQ-OS data for all time points are presented in Figure 32.

1.6.3.4 Primary and First Secondary Endpoints Across Subgroups

The treatment effect with patisiran on functional capacity (6MWT) and patients' experience of their health status and QoL (KCCQ-OS) was generally consistent across subgroups of baseline demographic and disease characteristics. Further considerations and analyses related to the effects of patisiran without or with background tafamidis and in NYHA class III patients are discussed below (Table 6; Figure 23).

Patisiran Monotherapy

For the most direct assessment of patisiran, the monotherapy treatment effect was investigated in patients not on background tafamidis. Approximately 75% of the patient population was in the monotherapy subgroup (N=268). Background tafamidis was a stratification factor, which allowed a valid, randomized comparison for patisiran monotherapy. For 6MWT, the patisiran monotherapy effect was 21.3 meters at Month 12 using the HL estimate of median difference (nominal p=0.0123); the LS mean difference was 26.5 meters (Table 16). For KCCQ-OS, a 4.3-point improvement was observed with patisiran compared with placebo in the monotherapy

group (nominal p=0.0415; Table 16). Thus, the effects of patisiran monotherapy were larger than in the overall population.

Background Tafamidis

Only 25% of the patient population was on background tafamidis (N=91; 46 on patisiran and 45 on placebo). While disease progression on tafamidis was required for study entry, the magnitude of decline in the placebo arm in the 12-month DB period was limited across the endpoints assessed resulting in point estimates with wide confidence intervals that either slightly favored patisiran or slightly favored placebo (Figure 23; Table 17). All considered, it is difficult to draw conclusions on treatment effect; thus, the treatment effect has not been established for patients on background tafamidis.

NYHA Class III Heart Failure

In the small subgroup of patients with NYHA class III HF at baseline (N=28; 15 on patisiran and 13 on placebo), the point estimates of the treatment effect were slightly negative for the 6MWT and of the same magnitude as the overall population for the KCCQ-OS. To better understand the treatment effects of patisiran in patients with advanced disease, other parameters were examined. Patisiran showed favorable effects among other subgroups indicative of greater HF severity, such as baseline 6MWT distance <360 meters or NT-proBNP ≥2000 ng/L (Figure 23). Each cutoff has been associated with an increased risk of death in patients with ATTR-CM (Vong et al 2021). Furthermore, in a post-hoc analysis of patients with a baseline KCCQ-OS score <50 (N=72), which typically reflects patients with NYHA class III or IV HF (Tran et al 2021), the treatment effects favor patisiran. The HL estimate of the 6MWT treatment difference was 9.9 meters (95% CI: −26.5–46.3), and the KCCQ-OS LS mean difference was 10.1 (95% CI: 2.1–18.1). Taken together, the data suggest that patisiran can benefit patients across a broad range of HF severity.

1.6.3.5 Other Secondary Endpoints

The secondary endpoints were tested following a pre-specified hierarchical order (as listed in Section 6.2.1.2). The first composite endpoint of all-cause mortality, frequency of CV events, and change from baseline in 6MWT over 12 months was not statistically significant; therefore, all subsequent p-values are nominal for all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in patients not on background tafamidis and in the overall study population (Section 6.2.7).

Overall, the number of hospitalizations, urgent HF visits and deaths was low in the 12-month DB period.

All-cause mortality was analyzed as a component of the composite endpoint. As specified in the statistical analysis plan, deaths due to COVID-19 were excluded, and cardiac transplant and left ventricular assist device (LVAD) placement were counted as equivalent to death. There were 4 deaths on patisiran and 10 on placebo during the DB period (hazard ratio [HR]=0.36; 95% CI: 0.11–1.14). The counts exclude 1 COVID-19 death in the patisiran arm and include 2 heart transplants in the placebo arm. While the number of events is small, the numerical trend favoring

patisiran is reassuring and indicates no detrimental effects. Further details on deaths are provided in Section 6.2.7.3.

1.6.3.6 Exploratory Endpoints

Cardiac Laboratory Parameters: NT-proBNP and Troponin I

NT-proBNP and troponin I are laboratory parameters that assess cardiac stress and injury utilized in clinical practice, in ATTR amyloidosis disease staging, and in expert consensus criteria for defining disease progression in ATTR-CM (Garcia-Pavia et al 2021; Pregenzer-Wenzler et al 2020). Further, NT-proBNP levels and increases in levels are strong prognostic indicators of outcomes in ATTR amyloidosis (Connors et al 2016; Damy et al 2016; Kristen et al 2017; Law et al 2022a; Law et al 2022b).

In APOLLO-B, all patients had substantially elevated NT-proBNP at baseline, indicative of the ongoing cardiac stress due to ATTR amyloidosis. Patisiran-treated patients showed modest increases of 11% and 13% in NT-proBNP and troponin I from baseline to Month 12, respectively (Figure 27; Figure 28). In contrast, placebo-treated patients showed steady worsening in cardiac laboratory parameters from baseline to Month 12 with a 38% increase in NT-proBNP and 30% increase in troponin I (Figure 27; Figure 28). A 30% increase in the level of either laboratory parameter has been suggested as a sign of disease progression in an expert consensus statement (Garcia-Pavia et al 2021). The median increase at Month 12 in the placebo and patisiran groups for NT-proBNP was 518 and 131 ng/L and for troponin I was 14.5 and 3.8 ng/L, respectively. A 500 ng/L increase in NT-proBNP over 12 months has been reported to be a strong predictor of mortality (Law et al 2022b).

1.6.4 Open-Label Extension Period Efficacy Findings

Following completion of the Month 12 efficacy visit, all patients in the placebo- and patisiran-treatment arms received patisiran in the OLE period. Patients remained blinded to their original treatment assignment. The Month 18 data for all patients remaining in the study are presented below and in Section 6.2.9. Some patients have completed study visits beyond Month 18 and these data are included for completeness. However, due to enrollment trajectories, not all patients had completed the later timepoints resulting in an incomplete dataset and limiting interpretation of the point estimates at Month 21 and beyond. Data from the OLE period will be available up to Month 24 by 13 September 2023.

6-Minute Walk Test and Kansas City Cardiomyopathy Questionnaire-Overall Summary Score

The patisiran group showed maintenance of the treatment benefit in the 6MWT and KCCQ-OS during the OLE period.

During the 12-month DB period, the placebo group showed steady declines in 6MWT performance and KCCQ-OS score. Upon starting patisiran at Month 12, the group appears to show a slower rate of decline by Month 18; however, longer term follow-up data will be required to confirm (Figure 31; Figure 32).

Composite of All-Cause Mortality, All-Cause Hospitalizations, and Urgent Heart Failure Visits

During APOLLO-B (DB + OLE), for the composite of all-cause mortality and frequency of all-cause hospitalization and urgent HF visits, the point estimate of the HR was 0.80 (95% CI: 0.57–1.12; Figure 33).

In the DB + OLE periods, there was a favorable trend for all-cause mortality (HR=0.55 [95% CI: 0.28–1.09]; Figure 34). There were 13 deaths (7.2%) in patients randomized to patisiran and 23 (12.9%) in patients randomized to placebo. The counts exclude 2 COVID-19 deaths in the patisiran group and include 5 heart transplants in the placebo group.

Cardiac laboratory parameters: NT-proBNP and Troponin I

During the OLE period, patients randomized to patisiran continued to demonstrate relative stability in both NT-proBNP and troponin I (Figure 35). Importantly, patients who received placebo during the DB period and then patisiran during the OLE period appeared to reproduce the pattern of the patisiran arm during the DB period. Upon initiating patisiran treatment at Month 12, both NT-proBNP (Figure 35, left panel) and troponin I (Figure 35, right panel) appeared to show a stabilization at Month 15 that has continued through Month 18. This stability follows the steady worsening in both parameters during administration of placebo in the DB period.

1.6.5 Clinical Meaningfulness of APOLLO-B Results

Additional post-hoc analyses below illustrate the clinical meaningfulness of the treatment effects measured in APOLLO-B.

1.6.5.1 6MWT

The minimal clinically important difference (MCID) is the smallest treatment effect in an outcome that a patient can perceive as meaningful. The Sponsor conducted a comprehensive, systematic PRISMA-based literature search to identify MCIDs for 6MWT across a range of conditions. No 6MWT MCID for patients with ATTR-CM was identified. In general, the MCID for an intervention depends upon the disease, the mechanism of action of the therapeutic intervention, and clinical characteristics of the patient population such as age and baseline 6MWT distance. Older HF patients, who have shorter 6MWT distances, report smaller changes in 6MWT distance as being meaningful (Bohannon and Crouch 2017; Khan et al 2023; Perera et al 2006).

To evaluate the clinical relevance of the patisiran treatment effect on 6MWT in APOLLO-B, a post-hoc analysis was conducted to determine an MCID and a range of clinically relevant walk distance thresholds. An anchor-based method was employed that was consistent with concepts from FDA Draft Guidance Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making (FDA 2023) and used the anchor-based Change Difference (CD), the most frequently used anchor-based statistical method for calculating the MCID (Mouelhi et al 2020). All data from placebo- and patisiran-treated patients were used, and sufficient correlation (0.47 at Month 12 for the observed values; 0.31 at Month 12 for the change from baseline values) was observed between 6MWT and KCCQ-OS,

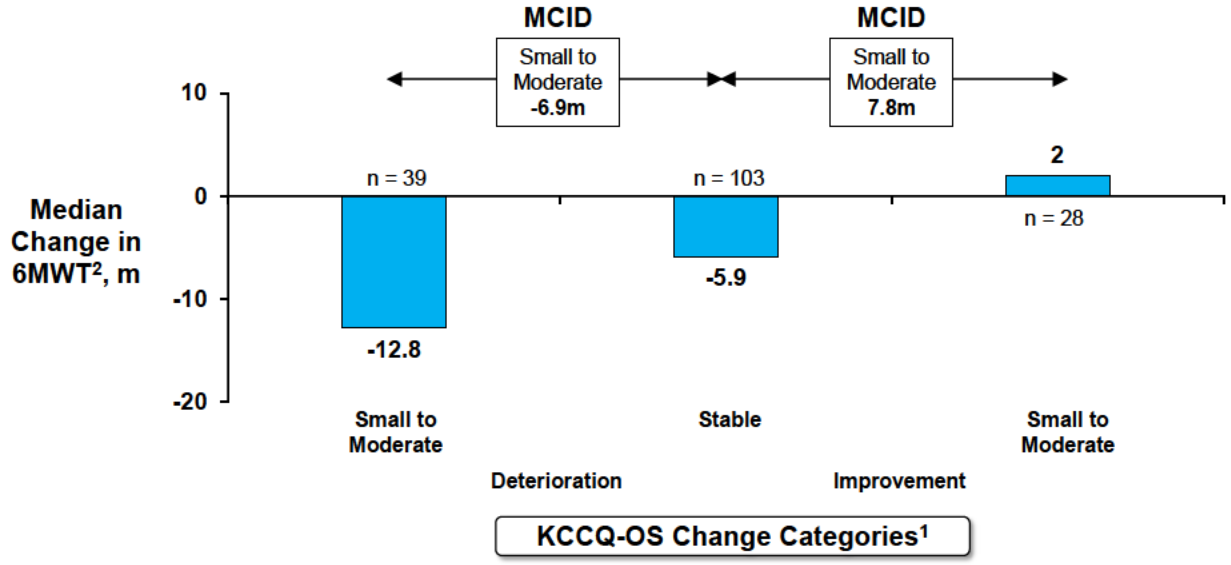
demonstrating internal consistency of the data. Correlations >0.3 are generally considered acceptable (Revicki et al 2008).

First, thresholds of 6MWT change were determined by using established thresholds of KCCQ-OS change (Figure 5) ranging from small-to-moderate deterioration to small-to-moderate improvement (Spertus et al 2005).

Second, the MCID in 6MWT distance was calculated as the difference in the median change from baseline in 6MWT between patients who had a stable KCCQ-OS score and patients who had a small-to-moderate deterioration or improvement in KCCQ-OS. This MCID was determined to be 6.9 meters for decline and 7.8 meters for improvement, which is comparable to MCIDs reported in older adults with cardiopulmonary conditions (Bohannon et al 2017; Perera et al 2006).

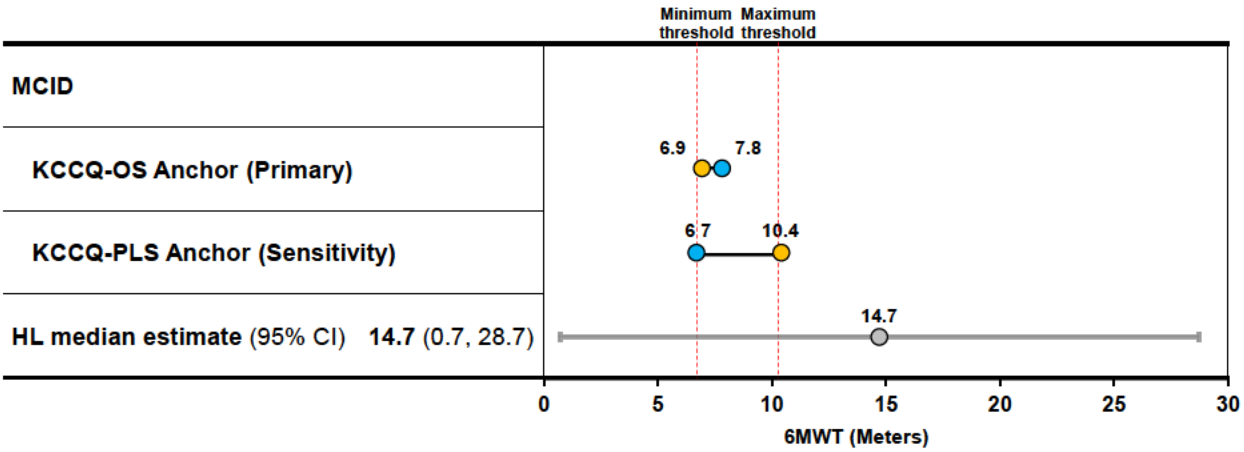
A sensitivity analysis was performed using the KCCQ-PLS (Physical Limitation Score) which evaluates the impact of the patient's HF on a number of activities across a range of increasing exertion. This yielded MCIDs of 6.7 meters (improvement in 6MWT from baseline) to 10.4 meters (decline in 6MWT from baseline; Figure 6). The overall treatment effect on 6MWT in APOLLO-B (median difference of 14.7 meters) exceeds the estimated MCID, suggesting that the 6MWT treatment effect observed in APOLLO-B corresponds to a difference in functional capacity that the majority of patients would consider meaningful (Figure 6). More patisiran- than placebo-treated patients exceeded the MCID for improvement, 7.8 meters, and more placebo- than patisiran-treated patients exceeded the MCID for decline, −6.9 meters (Figure 37).

Figure 5: Range of Clinically Meaningful Differences in 6MWT in APOLLO-B Based on KCCQ-OS Anchor



1. KCCQ-OS categories: Deterioration - Small to Moderate >-10 to -5, Stable >-5 to <5, Improvement - Small to Moderate 5 to <10.
2. APOLLO-B overall population.
6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; MCID=minimum clinically important difference.

Figure 6: 6MWT Treatment Effect Corresponds to a Difference that the Majority of Patients Experience as Clinically Meaningful



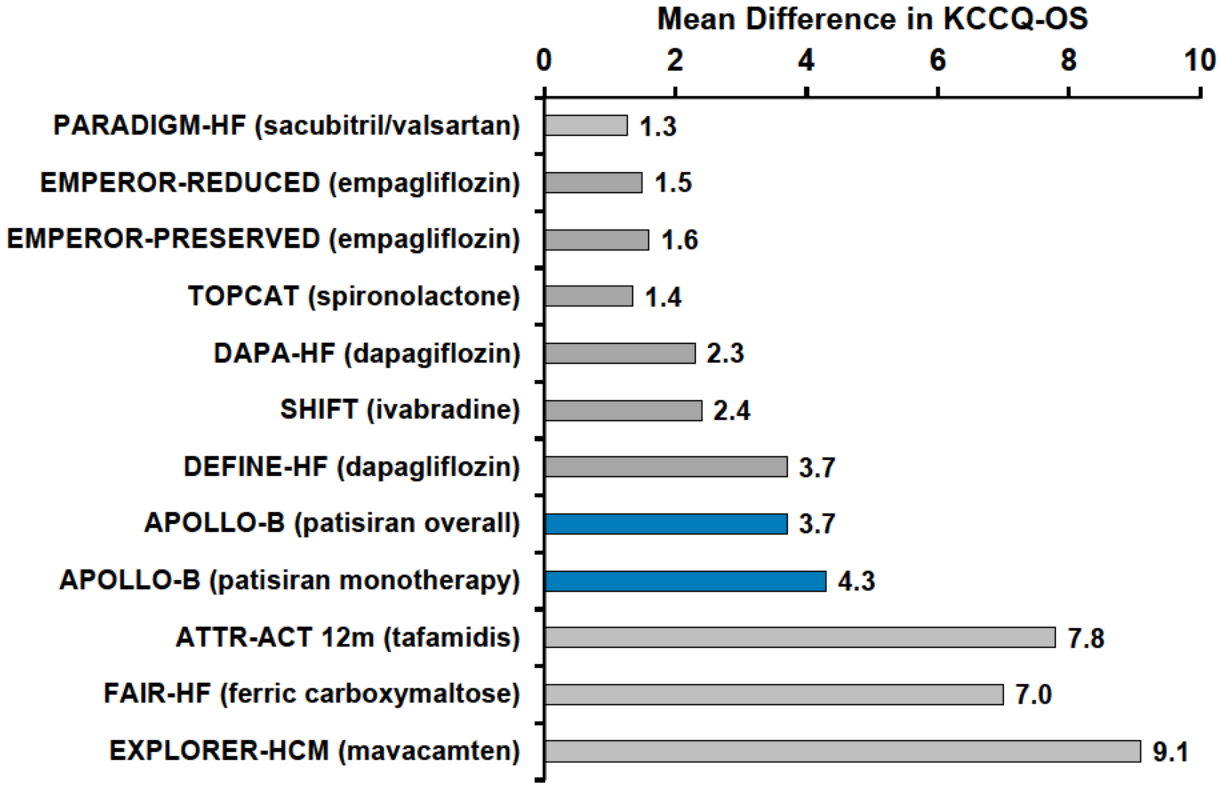
6MWT=6-minute walk test; HL=Hodges-Lehmann; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; KCCQ-PLS=Kansas City Cardiomyopathy Questionnaire-Physical Limitation Score; MCID=minimal clinically important difference.
Note: Yellow points correspond to MCID for decline and blue points correspond to MCID for improvement.
Note: MCID calculated using observed data.

1.6.5.2 KCCQ-OS

The impacts of patisiran on health status and QoL underscore the clinical meaningfulness of the 6MWT treatment effect. Consistent benefits were demonstrated in the KCCQ-OS, its domains of physical limitations, total symptoms, QoL, and social limitations, and questions in each domain that assess the specific impacts of HF in the daily lives of patients.

As quantified by the KCCQ-OS, the patisiran treatment effect on health status and QoL is in the range reported for other drugs prescribed to treat HF, such as sacubitril-valsartan and the sodium-glucose cotransporter-2 (SGLT2) inhibitors (Figure 7). In the ATTR-ACT study of tafamidis, the significantly higher rate of decline in the placebo arm, 10 points in KCCQ-OS at 12 months (Maurer et al 2018), than in APOLLO-B, contributes to the greater magnitude of the observed tafamidis treatment effect.

Figure 7: Mean Difference in KCCQ-OS for Heart Failure Treatments



Lewis et al 2016; Anker et al 2009; Lewis et al 2017; Butler et al 2021; Butler et al 2022; Kosiborod et al 2020; Nassif et al 2019; Spertus et al 2021.
Note: Study dates range from 2009 to 2022.
Note: Study timepoint of KCCQ-OS measurement (Paradigm-HF: 8 months, EMPEROR-REDUCED: 12 months, EMPEROR-PRESERVED: 12 months, TOPCAT: 12 months, DAPA-HF: 8 months, SHIFT: 22 months, DEFINE-HF: 3 months, APOLLO-B: 12 months, ATTR-ACT: Month 12 data shown, FAIR-HF: 6 months, EXPLORER-HCM: 7.5 months).
KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.

The personal impact of the treatment effect to patients is evident in the consistent treatment benefit across KCCQ domains (Section 6.2.5.1; Figure 22) and in their responses to individual questions in the KCCQ-OS, of which 19 out of 20 favored patisiran (Section 6.3.2; Figure 38). Patients with ATTR-CM experience a dramatic loss of strength and stamina, which are exacerbated by symptoms of dyspnea and fatigue (Rintell et al 2021). Thus, it is notable that the greatest treatment differences between the patisiran and placebo groups relate to those symptoms and activities such as hurrying or jogging, walking one block and climbing a flight of stairs. These and other impacts appeared to have a consequential impact on enjoyment of life, which showed the biggest difference favoring patisiran compared with placebo (Figure 38).

1.6.5.3 Disease Progression

Exploratory analyses in APOLLO-B of NYHA class and ATTR amyloidosis disease stage, both of which are used clinically to assess HF severity in patients with ATTR-CM, demonstrate favorable treatment effect with patisiran compared with placebo (Figure 39). Worsening of NYHA class at Month 12 was observed almost twice as often in the placebo group than patisiran

group, 24.1% and 13.6%, respectively (odds ratio [OR]: 0.6; nominal p=0.0226; Figure 40). Similarly, worsening by ATTR amyloidosis disease stage was observed more frequently in the placebo than patisiran group, 27.1% and 18.0%, respectively (OR: 0.6; nominal p=0.0273; Figure 40).

1.6.6 Safety Overview

The safety profile of patisiran has been well-established in both clinical trials and 5 years of post-marketing experience in patients with hATTR-PN. To date, there are over 8,500 patient-years of exposure to patisiran worldwide, with some patients treated for over 7 years. In APOLLO-B, the safety profile of patisiran was consistent with that previously observed, with no new or unexpected safety concerns.

1.6.6.1 Treatment Exposure

During the DB period in APOLLO-B, 181 patients with ATTR-CM were treated with patisiran at 0.3 mg/kg IV q3W or for patients weighing ≥100 kg at 30 mg IV q3W. The median duration of treatment in the patisiran group was 12.4 months (range: 0.0–14.0 months), with a cumulative treatment exposure of 180.7 patient-years.

Including data from the OLE, 347 patients with ATTR-CM have been treated with patisiran with a median treatment duration of 18.4 months (range: 0.0–37.0 months), cumulative treatment exposure of 482.0 patient-years, and 8,293 doses administered.

1.6.6.2 Safety Findings

In APOLLO-B, the incidence, nature, and severity of adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation were similar between the patisiran and placebo groups. A total of 14 patients died during the DB period: 5 in patisiran and 9 in placebo (Table 1).

Table 1: Overview of Safety in DB Period of APOLLO-B (Safety Analysis Set)

	Patisiran (N=181) n (%)	Placebo (N=178) n (%)
AE	165 (91.2)	168 (94.4)
SAE	61 (33.7)	63 (35.4)
Severe AE	47 (26.0)	52 (29.2)
AE leading to study drug interruption	20 (11.0)	23 (12.9)
AE leading to study drug discontinuation	5 (2.8)	5 (2.8)
Deaths[a]	5 (2.8)	9 (5.1)

a. Safety analysis includes deaths on-study and after withdrawal from the study. One placebo patient stopped study participation during the DB period and died after the pre-specified window for the statistical analysis of deaths during the DB period.
DB=double-blind; SAE=serious adverse event.

The most common AEs (≥10% of patients) in the patisiran group were cardiac failure, IRRs, and constipation (details in Section 7.4). Cardiac failure was the most common reported AE,

consistent with the patient population in APOLLO-B; although there were no clinically relevant differences observed between the groups, the incidence of cardiac failure events trended lower in patients treated with patisiran (38% vs. 47% in placebo patients). Other symptoms consistent with ATTR amyloidosis included atrial fibrillation and orthostatic hypotension, which also trended lower in the patisiran group. As expected, AEs of IRRs and those that are associated symptoms of IRRs occurred more often in patisiran-treated patients.

The proportions of patients experiencing SAEs were similar in the patisiran (33.7%) and placebo (35.4%) groups during the DB period. The most common SAEs (≥2% of patients) in either treatment group were cardiac failure (8.3% patisiran, 7.3% placebo), atrial fibrillation (2.8% patisiran, 2.2% placebo), AV block complete (1.1% patisiran, 2.2% placebo), amyloidosis (0.6% patisiran, 2.2% placebo), and syncope (1.1% patisiran, 2.2% placebo).

All deaths were evaluated by a blinded, external, independent adjudication committee to classify whether they were of CV or non-CV origin. Of the 5 deaths in the patisiran group, 2 were adjudicated as CV deaths (1 sudden cardiac death and 1 death due to cardiac failure) and 3 as non-CV deaths (1 COVID-19, 1 pancreatitis, and 1 undetermined). Of the 9 deaths in the placebo group, 4 were classified as CV deaths (all due to cardiac failure), and 5 were classified as non-CV deaths (1 infection, 1 cholangitis, 1 pancreatic cancer, and 2 undetermined).

1.6.6.2.1 Safety Topics of Interest

In order to characterize the safety profile of the product for this indication, careful review of all available safety data was performed including patient's vital signs, laboratory data, and evaluation of all AEs.

Safety topics were identified for enhanced data investigation based on the therapeutic class and mechanism of action of patisiran, observations from nonclinical studies, route of administration, and disease-related pathophysiology of ATTR-CM. Four major topics of interest included cardiac events, IRRs, hepatic events (because patisiran targets TTR synthesis in hepatocytes), and ocular events (because of the role of TTR as a major carrier for vitamin A). Additional safety analyses were done for extravasation or other infusion site complications, renal events, hypothyroidism, and immunogenicity.

For cardiac events, no clinically relevant differences were noted between the patisiran and placebo treatment groups and the frequencies of cardiac failure and arrythmia were similar or lower in the patisiran group. All IRRs were mild or moderate in severity; none were reported as serious. One patient discontinued in association with an IRR, that was mild in severity. There were no clinically important differences in hepatic AEs; one patient in each group had a severe, hepatic SAE, and a hepatic AE considered related to study drug. There were no hepatic events that resulted in discontinuation of study drug and no events of Hy's law or drug-induced liver injury. All ocular events were mild or moderate in severity and consistent with ocular symptoms and eye disorders observed in patients with ATTR amyloidosis and in this age group. None of the ocular AEs were serious, led to discontinuation of study drug, or were suggestive of vitamin A deficiency.

Additional details on all selected safety topics of interest are provided in Section 7.9.

1.7 Benefit-Risk Summary

ATTR-CM is a rare, serious, unrelentingly progressive, and fatal disease. Tafamidis is the only approved treatment in the US for ATTR-CM and works by binding and stabilizing the TTR tetrameric protein. Despite the availability of tafamidis, disease progression is common and a significant unmet need for new treatment options remains. Patients with ATTR amyloidosis experience disabling symptoms that limit their activities of daily living. In the Amyloidosis Forum, a June 2023 meeting held by the Amyloidosis Research Consortium and FDA, patients with ATTR amyloidosis expressed a strong interest in the development of new treatments that address disabling symptoms and preserve functional capacity, health status, and QoL (Amyloidosis Research Consortium 2023).

The APOLLO-B study demonstrated a statistically significant and clinically meaningful effect on the primary endpoint (6MWT) assessing functional capacity. Over the 12-month DB period, patients in the placebo group showed a steady decline in 6MWT distance, whereas patients in the patisiran group showed preservation of functional capacity with a change that was comparable to the age-related decline expected in healthy adults (approximately 5–6 meters; (Enright and Sherrill 1998)). On a relative basis, patisiran slowed the decline of functional capacity by 62% as measured by 6MWT compared with placebo. Patisiran treatment was also associated with preservation of health status and QoL, as assessed by the KCCQ-OS, the first secondary endpoint, with consistent favorable effects demonstrated across all KCCQ-OS domains (Physical Limitations, Total Symptoms, QoL, and Social Limitation). The results also show that across all response thresholds for both 6MWT and KCCQ, patisiran-treated patients consistently fared better than those on placebo. Results from the OLE, in which both treatment arms received patisiran, further corroborated the primary analysis, with continued efficacy in patisiran-treated patients.

The clinical meaningfulness of the patisiran treatment effect is supported by multiple complementary analyses. First, an MCID for the 6MWT treatment effect was derived from an anchor-based method based on patient-reported health status, using methods outlined in published literature and FDA Guidance. The median treatment effect of APOLLO-B exceeded the study-derived MCID, and results suggest that the observed treatment effect corresponds to a difference in functional capacity that the majority of patients would find clinically meaningful. Second, the mean difference in KCCQ-OS in APOLLO-B is comparable to or exceeds the mean differences observed for therapies approved for use in other forms of HF. Patisiran-treated patients reported more favorable KCCQ-OS scores than placebo patients at every response threshold and scored higher than placebo-treated patients on 19 of 20 individual questions in the KCCQ regarding symptoms, physical limitations, and QoL. And third, patisiran-treated patients experienced less disease progression as indicated by NYHA class and ATTR disease stage, both of which are commonly used clinical assessments in ATTR-CM. These findings are further supported by changes in important clinical cardiac laboratory parameters that are all consistent with reduced disease progression and the expected mechanism of action of patisiran. Taken together, the data suggest that patisiran-treated patients experienced substantially less progression of their disease with just one year on therapy. While statistical significance was not

met for the secondary endpoints of composite outcomes, the overall data in composite outcomes and all-cause mortality were numerically in favor of patisiran, suggesting no harmful effects.

The observed treatment effect of patisiran on 6MWT and KCCQ-OS was greater in the subgroup of patients who received patisiran monotherapy compared to the results in the overall population. In the subgroup with background tafamidis, due to the small sample size (N=91) and limited decline in the placebo group over 12 months, the treatment effect of patisiran is uncertain and has not been established.

In addition to the APOLLO-B results, the efficacy of patisiran in ATTR-CM is also supported by confirmatory evidence from the APOLLO study. Treatment with patisiran for up to 18 months resulted in substantial and sustained reduction in TTR and, in a prespecified subgroup of patients with evidence of cardiac amyloid involvement, corresponding improvements relative to placebo were observed for important exploratory measures of cardiac structure and function and NT-proBNP (Solomon et al 2019). Additionally, a post-hoc analysis in the overall population on APOLLO showed reductions in the composite endpoints of all-cause hospitalizations and all-cause deaths as well as cardiac hospitalizations and all-cause death. Importantly, the overall study results from APOLLO showed that patisiran was highly effective in patients with polyneuropathy due to hATTR amyloidosis, demonstrating that patisiran is disease-modifying in this closely related patient population.

Patisiran has been marketed in the US for 5 years for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and its safety profile has been favorable. In APOLLO-B, patisiran was generally well tolerated in patients with ATTR-CM. There were no new or unexpected safety concerns; cardiac events, and SAEs in the cardiac disorders System Organ Class (SOC) were similar in the patisiran and placebo groups. All IRRs were mild to moderate in intensity, and none were reported as serious. Risks of IRRs are mitigated by pre-medication. The frequency of hepatic AEs was low, and there were no differences between treatment groups. Ocular events were mild or moderate in severity and consistent with ocular symptoms and eye disorders that are frequently reported in the general population of this age. Patients are advised to take vitamin A supplementation (due to the role of TTR in vitamin A circulation). Safety during the OLE period was also similar compared with previous clinical study results and post-marketing experience, with over 8,500 patient-years of exposure to patisiran worldwide, with some patients treated for over 7 years.

Patisiran prevents the disease-causing deposition of circulating TTR as amyloid, by targeting the source of its production in the liver. In APOLLO-B, reduction of TTR by patisiran resulted in substantial delays in disease progression, as measured by functional capacity as well as health status and QoL. These results are further supported by confirmatory findings in patients with hATTR-PN in APOLLO and strong mechanistic data from both APOLLO and APOLLO-B. The totality of data supports a favorable benefit-risk profile for patients with cardiomyopathy due to wtATTR or hATTR amyloidosis. The results of the APOLLO-B study show an uncertain effect of patisiran on the background of tafamidis which can be addressed by appropriate language, to be discussed with FDA, in the label. Overall, these data support the expansion of the approved

indication for patisiran to include treatment of ATTR-CM to slow the decline in functional capacity and reduce symptoms.

2 BACKGROUND ON TRANSTHYRETIN-MEDIATED AMYLOIDOSIS

Summary

- ATTR amyloidosis is a rare, progressively debilitating, and fatal disease.
  - It is caused by misfolded TTR proteins, produced primarily in the liver, that aggregate as amyloid fibrils and plaques depositing in the extracellular space of various tissues including the heart, nerves, and gastrointestinal (GI) tract.
  - ATTR amyloidosis is widely accepted as one disease with the most serious presentations being polyneuropathy and cardiomyopathy; both forms are seen in patients, especially in those with hATTR amyloidosis.
  - Characteristic features of ATTR-CM include clinical HF, conduction abnormalities, and arrhythmias including atrial fibrillation. Progression of HF typically results in hospitalizations and death 2.5–5.5 years after diagnosis. The disease occurs predominantly in males aged >70 years.
- Amyloid deposition begins before symptom onset, and ongoing deposition drives disease progression. Targeting TTR protein production early in disease course is expected to reduce or halt this ongoing amyloid deposition, and in turn result in reduced loss of functional capacity, morbidity, and mortality.
- In recent years, technetium scintigraphy has replaced endomyocardial biopsy for the diagnosis of ATTR-CM leading to diagnosis earlier in the course of the disease.
- Reducing hepatic production of TTR with patisiran has been shown to halt or reverse disease progression of hATTR-PN.
  - Patisiran is the current standard of care in the US for the treatment of hATTR-PN.
- Tafamidis, a TTR tetramer stabilizer, is the only approved treatment for ATTR-CM (approved in 2019).
  - Disease progression continues to occur on tafamidis.
- Patients with ATTR amyloidosis consistently report a need for more treatment options that can help reduce the decline in functional capacity and symptoms which adversely affect their QoL.
- Additional treatment options are needed, ideally targeting the underlying pathophysiology of ATTR amyloidosis.

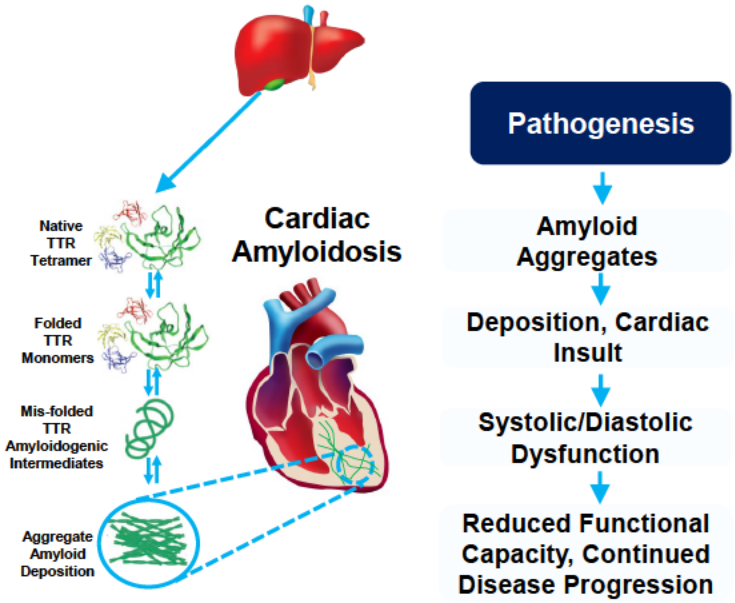
2.1 Overview of Transthyretin-Mediated Amyloidosis with Cardiomyopathy

Transthyretin, also known as pre-albumin, is a tetrameric protein produced by hepatocytes, the choroid plexus, and retina (Liz et al 2010). More than 95% of TTR in circulation is derived from the liver (Felding and Fex 1982). The primary function of TTR is to transport retinol (also known as vitamin A) through the circulation in a complex with retinol binding protein (RBP) and

vitamin A. However, vitamin A transport and tissue uptake can occur in the absence of circulating TTR (Episkopou et al 1993).

ATTR amyloidosis is a progressive, multisystem, debilitating, and ultimately fatal disease with hereditary (hATTR) and wild-type (wtATTR) forms (Adams et al 2019; Lane et al 2019; Ruberg et al 2019). In hATTR amyloidosis, inherited variants in the TTR gene encode an unstable protein. Dissociation of the circulating tetrameric protein into incorrectly folded (i.e., misfolded) monomers and oligomers results in their deposition as amyloid fibrils in organs and tissues (Figure 8). The heart, peripheral nerves, and GI tract are particularly affected, and the phenotypic expression varies depending on the predominant site of amyloid deposition. The most common manifestations are cardiomyopathy and polyneuropathy; most patients experience both over the course of their disease. In wtATTR amyloidosis, the wild-type protein becomes amyloidogenic for as-yet unknown reasons in older individuals; cardiomyopathy is the major manifestation in wtATTR.

Figure 8: Pathophysiology of Transthyretin-Mediated Amyloidosis with Cardiomyopathy



TTR=transthyretin.

2.1.1 Clinical Manifestations of ATTR Amyloidosis in Patients with Cardiomyopathy

Patients with ATTR-CM typically present with HF with preserved ejection fraction. Amyloid infiltration of the heart causes ventricular wall thickening and stiffening resulting in diastolic dysfunction. Systolic function is also impaired, as characterized by abnormal longitudinal strain. Amyloid can also disrupt cardiac conduction and cause arrhythmias, most commonly atrial fibrillation (Ruberg et al 2019).

*2.1.2 **Signs and Symptoms***

Patients with ATTR-CM report intolerance to activity, inability to exercise, insomnia, and fatigue as the most challenging consequences of their disease. Patients also report symptoms of shortness of breath, atrial fibrillation, and other arrhythmias (Rintell et al 2021). Worsening symptoms have a greater impact on QoL on older adults with HF, because of their lower functional capacity, than on younger patients (Masoudi et al 2004).

*2.1.3 **Natural History and Prognosis***

Ongoing amyloid deposition in the heart drives an unrelenting progression of cardiomyopathy (Fontana et al 2015; Martinez-Naharro et al 2019; Chacko et al 2020). Even at the mildest stage of disease, defined as ATTR amyloidosis disease stage 1a with NT-proBNP ≤500 ng/L or ≤1,000 ng/L if in atrial fibrillation, relatively preserved renal function (eGFR ≥45 mL/min/1.73 m^2), and a minimal diuretic requirement (<0.75 mg/kg/day furosemide equivalent), patients who were followed for a median of 28 months demonstrated significant morbidity with increasing diuretic use to manage congestion, worsening NYHA class and cardiac laboratory parameter levels, and CV events such as stroke or transient ischemic attacks, arrhythmia, and need for permanent pacing (Law et al 2022a).

At early stages of the disease, symptom progression and loss of functional capacity are relatively slow; however, disease progression accelerates at later stages with more rapid declines in functional capacity and QoL and rising mortality (Griffin et al 2021). Multiple natural history studies depict a progression of HF resulting in frequent hospitalizations and death 2.5–5.5 years after diagnosis (Antonopoulos et al 2022; Castano et al 2015; Damy et al 2016; Dungu et al 2012; Hawkins et al 2015). This pattern of slow, then accelerating disease progression has become especially clear in recent years because of growing disease awareness and the widespread adoption of diagnostic technetium scintigraphy.

2.1.4 ***Diagnosis***

Historically, a cardiac biopsy was required to make the diagnosis of ATTR cardiac amyloidosis. In 2016, a seminal publication demonstrated the high sensitivity and specificity of technetium scintigraphy using bone avid tracers to make the diagnosis after exclusion of amyloid light chain (AL) amyloidosis (Gillmore et al 2016). The simple, non-invasive test drove a dramatic shift from late to early diagnosis in a growing number of patients worldwide. A recent study from the United Kingdom National Amyloidosis Center reported that more than half of patients before 2016 were diagnosed at the more advanced stages and approximately 20% in the most severe amyloidosis disease Stage 3. After 2016, more than half were diagnosed in Stage 1, and approximately 10% in Stage 3. The authors noted that the apparent rate of disease progression has slowed noticeably because of earlier diagnosis and not because of novel therapies (Ioannou et al 2022).

2.1.5 *Current Methods for Monitoring Disease Progression*

The pattern of unrelenting disease progression is well understood. Anticipating novel therapies in development that could alter the course of disease, an expert panel recently recommended a set of criteria to monitor disease progression. The assessments for the criteria fall into 3 domains: NYHA class or KCCQ in the Clinical and Functional domain; NT-proBNP, troponin I, or ATTR amyloidosis disease stage in the Laboratory Biomarker domain; and echocardiographic assessments of LV structure or function in the Imaging and Electrocardiogram (ECG) domain (Garcia-Pavia et al 2021).

2.2 Current Treatment Options and Unmet Medical Need

Tafamidis (Vyndaqel/Vyndamax ®), the only drug for the treatment of ATTR-CM, was approved in the US in 2019. Other mainstays of clinical management include the symptomatic treatment of congestion with diuretics and arrhythmia with anti-arrhythmic drugs, implantation of pacemakers, and cardiac defibrillators, and ablation.

Tafamidis stabilizes TTR protein in the circulation. The Phase 3 ATTR-ACT study in patients with ATTR-CM demonstrated that compared with placebo, treatment with tafamidis was associated with lower all-cause mortality and CV-related hospitalization at Month 30 ($p<0.001$). Mortality at Month 30 was 43% in the placebo group and 30% with tafamidis. The mortality differences between the tafamidis and placebo arms emerged after Month 18. Consistent with the enrollment of patients in an era when they were diagnosed with more advanced disease, placebo-treated patients demonstrated substantial declines in functional capacity (6MWT) and health status and QoL (KCCQ-OS). Tafamidis-treated patients showed significantly slower declines compared with placebo, but the data suggest that the decline continues (Maurer et al 2018). In more recent years, when patients in general have been diagnosed with less advanced disease, several groups in the US, Europe, and Japan have identified a subset of tafamidis-treated patients who have declines in exercise capacity that are associated with signs of ongoing cardiac amyloid deposition (Badr Eslam et al 2022; Dalia et al 2021; Nakaya et al 2023).

With only one approved therapy for ATTR-CM, a high unmet need remains for additional treatment options that can suppress amyloid deposition and thus address the progressive loss of functional capacity and QoL associated with this devastating disease. Patisiran acts by suppressing the production of the amyloidogenic protein, an orthogonal and distinct mechanism of action compared with a tetramer stabilizer and has been shown to stabilize or reverse the polyneuropathy manifestations of hATTR amyloidosis. The rapid completion of enrollment of 200 patients with ATTR-CM into the patisiran US EAP who have progressed on standard of care highlights the current high unmet need in this patient population (additional details provided in Section 8). The incidence of disease progression among patients on tafamidis is substantial, as depicted by the 22% of patients on tafamidis alone whose HF worsened by NYHA class after 12 months in APOLLO-B.

3 PATISIRAN PRODUCT OVERVIEW

Summary

- Patisiran is comprised of an siRNA targeting the mRNA of the TTR gene, thereby specifically silencing the synthesis of both variant and wt TTR. It is formulated in an LNP for targeted delivery to the liver when administered via IV infusion.
- Patisiran treatment results in potent and sustained lowering of circulating TTR levels, thereby reducing the formation of amyloid, the fundamental cause of the manifestations of ATTR amyloidosis.
- The pivotal APOLLO study in adults with hATTR with polyneuropathy led to the initial approval of patisiran (ONPATTRO®) in August of 2018 for the treatment of the polyneuropathy of hATTR in adults.

3.1 Proposed Indication

The proposed indication for this sNDA is *"the treatment of cardiomyopathy of wt or hATTR amyloidosis in adults to slow the decline in functional capacity and reduce symptoms."*

3.2 Product Description

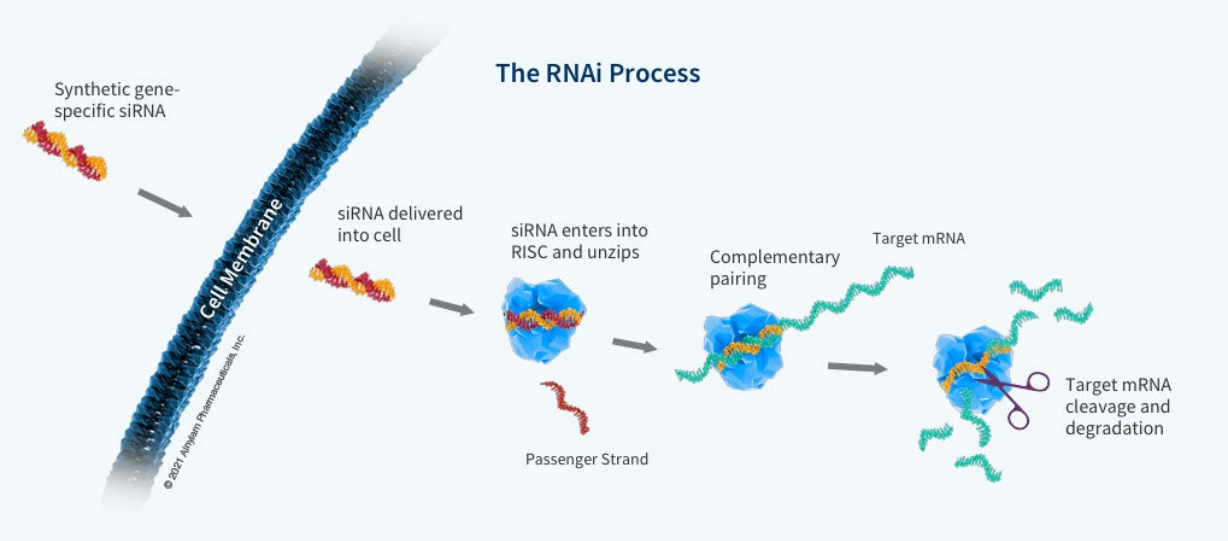
Patisiran comprises an siRNA formulated in an ionizable LNP comprised of four lipids for targeted hepatic delivery when administered via IV infusion (Akinc et al 2019; Coelho et al 2013). The proposed dose and regimen for the cardiomyopathy indication 0.3 mg/kg (30 mg maximum) q3W, the same as for the approved polyneuropathy indication. Consistent with the approved labeling for patisiran, it is recommended that infusions be preceded by a pre-medication regimen of oral steroids, antihistamines, and acetaminophen to reduce the risk of IRRs (ONPATTRO USPI).

3.3 Mechanism of Action

*3.3.1 **RNA Interference***

Patisiran works via the natural mechanism of RNAi. In hepatocytes, it binds and activates the RNA-induced silencing complex and thereby inhibits the transcription of TTR mRNA by specifically targeting the 3' untranslated region common to both wt and variant TTR protein. The mechanism of RNAi is depicted in Figure 9.

Figure 9: Mechanism of RNA Interference and Therapeutic Concept



mRNA=messenger RNA; RISC=RNA-induced silencing complex; RNAi=ribonucleic acid interference; siRNA=small interfering ribonucleic acid.
Adapted from Bumcrot et al 2006, Figure 1.

3.3.2 Therapeutic Hypothesis of Patisiran

TTR is a tetrameric protein produced by hepatocytes, the choroid plexus, and retina (Liz et al 2010). The liver produces 95% of TTR in the circulation (Felding and Fex 1982). By suppressing the liver production of circulating wt and all variant forms of the amyloidogenic TTR protein, patisiran reduces TTR deposition and thus further accumulation of amyloid deposits within tissues (Figure 1) (Akinc et al 2019; Fontana et al 2021), thereby stabilizing or improving the manifestations of cardiomyopathy and polyneuropathy in patients with ATTR amyloidosis.

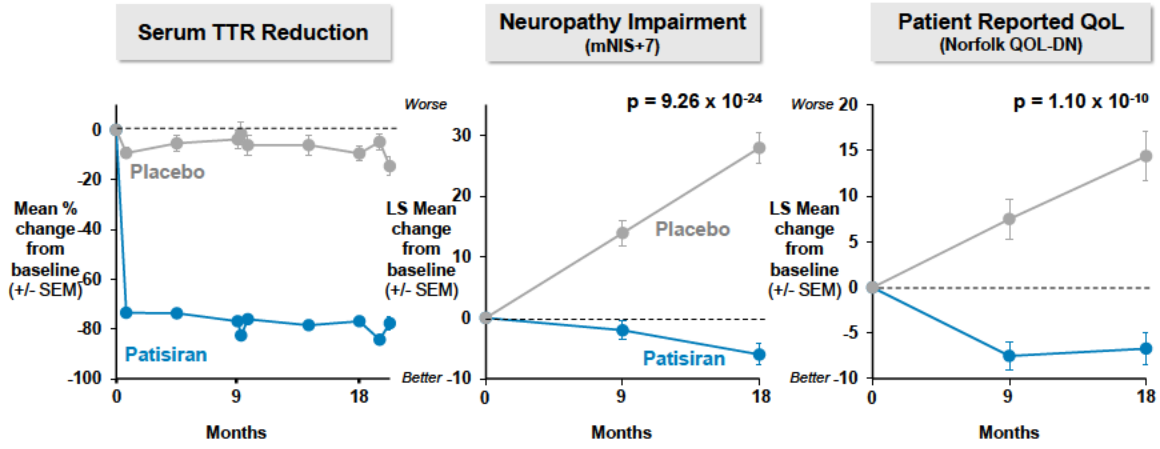
3.4 APOLLO Study in hATTR Amyloidosis with Polyneuropathy Confirmed Therapeutic Hypothesis

APOLLO was a global, randomized, DB, placebo-controlled trial in 225 patients designed to evaluate the efficacy and safety of patisiran in patients with hATTR-PN (Adams et al 2018). The primary objective was to evaluate the effect of patisiran on composite measures of neuropathy, including motor, sensory, and autonomic neuropathy with the mNIS+7 (range: 0–304, with higher scores indicating more impairment) compared with placebo at 18 months. QoL and effects on multiple other disease manifestations were also evaluated.

Patisiran demonstrated rapid and sustained reductions in serum TTR (Figure 10; left panel) resulting in stabilization or improvement of neuropathy impairment and QoL as early as Month 9 (Figure 10, center and right panel). Consistent with the well-described progression of hATTR amyloidosis, the placebo group showed rapid and steady worsening across multiple assessments of neuropathy. In contrast, patisiran-treated patients showed clinically meaningful and statistically significant improvements compared with placebo ($p<0.001$ for both mNIS+7 and Norfolk-QoL-DN). The results were consistent and significant across all other secondary

endpoints, which assessed other common manifestations of hATTR-PN (Adams et al 2018). A long-term follow-up study has shown that the treatment benefits observed in APOLLO are sustained and that the loss in functional ability of the placebo treated patients from the first 18 months of the study is not regained after initiating treatment (Adams et al 2021). The APOLLO study results supported the initial approval of patisiran in 2018 for the treatment of the polyneuropathy of hATTR amyloidosis in adults.

Figure 10: Change from Baseline in Serum TTR, mNIS+7, and Norfolk-QoL-DN Over 18 Months of Treatment in APOLLO (mITT Population)



mITT=modified Intent-to-Treat; mNIS+7=Neuropathy Impairment Score+7; Norfolk-QoL-DN=Norfolk Quality of Life-Diabetic Neuropathy; TTR=transthyretin.

Fifty-six percent of the patients in APOLLO also had pre-specified evidence of TTR cardiomyopathy, and planned exploratory analyses demonstrated a beneficial treatment effect of patisiran on cardiac structure and function as well as the cardiac laboratory parameter NT-proBNP. Additionally, a post-hoc analysis of the safety data showed a reduction in the composite endpoints of all-cause hospitalizations and all-cause deaths as well as cardiac hospitalizations and all-cause death (additional details provided in Section 6.1) (Solomon et al 2019). These findings further supported the concept that ATTR amyloidosis is a single disease and that substantially lowering the production of the pathogenic protein would slow or dramatically reduce the decline of functional capacity and symptoms in patients with ATTR cardiomyopathy. Thus, the APOLLO results provided the rationale for APOLLO-B to evaluate patisiran for the treatment of cardiomyopathy in wtATTR and hATTR amyloidosis.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Patisiran (ONPATTRO®) is approved for the treatment of the polyneuropathy of hATTR amyloidosis in more than 35 countries.
- The patisiran clinical development program in ATTR amyloidosis with cardiomyopathy was designed with input from the FDA and aligned with the principles outlined in the Agency's Guidance for Industry Treatment for Heart Failure: Endpoints for Drug Development (FDA 2019a).

4.1 Key Regulatory Milestones

The patisiran clinical development program in ATTR-CM was designed with input from the FDA through a series of formal meetings and is aligned with FDA's subsequent Draft Guidance for Industry Treatment for Heart Failure: Endpoints for Drug Development (FDA 2019a), issued shortly after the initiation of APOLLO-B. Major regulatory interactions and milestones are provided in Table 2.

Table 2: Key Regulatory Interactions and Milestones

Date	Milestone
December 2017	Orphan Drug Designation for "the treatment of transthyretin-mediated amyloidosis", encompassing the polyneuropathy and cardiomyopathy and variant and wt forms of ATTR amyloidosis
August 2018	Approval of patisiran in the US for hATTR-PN
December 2018	End of Phase 2 meeting with FDA discussing design of APOLLO-B
April 2019	IND application submitted
May 2019	IND cleared to proceed
September 2019	APOLLO-B initiated
November 2021	Type C written feedback confirming the acceptability of the format and contents of the planned sNDA and pooling strategy
June 2022	DB period completed
September 2022	Type B pre-sNDA meeting to discuss the top line data of APOLLO-B and planned sNDA submission
December 2022	sNDA submitted
February 2023	sNDA filed by the FDA
April 2023	sNDA amendment of APOLLO-B Month 18 data

ATTR=transthyretin-mediated amyloidosis; DB=double-blind; FDA=Food and Drug Administration; hATTR-PN=hereditary transthyretin-mediated amyloidosis with polyneuropathy; IND=Investigational New Drug; sNDA=supplemental New Drug Application; US=United States.

4.2 Clinical Development Program

The overall clinical development program of patisiran consists of 8 clinical trials across the spectrum of ATTR amyloidosis (Table 3).

The pivotal results demonstrating the efficacy and safety of patisiran in patients with ATTR-CM (wt or hereditary) are from the global, randomized, DB, placebo-controlled, Phase 3 APOLLO-B study as well as the OLE as outlined in Sections 6.2 and 7. APOLLO-B primary analysis treatment period was completed in June 2022 with database lock in July 2022. An additional OLE data cut inclusive of Month 18 data for all patients was performed in December 2022. Data from the OLE period will be available up to Month 24 by 13 September 2023.

Table 3: Clinical Development Program for Patisiran in ATTR Amyloidosis

Phase	Study Number (Type)	Study Design	Number of Patients Enrolled	Status
Patients with wt or hATTR amyloidosis with cardiomyopathy				
Phase 3	ALN-TTR02-011; APOLLO-B (Pivotal, Randomized DB, Interventional)	Randomized (1:1), DB, Placebo Controlled, Multicenter with a 36-month, OLE Period	360	DB Primary Analysis Complete
	ALN-TTR02-011 (OLE)[a]		334	Ongoing
Expanded Access	ALN-TTR02-014; US	EAP	200	Enrolled and Ongoing
Patients with hATTR amyloidosis with polyneuropathy				
Phase 1	ALN-TTR02-002 (Multiple Ascending Dose)	Open-Label, Multi-Dose, Dose Escalation Study	29	Complete
Phase 2	ALN-TTR02-003 (OLE)[b]	Multicenter, Open-Label, Extension Study	27	Complete
Phase 3	ALN-TTR02-004; APOLLO (Pivotal, Randomized DB, Interventional)	Randomized (2:1), DB, Placebo Controlled, Multicenter	225	Complete
Phase 3	ALN-TTR02-006 (OLE)[c]	Multicenter, Open-Label, Extension Study	211	Complete
Phase 3	ALN-TTRSC02-002; HELIOS-A[d] (Pivotal, Randomized, Open-Label Interventional)	Multicenter, Randomized (3:1), Open-Label, Study of Vutrisiran with Reference Comparator Arm of Patisiran and External Placebo Arm	164[e]	Ongoing
Phase 3b	ALN-TTR02-008 (Open-Label Interventional)	Multicenter, Open-Label, Study to Evaluate Safety Efficacy and PK	24	Complete

a. Study 011 OLE included patients who completed the double-blind period of Study 011.
b. Study 003 included patients who completed Study 002.
c. Study 006 included patients who completed Study 003 or Study 004.
d. Patisiran was used as reference comparator arm in the HELIOS-A study, conducted as part of the vutrisiran clinical development program.
e. A total of 42 patients in the patisiran reference comparator arm received patisiran through Month 18 and then transitioned onto treatment with vutrisiran for the remainder of the study. No patients remain on patisiran.
*Observational study ALN-TTR02-013; ConTTRibute is described further in Section 9 as no interventional treatment is administered or required.
ATTR=transthyretin-mediated amyloidosis; DB=double-blind; EAP=expanded access program; hATTR=hereditary transthyretin-mediated amyloidosis; OLE=open-label extension; PK=pharmacokinetic; US=United States; wt=wild-type.

4.3 APOLLO-B Development Program and Applicable FDA Regulatory Guidance

In seeking approval for patisiran as a treatment for ATTR-CM, the Sponsor considered how two relevant FDA guidance documents could be applied: 1) the 2019 Draft Guidance for the Industry Treatment for Heart Failure: Endpoints for Drug Development; and 2) the 2019 Draft Guidance for the Industry Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.

4.3.1 Heart Failure Guidance

The introduction to the guidance (FDA 2019a) states 2 objectives:

> *...1) to make it clear that an effect on symptoms or physical function, without a favorable effect on survival or risk of hospitalization, can be a basis for approving drugs to treat heart failure; and 2) to provide recommendations to sponsors on the need to assess mortality effects of drugs under development to treat heart failure...*

The guidance describes how endpoints, such as 6MWT and clinical outcomes assessments can be the basis for approving drugs to treat HF and states that in infiltrative cardiomyopathies where *"disease advancement can be slow…there is great interest in therapies that may slow or prevent disease progression."* Furthermore, the guidance states that when approval is based on an improvement of function or symptoms, the FDA will consider various factors in determining the extent of mortality and safety data needed, including the mortality and other safety findings of the drug in a closely related population in which at least a subset of patients had HF or were at risk for HF.

This guidance is relevant to the APOLLO-B study and sNDA in the following ways:

- APOLLO-B was designed to evaluate impact of patisiran in functional capacity and health status and QoL in ATTR-CM which is an infiltrative cardiomyopathy with slow progression in the pre- and peri-symptomatic stages of the disease, and
- Patisiran is approved for hATTR-PN based on the APOLLO study which demonstrated safety and encouraging mortality data, including in the cardiac subgroup which had evidence of ATTR-CM.

4.3.2 Substantial Evidence Guidance

As referenced in the Draft Guidance (FDA 2019b), associated regulations, and provisions in section 115 of the Food and Drug Administration Modernization Act, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness of a drug. The 2019 Draft Guidance describes four example criteria for acceptable confirmatory evidence, each of which on their own would be sufficient to support establishing effectiveness of the drug.

One criterion for confirmatory evidence is existing confirmatory evidence that may have been part of the drug's earlier development program and supported an approval for use in a closely related indication. Another criterion is data that provide strong mechanistic support that, together

with earlier phase clinical results or other data, provide compelling mechanistic evidence in the setting of well-understood disease pathophysiology.

This guidance is relevant to the APOLLO-B study and sNDA in the following ways:

- Patisiran is approved for the treatment of hATTR-PN, a different manifestation of the same disease that causes ATTR-CM, and
- The pathophysiology of ATTR amyloidosis is well-understood. Patisiran targets the cause of the disease at the source of its production. Two studies (APOLLO and HELIOS-A; Table 3) in hATTR patients have shown that reducing circulating TTR by silencing mRNA production in the liver results in improvements in clinical manifestations of the disease (Adams et al 2023; Adams et al 2018). Additionally, pre-specified analyses of patients in APOLLO with evidence of ATTR cardiomyopathy demonstrated patisiran-mediated reduction in circulating TTR lead to improvements in exploratory measures of cardiac structure and function (Solomon et al 2019).

5 CLINICAL PHARMACOLOGY

Summary

- After IV infusion of patisiran, the siRNA component of patisiran is rapidly delivered to hepatocytes.
- Once in the hepatocyte, the siRNA is metabolized by nucleases to nucleotides of various lengths in hepatocytes. Patisiran is not expected to cause clinical drug-drug interaction or be affected by inhibitors or inducers of CYP enzymes or transporters.
- Plasma protein binding of patisiran is low. The terminal elimination half-life (mean±standard deviation [SD]) of patisiran is approximately 3 days, with less than 1% of the administered dose of patisiran excreted renally. Thus, renal clearance is a minor pathway in the overall elimination of patisiran and hence patisiran plasma pharmacokinetic (PK) is not impacted by renal impairment.
- Population PK analysis did not identify any intrinsic and extrinsic factors that had a clinically meaningful impact on the PK of patisiran (additional details provided in Section 12.6).
- Administration of 0.3 mg/kg patisiran every 3 weeks (the currently approved dose for hATTR-PN) in APOLLO results in 90% TTR reduction over 18 months, achieving a near plateau in TTR reduction, supporting use of the same dosing regimen in APOLLO-B.
- In APOLLO-B, the observed mean TTR percent reduction at Month 12 was ≥85%. Population PK/pharmacodynamic (PD) modeling showed similar TTR reductions across all intrinsic and extrinsic factors, including tetramer stabilizer use, with no clinically meaningful differences (additional details provided in Section 12.7).
    - Similar TTR reduction was observed in variant and wild-type TTR.
    - Similar TTR reduction was observed in patients with and without concomitant tafamidis.
    - The model supported the recommended dose and regimen for all patients with ATTR-CM.

5.1 Overview of Clinical Pharmacology

The key clinical pharmacology characteristics of patisiran are summarized below with further details outlined in Appendices 12.5–12.8:

- The plasma concentration time-profile of patisiran was found to be generally consistent across studies and between healthy volunteers and patients with ATTR-PN and ATTR-CM. Population PK analysis did not identify any intrinsic and extrinsic factors that had a clinically meaningful impact on the PK of patisiran (additional details provided in Section 12.6).

- Healthy participants in Phase 1 (additional details in Appendix 12.8) show that single IV infusions of patisiran (dose range of 0.01 mg/kg to 0.5 mg/kg) reduced serum TTR in a dose-dependent manner, with median maximal TTR reduction of 83.2% at 0.3 mg/kg dose. Only a small additional reduction in TTR was observed at a dose higher than 0.3 mg/kg, suggesting that the 0.3 mg/kg dose was in the near plateau portion of the dose-response curve.
- Across all patisiran dose groups, nadir TTR levels were achieved by 7–14 days post-dose, and TTR levels returned to baseline by 6–8 weeks. The 0.3 mg/kg dose maintained median TTR reduction from baseline of ≥80% over 3 weeks in Study ALN-TTR02-001, resulting in the selection of this dose and regimen for future studies.
- A patisiran dosing regimen of 0.3 mg/kg q3W resulted in comparable PD effects across APOLLO-B, APOLLO, and HELIOS-A (where patisiran was used as a control arm in a study in the pivotal study of vutrisiran supporting its approval for the polyneuropathy of hATTR amyloidosis) with a similar magnitude of TTR reduction from baseline: median of 81.7% in APOLLO-B, 79.5% in APOLLO, and 79.5% in HELIOS-A at the end of 3 weeks. With repeat q3W dosing, the median steady-state trough TTR percent reductions were 87.2%, 81.2% and 78.2%, in APOLLO-B, APOLLO, and HELIOS-A, respectively. With repeat q3W dosing, the median steady-state peak TTR percent reductions were 90.8%, 88.5% and 88.3%, in APOLLO-B, APOLLO, and HELIOS-A, respectively.
- Population PK/PD modeling indicated intrinsic factors such as age, race, genotype, NYHA class, sex, mild to moderate renal impairment, mild hepatic impairment, and extrinsic factors such as tetramer stabilizer use did not meaningfully influence the PK or PD of patisiran, indicating that the recommended regimen is adequate for all subgroups of patients with ATTR-CM.
- An integrated analysis across studies (in healthy volunteers and patients with ATTR-CM and ATTR-PN) shows that the incidence of anti-drug antibodies (ADA) is low (2.3%) and transient with no impact on PK, PD, efficacy, or safety.
- Percent TTR reduction from baseline is comparable with overlapping ranges between subjects who were or were not on concomitant medications commonly used by ATTR-CM patients, including diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), calcium channel blockers, beta blockers, mineralocorticoid receptor agonists, and SGLT2 inhibitors.

5.1.1 ***Dose Justification***

In early Phase 1 and 2 studies of patisiran in healthy volunteers and patients with polyneuropathy (Appendix 12.8), a clear dose-response was observed across doses (dose range of 0.01 mg/kg to 0.5 mg/kg, Figure 11, left most panel). Pooled analysis across these dose groups and studies (healthy volunteers, patients with hATTR-PN) showed that TTR reduction reached a plateau after dosing at 0.3 mg/kg. The patisiran-LNP dose of 0.15 mg/kg was on the steep phase of the dose-response curve, resulting in less TTR reduction (75.4%) and greater variability in PD response compared with 0.3 mg/kg (Figure 11). Of note, the 0.5 mg/kg dose was not pursued in

clinical studies because of the minimal additional TTR reduction between 0.3 mg/kg and 0.5 mg/kg and the occurrence of an acute IRR at the start of infusion.

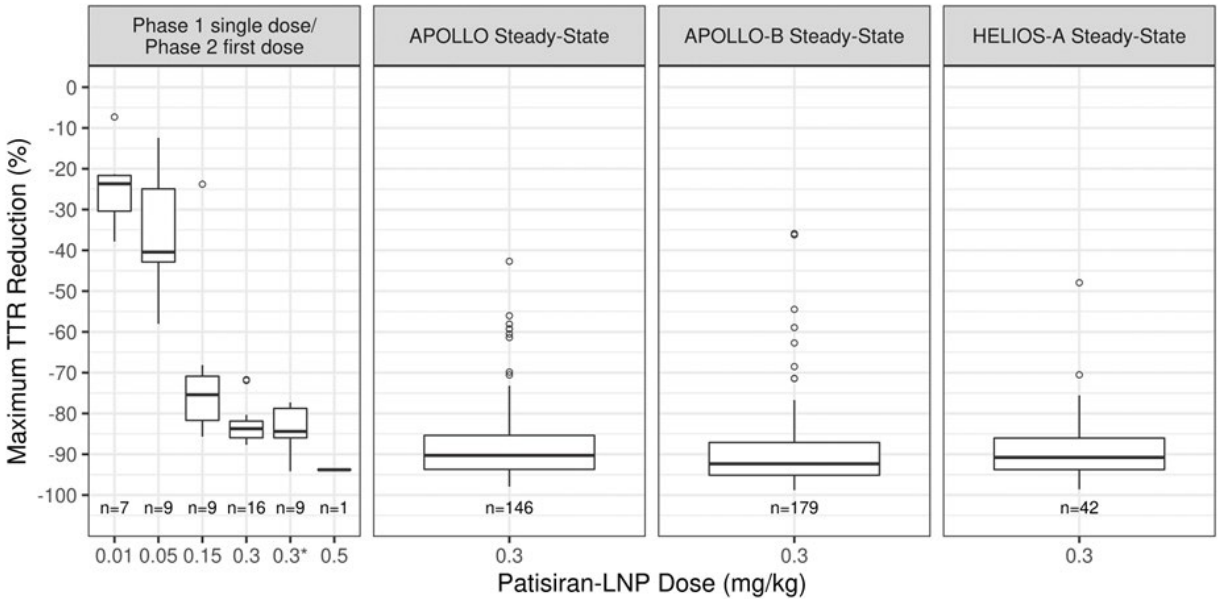
Based on PK/PD modeling (using pooled analysis of Studies 001, 005, 002, 003, and APOLLO), TTR reduction plateaus with concentrations $\geq IC_{80}$ following a 0.3 mg/kg dose. Therefore, the 0.3 mg/kg dose for patisiran was evaluated in the subsequent Phase 3 APOLLO-B and HELIOS-A studies. In these studies, the patisiran dose of 0.3 mg/kg q3W was found to be safe and well tolerated, resulted in sustained and robust TTR reduction (Figure 11), and was associated with clinically meaningful treatment effects.

Given the similarity in magnitude of TTR suppression between hATTR patients and healthy volunteers, no differences in TTR reduction between the polyneuropathy and cardiomyopathy populations were expected (Figure 11). In addition, given the near maximal TTR reduction and the established safety and tolerability profile of the 0.3 mg/kg q3W dosing regimen in patients with hATTR-PN, and it being the approved dose with an acceptable safety profile, the same dosing regimen was considered for patients with ATTR-CM and was evaluated in APOLLO-B.

In APOLLO-B, the median of the maximum TTR percent reduction over 12 months was 92.3% (interquartile range [IQR]: 87–95%), similar to results seen in APOLLO and HELIOS-A (Figure 11). Importantly, patisiran-mediated TTR reductions were associated with clinically and statistically significant improvements in clinical endpoints vs placebo (Section 6). These results demonstrated that patisiran-mediated TTR reduction improves cardiomyopathy disease manifestations and QoL with the recommended regimen of 0.3 mg/kg q3W.

Collectively, the observed data from across the patisiran development program, as well as the pooled population PK and population PK/PD data, support the recommended patisiran dosing regimen of 0.3 mg/kg administered q3W and fixed dose of 30 mg q3W for patients weighing >100 kg across all subgroups (Figure 11; Appendix 12.8). This dosing regimen provides clinical benefit with an acceptable safety profile for treatment of all patients with ATTR-CM. No dose adjustments are necessary for any subpopulations.

Figure 11: Relationship Between Patisiran-LNP Dose and Maximum % TTR Reduction Following Single/First Dose (Studies 001, 002, 005) or Multiple Doses (APOLLO, APOLLO-B, and HELIOS-A Studies)



LNP=lipid nanoparticle; TTR=transthyretin
Note: Study 001 (single dose), Study 002 (first dose), and Study 005: n=7, 9, 9, 16, 9 and 1 for 0.01, 0.05, 0.15, 0.3, 0.3,* and 0.5 mg/kg dose groups, respectively. Study 004 (n=146) and HELIOS-A (n=42) at Month 18 and 011 (n=179) at Month 12 following multiple doses of 0.3 mg/kg dose for patients <100 kg and 30 mg dose for patients weighing ≥100 kg administered every 3 weeks.
Note: * indicates that patients received reduced pre-medication.
Note: The ends of the box are the upper and lower quartiles, and the median is marked by the solid line inside the box. The top and lower lines are the range without outliers, and the symbols are outliers.

6 CLINICAL EFFICACY

Summary

- APOLLO formed the basis of further evaluation of patisiran in ATTR-CM in APOLLO-B by providing supportive evidence of efficacy as well as supportive mortality, enabling the design of a shortened study evaluating the effects on how patients function and feel consistent with FDA's Draft Guidance for Industry Treatment for Heart Failure: Endpoints for Drug Development (FDA 2019a).
- APOLLO-B is a global, randomized, DB, placebo-controlled study in 360 patients with ATTR-CM that was designed to study the effects of patisiran on patient functional capacity (primary endpoint, 6MWT) and health status and QoL (first secondary endpoint, KCCQ-OS) in a 12-month DB period. Additional endpoints included composite outcomes of all-cause mortality, CV events, and 6MWT, as well as all-cause mortality, all-cause hospitalizations and urgent HF visits, assessments of cardiac structure and function, prognostic laboratory parameters, and clinical disease staging.
- The study met the primary endpoint of change in 6MWT from baseline at Month 12, with patisiran treatment resulting in clinically meaningful and statistically significant improvements compared with placebo.
    - The HL estimate of the median difference between treatment groups (primary analysis method) was 14.7 meters (p=0.0162); the LS mean difference (sensitivity) was 18.1 meters (nominal p=0.0234).
    - The approximately −8 meter median change from baseline in the patisiran group at Month 12 is comparable to the expected annual age-related decline in healthy adults (approximately 5–6 meters/year) (Enright and Sherrill 1998) and 62% less than the decline observed in the placebo group.
- The study met its first secondary endpoint, demonstrating a stable health status and QoL with patisiran treatment as assessed by the KCCQ-OS, compared with a steady decline in the placebo group. The LS mean difference of 3.7 points (p=0.0397) favored patisiran. The data demonstrate stability in health status and QoL with patisiran over 12 months.
    - The treatment effect was consistent across all KCCQ-OS domains and summary scores.
    - The KCCQ-OS results are comparable to those of drugs that have been well characterized to improve HF patients' symptoms and QoL.
- The patisiran treatment effect on both 6MWT and KCCQ-OS was observed across the spectrum of response thresholds with the greatest improvements observed more frequently in the patisiran group and the greatest declines observed more frequently in the placebo group.
- For patients in the patisiran monotherapy subgroup, patisiran showed a greater effect on 6MWT and KCCQ-OS, compared with patients in the overall population.

- For patients in the background tafamidis subgroup, the small number of patients and limited decline in the placebo group at 12 months make it difficult to draw conclusions about the treatment effect. The treatment effect has not been established for patients on background tafamidis.
- Statistical significance was not met for the secondary endpoints of composite outcomes. However, the overall results in composite outcomes and in all-cause mortality were numerically in favor of patisiran, showing no detrimental effects.
- Exploratory analyses of prognostic laboratory parameters, clinical disease staging, and cardiac imaging results provided further evidence for the slowing of disease progression by patisiran.
    - Patisiran-treated patients were less likely to experience disease progression based on NYHA class and ATTR amyloidosis disease.
- During the OLE period in APOLLO-B at Month 18, continued treatment with patisiran demonstrated initial evidence of maintenance of effect.
- The clinical meaningfulness of the primary efficacy results is corroborated by multiple findings. Among them are: (1) The 6MWT treatment difference exceeds the MCID for the change in functional capacity as derived from a method anchored on patient-reported health status and QoL. (2) Patisiran-treated patients reported meaningful changes in health status and QoL, including favorable effects across 19 of 20 questions in the KCCQ-OS regarding symptoms, physical limitations, and QoL. (3) Patisiran-treated patients had less disease progression over 12 months compared with placebo, as indicated by laboratory, imaging and clinical assessments, including an approximately 40% lower risk of disease progression by NYHA class and ATTR disease stage than placebo-treated patients.

6.1 APOLLO: Treatment Effect of Patisiran on Cardiac Manifestations in hATTR Amyloidosis

*6.1.1 **Study Design***

APOLLO was a global, randomized (2:1), DB, placebo-controlled trial designed to evaluate the efficacy and safety of 0.3 mg/kg q3W patisiran in patients with hATTR-PN (Adams et al 2018). The eligibility criteria for APOLLO were selected to enroll a population of adults with hATTR amyloidosis that reflected the heterogeneity of the disease worldwide with respect to mutant TTR genotype (V30M and non-V30M), neuropathy severity (mild to severe, with baseline NIS of 5–130) and the presence of other disease manifestations (e.g., cardiac involvement). Background use of TTR stabilizers was not allowed.

The primary objective was to evaluate the effect of patisiran on composite measures of neuropathy, including motor, sensory, and autonomic neuropathy with the mNIS+7 compared with placebo at 18 months. QoL and disease manifestations including gait speed, nutritional status, and disability were also investigated. As described earlier in Section 3.4, the study met the primary and all secondary endpoints, with patisiran treatment resulting in halting or reversal of neuropathy of a wide range of important disease manifestations. The effects of patisiran on

cardiomyopathy manifestations of hATTR amyloidosis were assessed in a pre-specified cardiac subpopulation and exploratory analyses of LV structure and function and NT-proBNP.

6.1.2 Patient Population

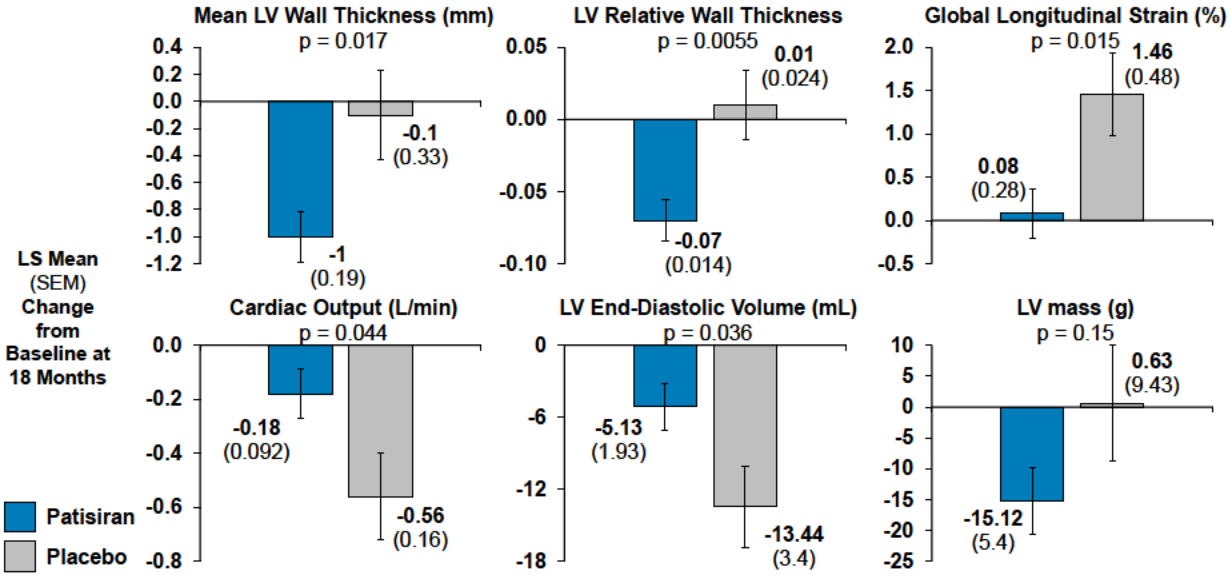
Patients were randomized 2:1 to patisiran (N=148) or placebo (N=77). The treatment arms were well balanced for age, sex, neuropathy, and baseline mNIS+7, and prior tetramer stabilizer use. A total of 126 patients (56%; referred to as the "cardiac subpopulation") had pre-specified evidence of cardiac amyloid involvement (baseline LV wall thickness ≥13 mm and no history of hypertension or aortic valve disease).

6.1.3 Change from Baseline in Echocardiographic Parameters and NT-proBNP with Patisiran Compared with Placebo

At baseline, 60.3% of the cardiac subpopulation were in NYHA class II heart failure. LV wall thickness was significantly increased (median: 16.4 mm; IQR: 14.8–18.3), as was NT-proBNP (median: 837.2 ng/L, IQR: 292.4–2354.1; geometric mean: 722.5, coefficient of variation: 210.1). Of note, among the patients in APOLLO who were not in the cardiac subpopulation, more than half (55.6%) had a baseline LV wall thickness ≥13 mm. Many of these patients likely had cardiac amyloid involvement but were excluded from the cardiac subpopulation primarily because of a history of hypertension.

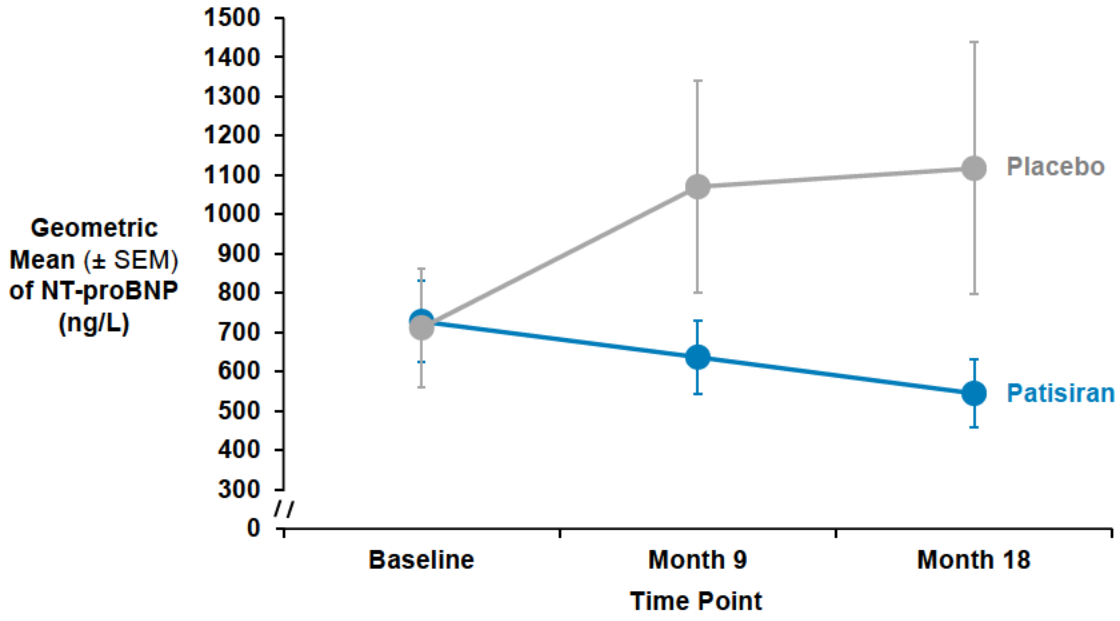
At Month 18, echocardiographic assessments demonstrated significant improvements with patisiran compared with placebo in LV wall thickness and end-diastolic volume, signs consistent with the suppression of ongoing amyloid deposition in the heart, and associated improvements compared with placebo in cardiac output and global longitudinal strain, the latter a measure of systolic function (Figure 12) (Solomon et al 2019). Effects on NT-proBNP were detected at Month 9, earlier than echocardiographic changes (Figure 13). Compared with placebo, patisiran reduced NT-proBNP by 37% and 55%, respectively at Months 9 and 18 in the cardiac subpopulation (Month 9 ratio of fold change patisiran/placebo: 0.63; 95% CI: 0.50–0.80; Month 18: 0.45; 95% CI: 0.34–0.59; p≤0.001) (Solomon et al 2019).

Figure 12: Change in Echocardiographic Parameters at Month 18 in APOLLO Cardiac Subpopulation



LV=left ventricular.

Figure 13: NT-proBNP Over 18 Months in APOLLO Cardiac Subpopulation

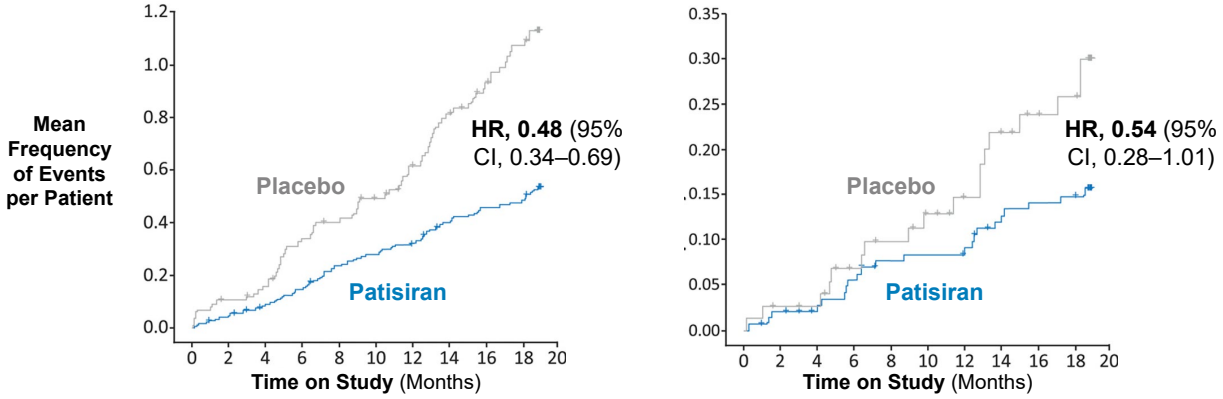


NT-proBNP=N-terminal prohormone B-type natriuretic peptide.

6.1.4 Composite Rate of All-Cause and Cardiac Hospitalization and/or Death and Rate of All-Cause Mortality

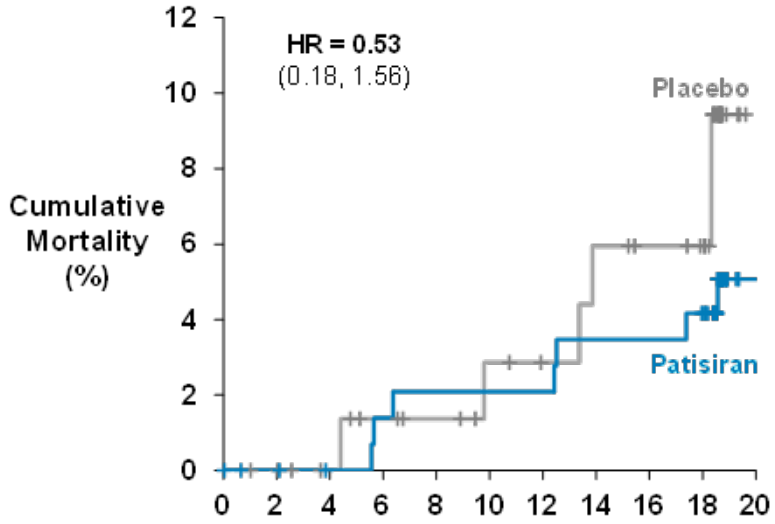
A post-hoc analysis of safety data from the Modified Intent-to-Treat (mITT) population (i.e., all randomized patients who received ≥ 1 dose of the study drug) evaluated the rates of all-cause or cardiac hospitalization and all-cause death (Figure 14). The rates of all-cause hospitalization and/or all-cause death were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups, respectively (Andersen–Gill HR0.48 with 95% CI: 0.34–0.69). The rates of cardiac hospitalization and/or all-cause death were 18.7 and 10.1 per 100 patient-years in the respective groups (Andersen–Gill HR=0.54 with 95% CI: 0.28–1.01). Over 18 months, the reductions in event rates for patisiran compared with placebo were approximately 50% for all-cause hospitalization and/or all-cause death and 45% for cardiac hospitalization and/or all-cause death (Solomon et al 2019). Post-hoc analysis of all-cause mortality in the mITT population also favored patisiran (HR: 0.53, 95% CI: 0.18–1.56; Figure 15). In the cardiac subpopulation, there was a similar reduction in event rates for patisiran compared with placebo. For all-cause hospitalization and/or all-cause death, the Andersen-Gill HR was 0.44 with a 95% CI of 0.28–0.70, showing an approximately 55% reduction in event rates. For cardiac hospitalization and/or all-cause death, the Andersen-Gill HR was 0.55 with a 95% CI of 0.24–1.26, showing a 45% reduction in event rates. All-cause mortality also favored patisiran (HR: 0.46, 95% CI: 0.12–1.73).

Figure 14: Post-Hoc Analysis in APOLLO mITT population: Composite Rate of All-Cause Hospitalization and All-Cause Death (Left Panel) and Composite Rate of Cardiac Hospitalization and All-Cause Death (Right Panel)



HR=hazard ratio; mITT=Modified Intent-to-Treat.

Figure 15: Post-Hoc Analyses in APOLLO mITT Population: All-Cause Mortality



HR=hazard ratio; mITT=Modified Intent-to-Treat.

Taken together, these results from APOLLO formed the basis of further evaluation of patisiran in ATTR-CM in APOLLO-B by providing supportive evidence of efficacy as well as supportive mortality and other safety data, enabling the design of a shortened study evaluating the effects on how patients function and feel consistent with FDA's Draft Guidance for Industry Treatment for Heart Failure: Endpoints for Drug Development (FDA 2019a).

6.2 APOLLO-B: Pivotal Study in Cardiomyopathy

*6.2.1 **Study Design***

APOLLO-B is an ongoing, global, Phase 3 study to evaluate the efficacy and safety of patisiran in patients with ATTR-CM.

The study is comprised of two parts (Figure 16):

- a completed, 12-month, DB, placebo-controlled period, and
- an ongoing, 36-month, OLE period, in which all patients receive patisiran.

The study population was designed to include approximately 80% of patients with wtATTR amyloidosis and approximately 20% of patients with hATTR amyloidosis, as well as other demographic characteristics and disease features and severity that broadly represent the current global population of patients with ATTR-CM (additional details are provided in Sections 6.2.2.2 and 6.2.2.3). Eligible patients were required to have the diagnosis of ATTR-CM confirmed by either biopsy or technetium scintigraphy; the latter was allowed because of the rapid, widespread adoption of non-invasive diagnosis in the few years prior to the start of APOLLO-B.

For the DB, placebo-controlled period, patients were randomized (1:1) to receive either patisiran (0.3 mg/kg for patients weighing <100 kg; 30-mg fixed-dose for patients weighing ≥100 kg) or matching placebo q3W. Randomization was stratified by background tafamidis treatment (Yes vs

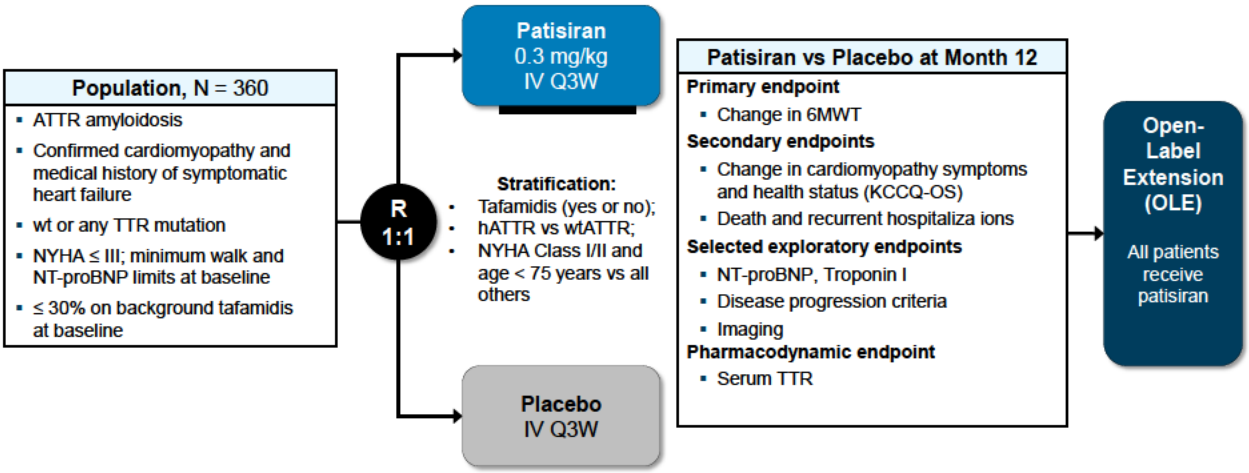
No), type of amyloidosis (wtATTR vs hATTR), and NYHA class and age (NYHA class I or II and <75 years vs all other).

To maintain the DB, the Investigator and any study personnel who managed the care of the patient could not perform assessments related to the primary and secondary endpoints, and any laboratory results that might reveal the treatment assignment (e.g., TTR levels) were not sent to the site. Also, study personnel involved in a patient's medical care also agreed not to obtain local laboratory results that could unblind them (e.g., pre-albumin, vitamin A, and RBP) to the patient's treatment until after the study was unblinded. In addition, the patisiran and placebo-treatment arms both received pre-medications prior to each dose that reduce the risk of IRR (corticosteroid, H1- and H2-receptor blockers, and paracetamol/acetaminophen). During the ongoing OLE, all patients are being treated with patisiran.

Prior TTR-lowering treatments and investigational drugs, such as TTR-targeted gene therapy, were not allowed. However, patients who had been treated with tafamidis for ≥6 months and were experiencing disease progression, in the opinion of the Investigator, were permitted to enter the study and remain on tafamidis. Enrollment of patients receiving tafamidis was limited to 30% of the overall study population to minimize confounding effects on safety or efficacy. In addition, any patient was allowed to start tafamidis during the study if the drug became approved and commercially available in their region and if the Investigator felt it in the best interest of the patient. Certain exclusion criteria disallowed patients who were taking concomitant medications generally deemed to be contraindicated, e.g., non-dihydropyridine calcium channel blockers. These study design elements ensured consistency of the standard of care in the global study with that in the US.

The APOLLO-B primary analysis treatment period was completed in June 2022 with database lock on 26 July 2022. An additional OLE data cut, inclusive of Month 18 data on all patients, was performed on 19 December 2022. Data from the OLE period will be available up to Month 24 by 13 September 2023.

Figure 16: Phase 3 APOLLO-B (DB+OLE) Study Design



Note: Follow-up period is 28 days after last dose of study drug.
6MWT=6-minute walk test; ATTR=transthyretin-mediated amyloidosis; DB=double-blind; hATTR=hereditary transthyretin-mediated; IV=intravenous; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP=N-terminal pro-brain natriuretic peptide; NYHA=New York Heart Association; OLE=open-label extension; Q3W=once every 3 weeks; R=randomized; TTR=transthyretin; wt=wild-type.

6.2.1.1 Key Enrollment Criteria

Participants in the study were enrolled in 69 study centers in 21 countries. Key enrollment criteria for APOLLO-B included:

- ≥18 and ≤85 years of age,
- Diagnosis of wt or hATTR amyloidosis with cardiomyopathy, confirmed by either biopsy or technetium scintigraphy with exclusion of monoclonal gammopathy if the latter is utilized,
- Medical history of HF with ≥1 prior hospitalization for HF or clinical evidence of HF manifested by signs and symptoms of volume overload or elevated intracardiac pressures that required treatment with a diuretic,
- One of the following:
  - Not on background tafamidis, which included those who had been on tafamidis for ≤30 days total and had not received any tafamidis in the 6 months prior to baseline, or
  - On background tafamidis for ≥6 months and with disease progression as determined by the Investigator,
- Clinically stable with no CV-related hospitalizations ≤6 weeks prior to randomization,
- Able to complete ≥150 m on 6MWT, and
- NT-proBNP >300 ng/L and <8,500 ng/L; in patients with permanent or persistent atrial fibrillation, NT-proBNP >600 ng/L and <8,500 ng/L.

Patients were ineligible if they had known AL amyloidosis or leptomeningeal amyloidosis. Patients were also excluded if they were both NYHA class III and ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3,000 ng/L and eGFR <45 mL/min/1.73 m^2; Gillmore et al 2018), were NYHA class IV, or had a PND score IIIa, IIIb, or IV (required cane or stick to walk, or was wheelchair bound) as assessed by the Investigator.

A full list of eligibility criteria is provided in Appendix 12.1.

6.2.1.2 Study Endpoints

Endpoints in APOLLO-B were selected to evaluate the efficacy of patisiran on functional capacity and other clinically meaningful measures relevant to patients with ATTR-CM, including QoL, key clinical outcomes, and physiological manifestations of ATTR amyloidosis in the heart.

Primary Endpoint

- 6MWT; change from baseline at Month 12

Secondary Endpoints

- KCCQ-OS; change from baseline at Month 12
- Composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits) and change from baseline in 6MWT over the 12-month DB period
- Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month DB period in patients not on tafamidis at baseline
- Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month DB period in the overall population

Exploratory Endpoints

- Composite endpoint of all-cause mortality and frequency of CV events (CV hospitalizations and urgent HF visits) over the 12-month DB period
- Change from baseline at Month 12 in:
  - NT-proBNP
  - Troponin I
  - Echocardiographic parameters
  - Technetium scintigraphy parameters
  - NYHA class
  - ATTR amyloidosis disease stage

6.2.1.2.1 6-Minute Walk Test (6MWT)

The 6MWT measures the distance that an individual can walk in 6 minutes using highly standardized procedures. It is a clinically relevant assessment of functional capacity and has been used to describe the age-related decline of normal aging (5–6 meters/year) (Enright et al 1998).

The 6MWT has been used as a primary endpoint in pivotal clinical trials supporting the approval of treatments for pulmonary arterial hypertension (Gabler et al 2012) and in the evaluation of patients with HF (Bittner et al 1993; Flynn et al 2009; Flynn et al 2012; Mangla et al 2013; Masoudi et al 2004; Olivotto et al 2020). Importantly, functional capacity is recognized by the FDA as an acceptable efficacy endpoint in HF studies that would be able to establish effectiveness and support the approval of drugs to treat HF (FDA 2019b).

ATTR-CM is characterized by inexorable decline in functional capacity across the range of HF severity, as exemplified by worsening 6MWT performance (Lane et al 2019; Nativi-Nicolau et al 2021). In the ATTR-ACT study, which evaluated tafamidis in patients with ATTR-CM, 6MWT performance in the placebo arm rapidly and steadily declined over time, with an approximately 60-meter decline from baseline observed at 12 months (Maurer et al 2018). Nativi-Nicolau et al. (2021) also showed that patients with more severe HF show a steeper rate of decline in 6MWT distance than patients with milder symptoms. Maurer (2022) has suggested, however, that in recent years the rate of decline in the 6MWT has been slower because of the early diagnosis of patients with less advanced disease than in the past (Ioannou et al 2022).

In APOLLO-B, rigorous procedures were followed for the 6MWT, and the test was conducted in accordance with guidelines established by the American Thoracic Society (A. T. S. Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002). The 6MWT was performed on an approved course and was administered by staff trained, blinded, and certified on the procedure, with oversight in the operational aspects provided by an expert central vendor using highly standardized and validated techniques. The staff administering the 6MWT were different from the Investigator or designee managing the care of the patient. These and other measures ensured high data completeness, with >90% of patients having evaluable 6MWT and KCCQ-OS data.

The schedule of 6MWT assessments was set to minimize the potential impact of a training effect, a result of individuals learning to pace themselves on the course. The effect, however, is lesser in older patients with HF (Adsett et al 2011, Ingle et al 2005). Furthermore, the training effect wanes after 2 months (Wu et al 2003). During the DB period, 6MWTs were obtained at Months 6, 9, and 12 after the baseline assessment.

6.2.1.2.2 Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS)

The KCCQ (Green et al 2000) is a self-administered questionnaire, which measures patients' perception of health status, including HF symptoms and the impact of HF on physical and social function, and QoL within a 2-week recall period. The KCCQ-OS, which was assessed at Month 12 as the first secondary endpoint, encompasses the following domains (Spertus et al 2005; Spertus et al 2020):

- Physical Limitations (including activities across a range of exertion)
- Total Symptoms (fatigue, dyspnea, edema, and orthopnea)
- QoL (i.e., the discrepancy between actual and desired health and functioning)
- Social limitations (i.e., the extent to which HF symptoms impair patients' ability to interact in gender-neutral social activities)

KCCQ-OS scores range from 0 to 100, with higher scores indicating better health status as follows: 0 to 24 is very poor to poor; 25 to 49 is poor to fair; 50 to 74 is fair to good; and 75 to 100 is good to excellent (Spertus et al 2005). Correlation between the KCCQ domains and other HF assessments, such as 6MWT, NYHA class, and QoL assessed by Short Form 36 were reported by the developers of the instrument, and the KCCQ was found to be a valid, reliable, and responsive health status measure for patients with congestive HF (Green et al 2000). The KCCQ-OS was found to most accurately reflect clinical change, followed by the NYHA and the 6MWT. In an early study of the ability of different techniques to accurately monitor short-term (6±2 weeks) clinical change in HF patients, changes in the KCCQ-OS correlated with the magnitude and direction of clinical change as assessed by a cardiologist (Spertus et al 2005). Of note, however, patients themselves can perceive smaller mean changes in KCCQ-OS scores as clinically meaningful (Butler et al 2020; Dreyer et al 2016).

The KCCQ has been adopted as a common assessment in studies of HF interventions and has been shown to be an independent predictor of prognosis in HF (Heidenreich et al 2006). Like the 6MWT, KCCQ has been shown to rapidly and consistently decline over time in patients with ATTR-CM making this an effective measure of patients' perception of health status (Maurer et al 2018; Lane et al 2019). The KCCQ has been qualified by FDA as a validated clinical outcome assessment for the evaluation of HF.

6.2.1.2.3 Clinical Outcomes: Deaths, Hospitalizations, and Urgent Heart Failure Visits

Composite endpoints that assessed mortality, hospitalization, and urgent HF visits were included below the KCCQ-OS in the secondary endpoint hierarchy with the understanding that the study size and duration may not have been sufficient to detect a potentially significant effect. Events of death, hospitalizations, and urgent HF visits were analyzed to characterize the safety and effect of patisiran on patient outcomes, in accordance with FDA feedback and guidance for industry. A blinded independent Adjudication Committee reviewed deaths and non-elective hospitalizations and attributed a cause (CV vs non-CV). Heart transplantation and ventricular assist device placement were treated as deaths. Deaths, all-cause hospitalizations, and urgent HF visits due to COVID-19 were excluded from analysis, unless otherwise specified.

6.2.1.2.4 Cardiac Laboratory Parameters

NT-proBNP and troponin I assess cardiac stress (HF severity) and myocardial injury, respectively. These laboratory parameters are monitored in clinical practice and are incorporated into recognized ATTR amyloidosis disease staging systems and expert consensus for defining disease progression (Garcia-Pavia et al 2021; Pregenzer-Wenzler et al 2020). Furthermore, NT-proBNP has been shown to be prognostic of outcomes in HF, including in ATTR amyloidosis (Damy et al 2016; Kristen et al 2017; Merlini et al 2016). NT-proBNP has thus been incorporated in combination with eGFR into a commonly utilized ATTR Amyloidosis Disease Staging system (Gillmore et al 2018). NT-proBNP is a strong predictor of mortality over a continuous range of increase from baseline in patients with wtATTR amyloidosis with cardiomyopathy. The HR is 1.04 with each 500 ng/L increase over 12 months. Stratified by thresholds of 500 ng/L, 1000 ng/L, or 2000 ng/L, the HRs are 1.65, 1.92, and 2.87, respectively (Law et al 2022b). Measurements of NT-proBNP and troponin I levels are routine in clinical practice because they are low in cost and easily interpretable.

6.2.1.2.5 Clinical Disease Staging

Clinical disease staging was evaluated using NYHA class and ATTR amyloidosis disease staging. The latter is a prognostic staging system that stratifies patients with ATTR-CM based on serum NT-proBNP level and eGFR, which are simple and routine measurements (Gillmore et al 2018). Patients are categorized as follows:

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

Worsening by NYHA class or ATTR amyloidosis disease stage are considered to provide evidence of disease progression according to a recent expert consensus statement (Garcia-Pavia et al 2021).

6.2.1.2.6 Cardiac Imaging

Echocardiographic Parameters

Echocardiography was used to assess cardiac structure and function in APOLLO-B. In patients with ATTR-CM, amyloid infiltration of the heart causes the myocardium to become thickened and stiff, with impaired ability to contract (systolic dysfunction) and relax (diastolic dysfunction). This abnormal pathology causes congestive HF, decreased functional capacity, and ultimately death from HF or arrhythmia. To elucidate the impact of patisiran on important elements of the pathophysiology, key echocardiographic measures included:

- LV mass and mean and relative LV wall thickness to evaluate deleterious structural changes due to amyloid infiltration,
- Global LV longitudinal strain to evaluate impaired systolic function,
- Left-ventricular end-diastolic volume to evaluate impaired diastolic function, and
- Overall cardiac output.

Decreases in LV mass, LV wall thickness, and global LV longitudinal strain and increases in LV end-diastolic volume and cardiac output represent improvements.

Echocardiographic imaging was overseen by a central imaging laboratory following guidance for clinical trial imaging (FDA 2018).

Technetium Scintigraphy Imaging Parameters

Technetium scintigraphy is a non-invasive method of characterizing TTR amyloid burden in the myocardium. Its utility in the diagnosis and prognosis of ATTR-CM amyloidosis is well established and is now the standard diagnostic tool for cardiac ATTR amyloidosis (Fontana et al 2015; Gillmore et al 2016; Martinez-Naharro et al 2019; Kittleson et al 2020).

In APOLLO-B, as part of a ‘Technetium sub-study' in a limited number of sites, cardiac technetium uptake was quantitatively assessed as an exploratory analysis by normalizing counts of radiotracer uptake in the heart to either the total amount of radiotracer administered

(normalized LV uptake) or to the contralateral lung to account for background (heart-to-contralateral lung ratio). For both assessments, increasing values reflect greater cardiac retention of technetium (worsening) and decreasing values indicate less cardiac retention of technetium (improvement).

Technetium uptake was also summarized using the Perugini grading scale, a semi-quantitative, 4-point grading system based on visual assessment of technetium uptake in the myocardium compared with that in the bones (Grade 0: no cardiac uptake and normal bone uptake; Grade 1: cardiac uptake that is less than bone uptake; Grade 2: cardiac uptake with intensity similar to bone uptake; Grade 3: cardiac uptake with intensity higher than that in bone) (Hutt et al 2017; Perugini et al 2005). Technetium scintigraphy that shows Perugini Grade 2 or 3 uptake can be reliably used to diagnose cardiac ATTR amyloidosis in patients with consistent clinical findings and absence of evidence for AL amyloidosis (Gillmore et al 2016).

6.2.1.3 Statistical Analyses

6.2.1.3.1 Populations Analyzed

The following patient populations were evaluated and used for presentation and analysis of the data:

- Full Analysis Set: All randomized patients who received any amount of study drug. Patients were analyzed according to the treatment to which they were randomized.
- Safety Analysis Set: All randomized patients who received any amount of study drug. Patients were summarized according to the treatment actually received.
- PK Analysis Set: All randomized patients who received at least one complete dose of study drug and had at least 1 post-dose blood sample for PK parameters and had evaluable PK data.
- PD Analysis Set: All randomized patients who received at least one complete dose of study drug and who had an evaluable baseline and at least one evaluable post-baseline TTR sample.
- All Patisiran Treated Set: All randomized patients who received any amount of patisiran, including patients who took patisiran during the DB period and patients who first took placebo during the DB Period and switched to patisiran during the OLE period.
- Technetium Analysis Set: All patients who were randomized and received any amount of study drug and who had at least one technetium scintigraphy assessment at baseline or post-baseline. Patients were analyzed according to the treatment to which they were randomized.

6.2.1.3.2 Statistical Methods

When APOLLO-B was designed, there was limited information to inform the expected powering of the trial. The most contemporaneous set of data were from the ATTR-ACT study of tafamidis (Maurer et al 2018). The ATTR-ACT study, however, could not inform either the effect of patisiran on a background of tafamidis or help understand if evolution in diagnostic technique

from cardiac biopsy to non-invasive imaging with technetium scintigraphy, and growing disease awareness, would meaningfully impact natural history of disease progression. Using the data from ATTR-ACT, which showed a 57-meter decline in placebo patients and a 24-meter decline in tafamidis patients, the same treatment effect for patients not on background tafamidis in APOLLO-B was assumed. In patients on background tafamidis, a 40% smaller effect size was assumed due to the anticipated slowing of decline in 6MWT in the placebo arm. With 70% of patients not on background tafamidis and 30% on background tafamidis, the expected decline in the overall placebo arm was 47 meters (SD=75) and the expected decline in the overall patisiran arm was 18 meters which equates to a 62% slowing of decline compared to placebo. A sample size of 300 provided >90% power to detect a mean difference between treatment arms using a 2-sided alpha level of 0.05. As further described in Section 2.1.4, the shift from cardiac biopsy to technetium scintigraphy enabled a dramatic trend toward the diagnosis of patients at earlier stages of disease and who thus had slower disease progression in APOLLO-B compared with prior studies (Ioannou et al 2022, Peikert et al 2023).

The statistical methods for APOLLO-B were pre-specified and developed with input from FDA. Formal statistical hypothesis testing was performed on the primary and secondary efficacy endpoints with all tests conducted at the nominal 2-sided 0.05 significance level. The overall familywise error rate was controlled at the 2-sided 0.05 significance level for the primary and secondary endpoints by a hierarchical ordering procedure, as listed in Section 6.2.1.2. There were no multiplicity adjustments for exploratory endpoints.

Estimand

For the objective of evaluating the efficacy of patisiran compared with placebo on 6MWT, the estimand is defined as follows:

- Target patient population: patients with hATTR or wtATTR amyloidosis with cardiomyopathy. Patients may or may not be taking tafamidis at study entry.
- Treatment condition: Patisiran 0.3 mg/kg or placebo administered as an IV infusion q3W with or without background tafamidis.
- Endpoint: Change from baseline in 6MWT at Month 12.
- Population-level summary: The stratified HL estimate of the median difference in the change from baseline in 6MWT at Month 12 between the patisiran and placebo arms. The p-value for the treatment difference will be estimated using the stratified Wilcoxon Rank Sum test.

Intercurrent events and strategies

Intercurrent events include treatment discontinuation, serious COVID-19 AE, tafamidis drop-in, missing dose(s) due to COVID-19, inability to walk due to progression of ATTR amyloidosis, and death. They require different handling strategies, which are described in Table 28.

An overview of the analyses of 6MWT, the primary endpoint, is provided in Table 4. For patients who had missing data because of death or inability to walk due to progression of ATTR amyloidosis, the missing 6MWT changes from baseline at Month 12 were imputed with the

worst 10th percentile change using data from all patients. Missing data due to other reasons were assumed as missing at random (MAR). Assessments collected after a COVID-19 SAE were excluded from the primary analysis and treated as MAR. In the primary analysis, data assumed as MAR were imputed using a multiple imputation approach based on the Markov chain Monte Carlo method with pre-specified covariates.

Table 4: Analysis of Primary Endpoint 6MWT in APOLLO-B

Analysis	Analysis Model
Primary	Stratified Wilcoxon Rank Sum test • Stratification factor: background tafamidis use (yes vs no)
Sensitivity 1	Stratified Wilcoxon Rank Sum test including all 6MWT assessments (i.e., including assessments that occur on or after the onset of a COVID-19 SAE) • Stratification factor: background tafamidis use (yes vs no)
Sensitivity 2	Stratified Wilcoxon Rank Sum test implementing control-based imputation for missing data in off-treatment patisiran patients based on data from the placebo group • Stratification factor: background tafamidis use (yes vs no)
Sensitivity 3	MMRM • Continuous covariate: baseline 6MWT • Categorical factors: treatment, visit (Months 6, 9, or 12), background tafamidis use (yes vs no), type of amyloidosis (hATTR vs wtATTR), age at randomization (<75 vs ≥75 years) • Interaction terms: treatment-by-visit, treatment-by-background tafamidis, visit-by-background tafamidis, treatment-by-visit-by-background tafamidis
Binary[a]	Stratified CMH • Stratification factor: background tafamidis use (yes vs no)

a. Evaluated change from baseline in 6MWT ≤0 meters and >0 meters as well as change from baseline in 6MWT <0 meters and ≥0 meters.
6MWT=6-minute walk test; CMH=Cochran-Mantel-Haenszel; hATTR=hereditary transthyretin-mediated amyloidosis; MMRM=mixed-effect model repeated measures; SAE=serious adverse event; wtATTR=wild-type transthyretin-mediated amyloidosis.

6.2.1.3.3 Kansas City Cardiomyopathy Questionnaire-Overall Summary

An overview of the analyses of KCCQ-OS, the secondary endpoint, is provided in Table 5. The change from baseline at Month 12 in KCCQ-OS was analyzed using a mixed effect model repeated measures (MMRM) model similar to 6MWT, while adjusting for baseline KCCQ-OS as a continuous covariate. The population-level summary is the LS mean difference in the change from baseline in KCCQ-OS at Month 12 between the patisiran and placebo arms. Strategies to handle intercurrent events are described in Table 29.

Table 5: Analysis of Secondary Endpoint KCCQ-OS in APOLLO-B

Analysis	Analysis Model
Primary	MMRM • Continuous covariate: baseline KCCQ-OS • Categorical factors: treatment, visit (Months 6, 9, or 12), background tafamidis use (yes vs no), type of amyloidosis (hATTR vs wtATTR), age at randomization (<75 vs ≥75 years) • Interaction terms: treatment-by-visit, treatment-by-background tafamidis, visit-by-background tafamidis, treatment-by-visit-by-background tafamidis
Sensitivity 1	MMRM Model Including All Censored Data • Included all KCCQ-OS assessments (i.e., assessments that occurred on or after the onset of a COVID-19 SAE were not treated as missing) using the same MMRM model as was used for the primary analysis of KCCQ-OS
Sensitivity 2	PMM • To assess the robustness of the primary MMRM results accommodating situations where the missingness mechanism may be MNAR
Binary	Stratified CMH • Stratification factor: background tafamidis use (yes vs no)

CMH=Cochran-Mantel-Haenszel; hATTR=hereditary transthyretin-mediated amyloidosis; KCCQ-OS= Kansas City Cardiomyopathy Questionnaire-Overall Summary; MMRM=mixed-effect model repeated measures; MNAR=missing not at random; PMM=pattern mixture model; SAE=serious adverse event; wtATTR=wild-type transthyretin-mediated amyloidosis.

6.2.1.3.4 Composite Endpoints

The composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits) and change from baseline in 6MWT was analyzed using the stratified win ratio method (Dong et al 2018), stratified by background tafamidis use.

The composite endpoints of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in patients who were not on tafamidis at baseline and in the overall population were analyzed using an Andersen-Gill model, including treatment, type of amyloidosis (hATTR vs wtATTR), baseline NYHA class (I/II vs III), and age at randomization (<75 vs ≥75 years) as covariates.

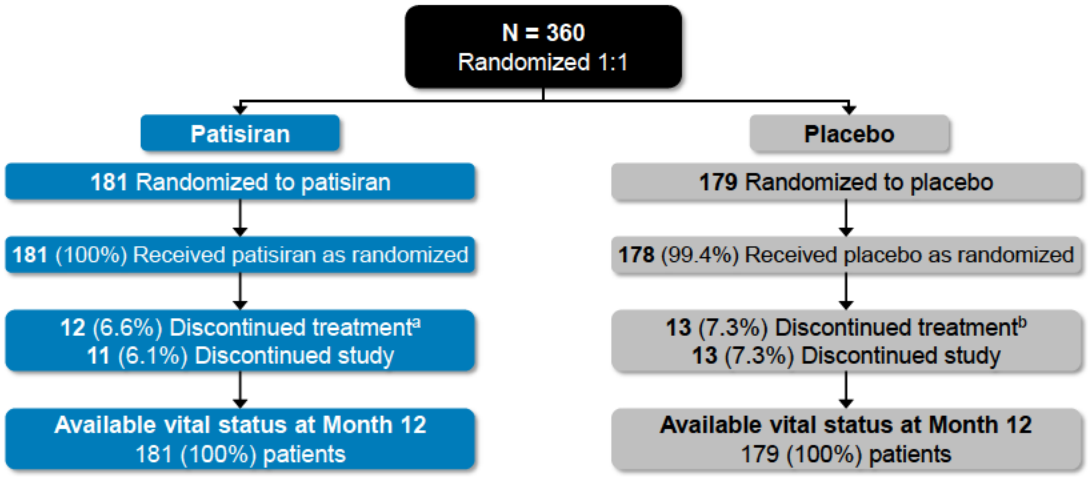
*6.2.2 **Patient Disposition and Baseline Characteristics***

6.2.2.1 Disposition

A total of 360 patients were randomized (1:1) to either patisiran or placebo (Figure 17). Of these patients 181 received patisiran and 178 patients received placebo. Although the study was conducted during the COVID-19 pandemic, the rate of treatment discontinuation was low (6.6% and 7.3% in the patisiran and placebo arms), and the vital status of 100% of patients was ascertained.

A total of 168 patients in the patisiran group and 166 patients in the placebo group continued from the DB period to the OLE period. Study treatment and participation is ongoing for the majority of patients in both groups.

Figure 17: Patient Disposition in 12-Month DB Period of APOLLO-B



a. Reasons for discontinuing patisiran treatment: AE (3 [1.7%]), death (3 [1.7%]), other (6 [3.3%]).
b. Reasons for discontinuing placebo treatment: AE (5 [2.8%]), death (3 [1.7%]), physician decision (1 [0.6%]), other (4 [2.2%]).
Other excludes AE, death, lost to follow-up, physician decision, pregnancy, protocol deviation, study terminated by Sponsor, and non-compliance to study drug.
AE=adverse event; DB=double-blind.

6.2.2.2 Baseline Demographics

Baseline demographics were similar between the patisiran and placebo groups and generally well balanced across regions (Table 6). Consistent with the ATTR amyloidosis global patient population, the median age at screening was 76.0 years (range: 41–85 years) and most patients were male (89.4%) (Connors et al 2016; Dispenzieri et al 2022; Bhuiyan et al 2011; Kroi et al 2021). The majority of patients were white (77.4%). Approximately 11–12% of patients were Hispanic or Latino, and 8–9% were black or African American. US baseline demographics are provided in Appendix 12.2.

Baseline demographics were also similar for patients who were on patisiran monotherapy vs those on background tafamidis.

Table 6: Baseline Demographics in APOLLO-B (Safety Analysis Set)

Characteristic	Patisiran (N=181)	Placebo (N=178)
Age at screening (years), median (min, max)	76.0 (47, 85)	76.0 (41, 85)
Age group, n (%)		
<45	0	2 (1.1)
45 to <65	13 (7.2)	15 (8.4)
65 to <75	61 (33.7)	59 (33.1)
≥75	107 (59.1)	102 (57.3)
Male, n (%)	161 (89.0)	160 (89.9)
Race, n (%)		
White	138 (76.2)	140 (78.7)
Asian	23 (12.7)	15 (8.4)
Black or African American	16 (8.8)	15 (8.4)
Other or not reported	4 (2.2)	8 (4.5)
Ethnicity, n (%)		
Not Hispanic or Latino	153 (84.5)	150 (84.3)
Hispanic or Latino	21 (11.6)	20 (11.2)
Not reported	5 (2.8)	4 (2.2)
Unknown	2 (1.1)	4 (2.2)
Region, n (%)		
United States	45 (24.9)	52 (29.2)
Western Europe	70 (38.7)	67 (37.6)
Rest of World	66 (36.5)	59 (33.1)

6.2.2.3 Baseline Disease Characteristics

The majority of baseline disease characteristics were largely overlapping and clinically comparable between the patisiran-treated and placebo-treated populations (Table 7). However, baseline NT-proBNP levels were higher for patients in the patisiran arm compared with placebo. Overall, baseline disease characteristics reflected a wide range of disease severity. The study population was generally representative of the current US and global population of patients with ATTR-CM.

As expected, the majority (80.2%) of patients had wtATTR amyloidosis and 19.8% had hATTR amyloidosis. Among the patients with hATTR amyloidosis, there were 16 TTR variants with VAL-122-ILE (40.8%), THR-60-ALA (16.9%) and ALA-97-SER (14.1%) being the most common. The majority of patients were diagnosed within a year of starting the study and the median age at symptom onset was 74 (range: 35–85) years. Most (85.2%) patients had NYHA class II HF and had ATTR amyloidosis disease stage 1 (68.0%) or stage 2 (25.3%); these

particular characteristics are consistent with the fact that patients in recent years are being diagnosed early in their disease course.

Overall, 25.3% of patients were on background tafamidis, and most of them (77/91, 85%) were from the US. Baseline disease characteristics were similar for patients who were on background tafamidis compared with patients on patisiran monotherapy. More patients in the background tafamidis group had wtATTR (approximately 89%) compared with those on patisiran monotherapy (approximately 76.3%). After randomization, 8 patients initiated tafamidis during the DB period: 5 in the patisiran group and 3 in the placebo group.

Table 7: Baseline Disease Characteristics in APOLLO-B (Safety Analysis Set)

Parameter	Patisiran (N=181)	Placebo (N=178)
ATTR amyloidosis type, n (%)		
wtATTR	144 (79.6)	144 (80.9)
hATTR	37 (20.4)	34 (19.1)
Time since diagnosis (years), median (min, max)	0.8 (0, 6)	0.4 (0, 10)
Background tafamidis use, n (%)	46 (25.4)	45 (25.3)
NYHA class, n (%)		
Class I	10 (5.5)	15 (8.4)
Class II	156 (86.2)	150 (84.3)
Class III	15 (8.3)	13 (7.3)
NT-proBNP level (ng/L), median (min, max)	2008 (288, 8530)	1813 (273, 12234)
ATTR amyloidosis stage[a], n (%)		
Stage 1	124 (68.5)	120 (67.4)
Stage 2	46 (25.4)	45 (25.3)
Stage 3	11 (6.1)	13 (7.3)
6MWT (m), mean (SD)	360.5 (102.3)	374.6 (102.4)
KCCQ-OS score, mean (SD)	69.8 (21.2)	70.3 (20.7)

a. ATTR amyloidosis disease stage is defined by a combination of NT-proBNP and eGFR thresholds (Gillmore et al 2018).
6MWT=6-minute walk test; ATTR=transthyretin-mediated amyloidosis; eGFR=estimated glomerular filtration rate; h=hereditary; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; wt=wild-type.

As described earlier in Section 6.2.1, patients on background tafamidis were permitted to enter APOLLO-B, if in the opinion of the Investigator, the patient was experiencing disease progression. The vast majority of signs or symptoms of disease progression were due to worsening HF, with multiple signs and symptoms (Table 8). Note that these data on manifestations of disease progression were collected after database lock by querying sites.

Table 8: Signs or Symptoms of Disease Progression Occurring in ≥25% of Patients on Background Tafamidis in APOLLO-B

Sign or Symptom	Patients on Background Tafamidis N=91 n (%)
Shortness of breath/dyspnea on exertion	54 (59.3)
Atrial fibrillation	45 (49.5)
Increasing diuretic requirement	29 (31.9)
Decreased exercise tolerance	28 (30.8)
Peripheral edema	27 (29.7)
Increased cardiac biomarkers	27 (29.7)
≥2 cardiac signs or symptoms of worsening heart failure	50 (54.9)

6.2.3 Change from Baseline in Serum TTR Levels with Patisiran Compared with Placebo

During the DB period, patisiran administration resulted in rapid and sustained reduction in TTR, the fundamental pathogenic protein, as measured by mean percent change from baseline over time in patients with ATTR-CM (Figure 2). The mean (SEM) serum TTR reduction from baseline at Month 12 was 86.8% (1.1%).

6.2.4 Primary Endpoint – Change from Baseline to Month 12 in 6MWT with Patisiran Compared with Placebo

Patients in the placebo group showed a steady decline in functional capacity, with a median change from baseline in 6MWT distance of −21.3 meters at Month 12. In contrast, a decline of –8.2 meters was observed in the patisiran group at Month 12 (Table 9). The treatment effect represents a clinically meaningful and statistically significant improvement in functional capacity at Month 12 with patisiran compared with placebo (HL estimate of the median difference, 14.7 meters; p=0.0162). 6MWT data collected at all timepoints are shown in Figure 31.

It is noteworthy that the observed change from baseline in 6MWT in the patisiran group over the 12-month DB period is comparable to the age-related decline expected in healthy adults of approximately 5–6 meters/year, (Enright and Sherrill 1998) thus indicating relative stability. In relative terms, over 12 months, patisiran treatment slowed the decline in functional capacity by 62% compared with placebo.

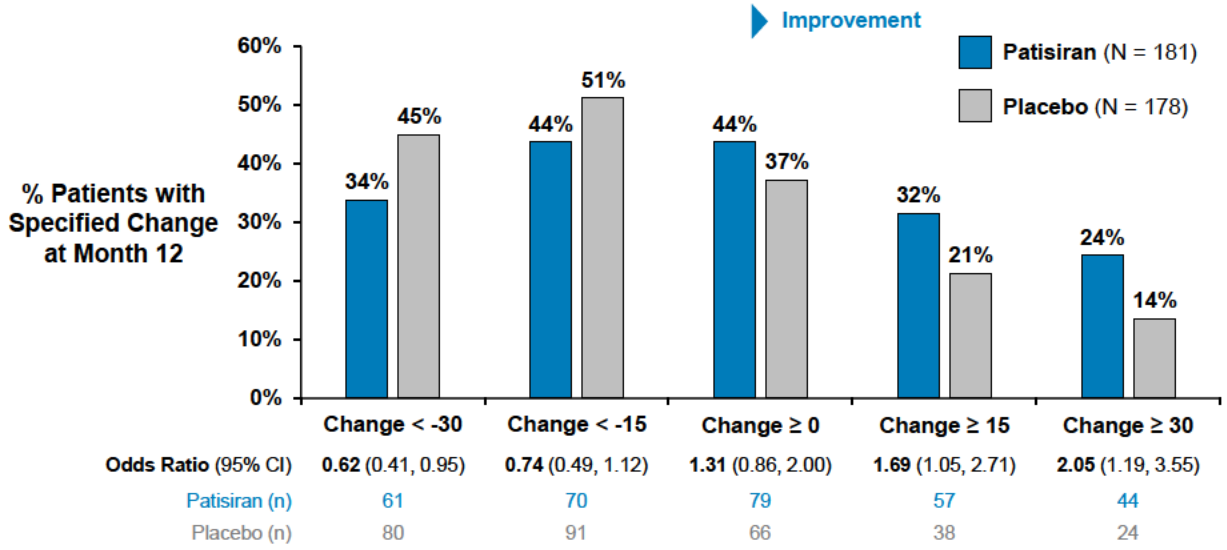
Table 9: Change from Baseline to Month 12 in 6MWT in APOLLO-B (Full Analysis Set)

	6MWT	
	Patisiran (N=181)	Placebo (N=178)
Median change from baseline at Month 12, meters	-8.2	-21.3
HL estimate of median difference at Month 12	14.7 (0.7, 28.7)	
p-value	0.0162	
Reduction in rate of decline relative to placebo at Month 12	62%	

6MWT=6-minute walk test; HL=Hodges Lehmann.

The effect of patisiran over placebo was favorable across the range of response thresholds (Figure 19; Figure 43). At specific thresholds, the likelihood of an improvement ≥15 meters was greater with patisiran (OR for improvement: 1.69; nominal p=0.0299) with a similar observation at ≥30 meters (OR for improvement: 2.05; nominal p=0.0090; Figure 18). Conversely, the risk of a decline >15 meters was numerically lower with patisiran (OR for decline: 0.74; nominal p=0.1572) with a similar observation at >30 meters (OR: 0.62 for decline; nominal p=0.0295; Figure 18).

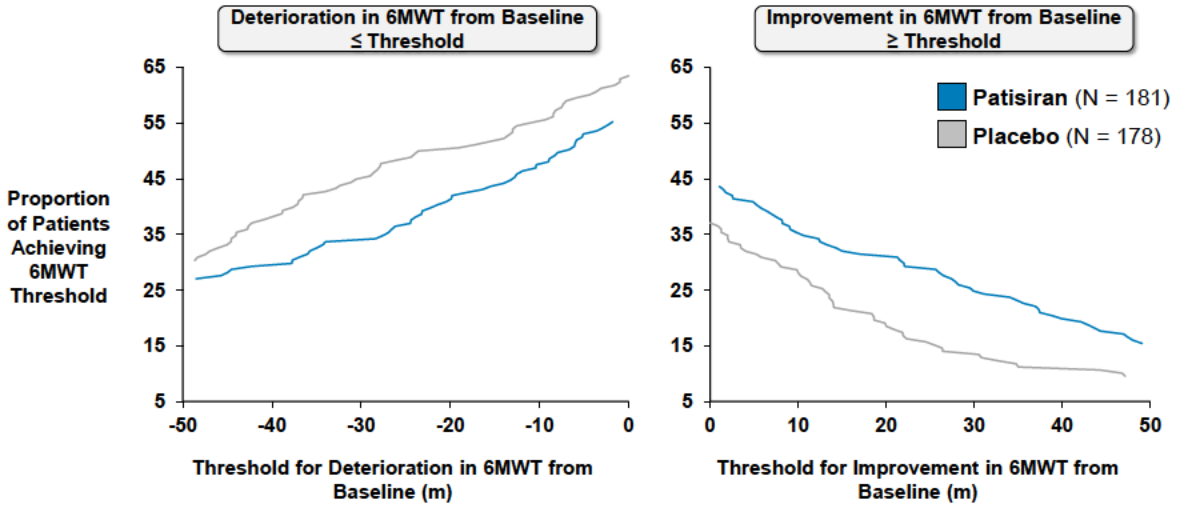
Figure 18: Proportion of Patients Achieving Treatment Effect Thresholds for Change from Baseline in 6MWT at Month 12 in APOLLO-B



Note: Change is in meters. Summaries are based on observed and imputed 6MWT data; for each patient, the change from baseline is averaged across 100 complete datasets. For each threshold, non-COVID-19 death or inability to walk due to progression of ATTR amyloidosis are summarized in the worse change category.
6MWT=6-minute walk test.

Across a broad range of thresholds of deterioration (i.e., change <0 meters), a consistently greater percentage of placebo- than patisiran-treated patients showed a decline. Likewise, a consistently greater percentage of patisiran- than placebo-treated patients showed an improvement at thresholds of change >0 meters (Figure 19).

Figure 19: Percent of Patients Who Deteriorate or Improve Across 6MWT Distance Thresholds at Month 12



Note: Assessments where the timer was stopped after ≤4 minutes or conducted using unapproved walking aid or collected after a serious COVID-19 AE are excluded from the analysis.
Figure displayed observed and imputed 6MWT data; for each patient, the change from baseline is average across 100 complete datasets.
6MWT=6-minute walk test.

6.2.4.1 6MWT Handling of Missing Data

The missing data handling strategy for 6MWT was pre-specified and aligned with the FDA prior to study unblinding. Table 10 summarizes the 6MWT data completeness at Month 12 and the missing data handling approach implemented for each type of missing data. A detailed description of the intercurrent event strategy for the primary analysis of 6MWT is also provided in Table 11.

Table 10: Summary of 6MWT Data Completeness at Month 12 and Missing Data Handling (Full Analysis Set)

Month 12 Data	Missing Data Handling Rule	Patisiran (N=181) n (%)	Placebo (N=178) n (%)	Comment
Non-missing	N/A	166 (91.7%)	161 (90.4%)	
Missing due to non-COVID death or inability to walk	Single imputation with worst 10th percentile change observed in the double-blind period, capped by the worst possible change for the patient (i.e., 0 minus baseline 6MWT)	5 (2.8%)	9 (5.1%)	• There were more patients on placebo requiring this type of imputation. • It would favor the patisiran arm if the Sponsor used a more conventional approach (i.e., impute 0 meters for the missing 6MWT distance).
All other missing data	Multiple imputation assuming data are MAR	10 (5.5%)	8 (4.5%)	• Imputation performed by treatment arm/background tafamidis use group, accounting for baseline demographic characteristics and disease severity as well as change in 6MWT at previous visits.

6MWT=6-minute walk test; MAR=missing at random; N/A=not applicable.

6.2.4.2 6MWT Sensitivity Analyses

The robustness of the primary result was confirmed by sensitivity analyses utilizing multiple methods. They demonstrated a consistent benefit of patisiran compared with placebo on the change from baseline to Month 12 in 6MWT (Table 11).

Table 11: Results of Primary and Sensitivity Analyses for 6MWT

Pre-Planned Methods	Method	Intercurrent Events and Missing Data Handling	Treatment Difference (patisiran-placebo), (95% CI)	P-value
Primary analysis	Stratified Wilcoxon Rank Sum Test for p-value HL estimate for median difference	• Treatment policy: including on-treatment and off-treatment data • Data censored for COVID-19 SAE • Death and inability to walk imputed with worst 10th percentile change[a] • Assuming MAR	14.7 (0.7, 28.7)	0.016
Sensitivity 1		• Data not censored for COVID-19 SAE • Assuming MAR	14.1 (0.34, 27.9)	0.017
Sensitivity 2		• Assuming MNAR; missing data for off-treatment patisiran patients followed placebo trajectory	14.5 (0.4, 28.5)	0.018
Sensitivity 3[b]	MMRM	• Same as primary analysis	18.1 (2.5, 33.8)	0.023

a. Includes deaths not due to COVID-19 and patients who become unable to walk due to progression of ATTR amyloidosis.
b. Erroneous 6MWT were corrected for the 2 patients at Site 327.
6MWT=6-minute walk test; HL=Hodges-Lehmann; MAR=Missing at Random; MMRM=mixed-effect model repeated measures; MNAR=Missing Not at Random; SAE=serious adverse event.

6.2.5 First Secondary Endpoint – Change from Baseline to Month 12 in KCCQ-OS with Patisiran Compared with Placebo

Over the DB period, patients in the placebo group showed a steady decline in KCCQ-OS, with a mean change from baseline of −3.4 points. In contrast, the patisiran group showed an increase of +0.3 points. Thus, a statistically significant change in KCCQ-OS at Month 12 was demonstrated with patisiran compared with placebo (LS mean difference, 3.7 points; p=0.0397) (Table 12) indicating the stability of health status and QoL with patisiran treatment.

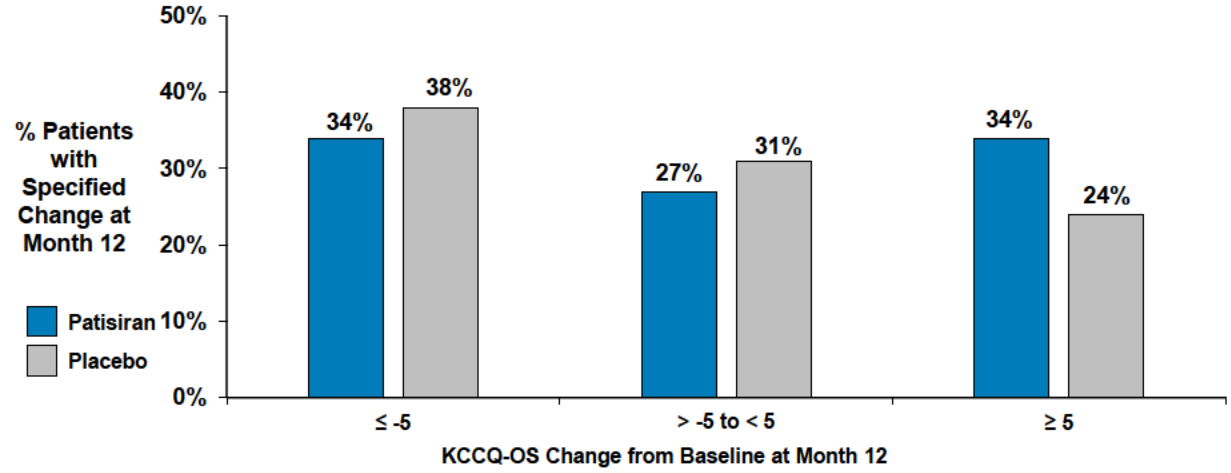
Table 12: Change from Baseline to Month 12 in KCCQ-OS in APOLLO-B (Full Analysis Set)

	KCCQ-OS	
	Patisiran (N=181)	Placebo (N=178)
LS mean change from baseline at Month 12	0.3	-3.4
LS mean difference at Month 12 (95% CI)[a]	3.7 (0.2, 7.2)	
p-value	0.0397	

a. Based on MMRM analysis.
KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; MMRM=mixed-effect model repeated measures.

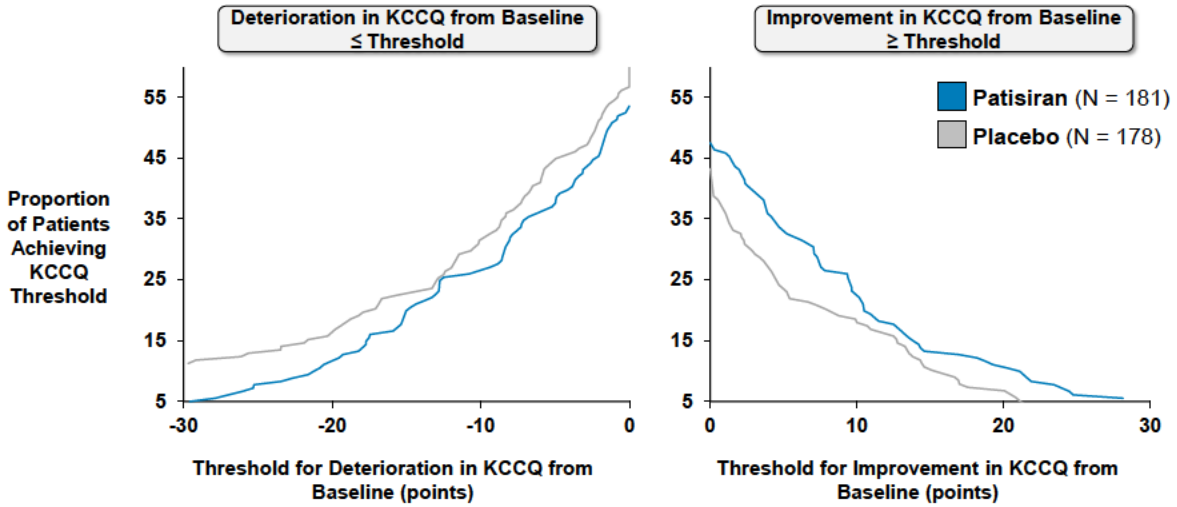
As depicted in Figure 20, when treatment thresholds are considered, more patisiran-treated patients experienced increases of ≥5 points, while fewer patisiran-treated patients experienced KCCQ-OS declines of ≤−5 points. Indeed, across all treatment response thresholds the best KCCQ results were more frequent on patisiran and the worst KCCQ results were more likely on placebo (Figure 21; Figure 44).

Figure 20: KCCQ-OS by Response Threshold During 12-Month DB Period in APOLLO-B



DB=double-blind; KCCQ-OS= Kansas City Cardiomyopathy Questionnaire-Overall Summary.

Figure 21: Percent of Patients Who Deteriorate or Improve Across KCCQ-OS Response Thresholds at Month 12

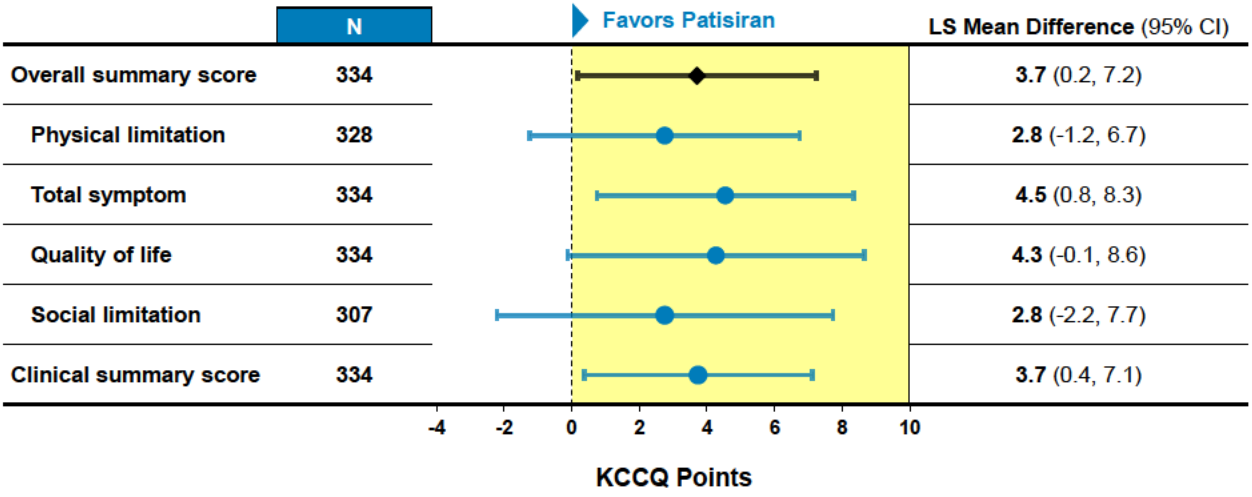


Note: Patients who are missing Month 12 due to COVID-19 or who had their Month 12 assessment on or after a serious COVID-19 adverse event are excluded from the analysis.
Note: Figure presents observed and imputed KCCQ-OS data; for each patient, the change from baseline is average across 100 complete datasets.
KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.

6.2.5.1 Change from Baseline to Month 12 in KCCQ Individual Domains with Patisiran Compared with Placebo

Results across all KCCQ-OS domains, including physical limitation, total symptom, QoL, and social limitation, were consistent with the overall results of KCCQ-OS with patisiran compared with placebo (Figure 22). The treatment benefit with patisiran was also observed in the Clinical Summary Score, which is an established summary score comprised of the Physical Limitations and Total Symptom domains.

Figure 22: Change from Baseline in KCCQ Individual Domains During 12-Month DB Period in APOLLO-B (Full Analysis Set; MMRM)



DB=double-blind; KCCQ=Kansas City Cardiomyopathy Questionnaire; MMRM=mixed-effect model repeated measures.

6.2.5.2 KCCQ-OS Sensitivity Analyses

The robustness of these results was confirmed by sensitivity analyses demonstrating a consistent benefit of patisiran compared with placebo on the KCCQ-OS at Month 12 using multiple methods to assess the impact of missing data (Table 13).

Table 13: Results of Primary and Sensitivity Analyses for KCCQ-OS

Pre-Planned Methods	Method	Intercurrent Events and Missing Data Handling	Treatment Difference (patisiran-placebo), (95% CI)	P-value
Primary analysis	MMRM	• Treatment policy: including on-treatment and off-treatment data • Data censored for COVID-19 SAE • Assuming MAR	3.7 (0.2, 7.2)	0.0397
Sensitivity 1	MMRM	• Data not censored after COVID-19 SAE (assume MAR)	3.8 (0.3, 7.3)	0.0343
Sensitivity 2	Pattern-Mixture Model	• Assuming MNAR; missing data for off-treatment patisiran patients followed placebo trajectory • Death[a] imputed with the worst 10th percentile change	4.6 (0.9, 8.4)	0.0161

a. Death not due to COVID-19.
MAR=Missing at Random; MMRM=mixed-effect model repeated measures; MNAR=Missing Not at Random; SAE=serious adverse event.

6.2.6 Subgroup Analyses of 6MWT and KCCQ-OS

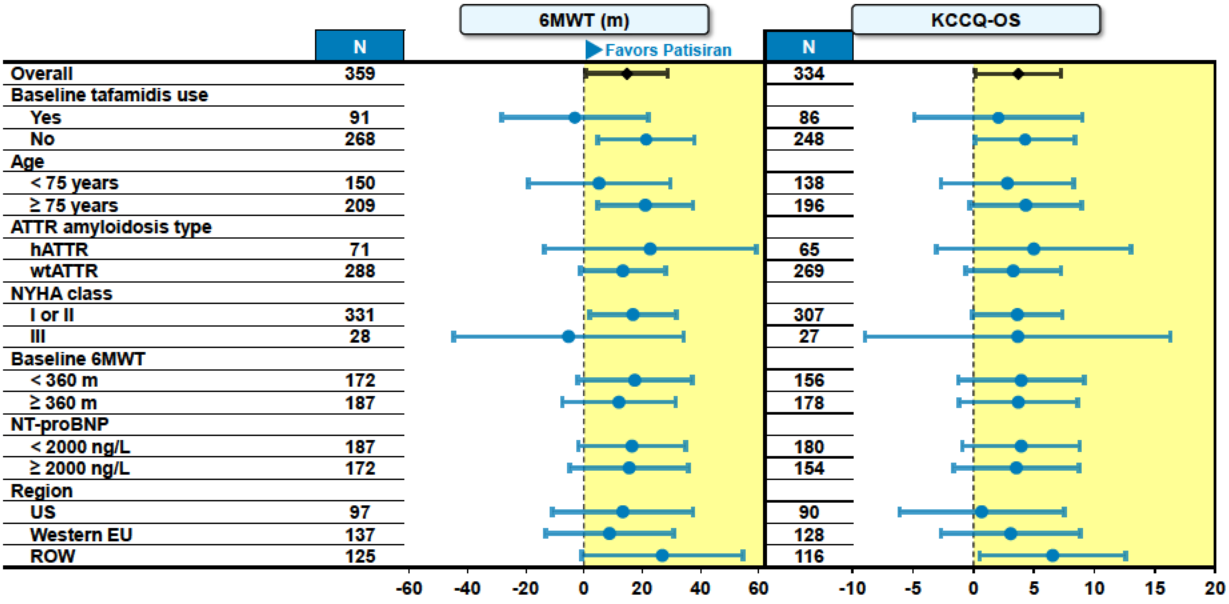
The treatment effect with patisiran on functional capacity (6MWT) and patients' experience of their health status and QoL (KCCQ-OS) was generally consistent across the majority of subgroups of baseline demographic and disease characteristics (Figure 23; Section 6.4).

In the subgroup of patients on background tafamidis, the point estimates favor patisiran for the KCCQ-OS but not the 6MWT (Figure 23). The small sample size (N=91) and limited decline in the placebo group over 12 months make it difficult to draw definitive conclusions. Please see Section 6.4.2 for additional details.

In the subgroup with NYHA class III HF (N=28; patisiran, n=15 and placebo, n=13), the point estimate of the treatment effect in the 6MWT was slightly negative for patisiran, whereas the point estimate for the KCCQ-OS was of same magnitude as in the overall population (Figure 23). Patisiran did, however, show a consistent treatment benefit in larger subgroups that encompass patients with more severe HF, such as a baseline 6MWT distance <360 m and NT-proBNP ≥2000 ng/L. The cutoffs are the median baseline values in the APOLLO-B study population and have been reported to be associated with an increased risk of death in patients with ATTR-CM

(Vong et al 2021). Notably, a subgroup of patients (N=72) had a baseline KCCQ-OS score <50, which typically reflects patients with NYHA class III or IV HF (Tran et al 2021). In this subgroup, the treatment effects favor patisiran in the 6MWT (HL median difference 9.9 meters; 95% CI: −26.5–46.3) and in the KCCQ-OS (LS mean difference 11.3; 95% CI: 1.8–20.7). The collective data suggest that patisiran can benefit patients across a broad range of HF severity.

Figure 23: 6MWT and KCCQ-OS Subgroup Analyses of Change from Baseline to Month 12 in DB Period of APOLLO-B (Full Analysis Set)

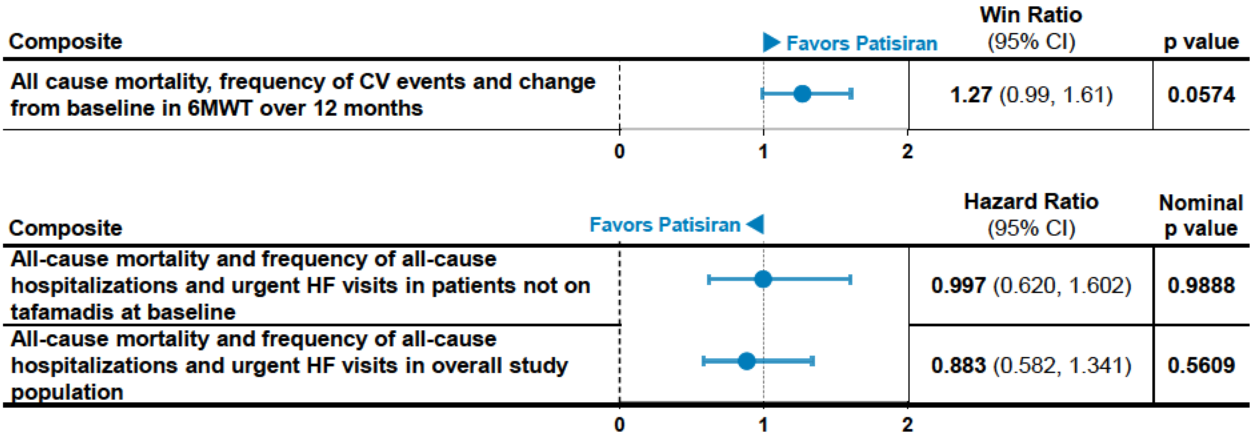


6MWT=6-minute walk test; ATTR=transthyretin-mediated amyloidosis; DB=double-blind; EU=European Union; hATTR=hereditary transthyretin-mediated amyloidosis; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; ROW=rest of world; US=United Staes; wtATTR=wild-type transthyretin-mediated amyloidosis.

6.2.7 Composite Endpoints

The numerical trends in the pre-specified secondary composite endpoints favoring patisiran, while not statistically significant, are reassuring, indicating no detrimental effects (Figure 24).

Figure 24: Composite Outcomes Endpoints Over 12 Month DB Period in APOLLO-B (Full Analysis Set)



Note: Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization handled in same manner as death in analysis.
6MWT=6-minute walk test; CV=cardiovascular; DB=double-blind; HF=heart failure.

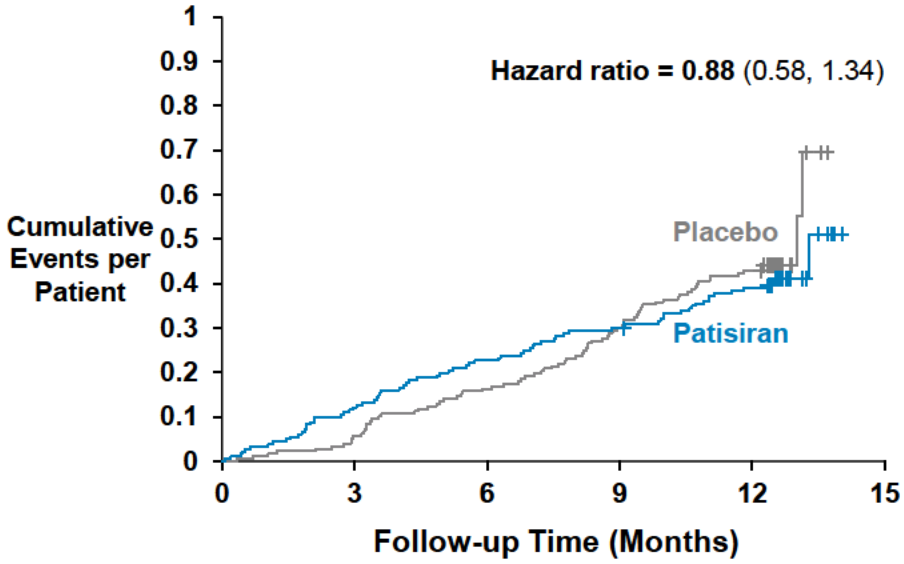
6.2.7.1 *All-Cause Mortality, Frequency of Cardiovascular Events, and Change from Baseline in 6MWT*

At Month 12, the stratified win ratio for the composite endpoint of all-cause mortality, frequency of CV events, and change from baseline in 6MWT was 1.27 (p=0.0574) (Figure 24).

6.2.7.2 *All-Cause Mortality, Frequency of All-Cause Hospitalizations, and Urgent Heart Failure Visits*

For patients not on background tafamidis, the composite of all-cause mortality and frequency of all-cause hospitalization and urgent HF visits, the point estimate of the HR was 1.00 (nominal p=0.9888; Figure 24). For the composite of all-cause mortality and frequency of all-cause hospitalization and urgent HF visits in the overall population, the point estimate of the HR was 0.88 (nominal p=0.5609; Figure 25). There were fewer deaths in the patisiran group compared with the placebo group; the frequencies of all-cause hospitalizations and urgent HF visits were similar between groups.

Figure 25: All-Cause Mortality, All-Cause Hospitalizations, and Urgent Heart Failure Visits During 12-Month DB Period of APOLLO-B (Full Analysis Set)

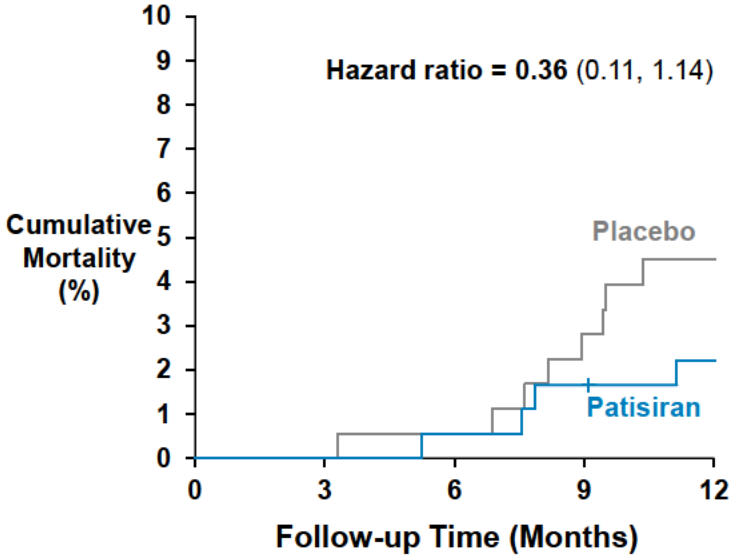


Note: Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis. For patients who discontinued treatment during the DB period, events occurring after Day 417 were excluded. For patients who discontinued treatment during the OLE period, events occurring >90 days after last patisiran dose were excluded.
DB=double-blind; HF=heart failure; OLE=open-label extension.

6.2.7.3 All-Cause Mortality

All-cause mortality was a component of the composite endpoint analyses. The all-cause mortality efficacy analysis counted deaths according to the pre-defined statistical analysis plan which excluded deaths due to COVID-19 and treated cardiac transplant and LVAD placement in the same manner as death. Using this approach, the number of deaths in the all-cause mortality efficacy analysis was 4 (2.2%) in the patisiran group and 10 (5.6%) in the placebo group which excludes 1 COVID-19 death in the patisiran arm and include 2 heart transplants in the placebo arm. For all-cause mortality, the HR was 0.36 (95% CI: 0.11–1.14; Figure 26). Of the deaths, 2 in the patisiran and 5 in the placebo arm were adjudicated to be CV-related.

Figure 26: All-Cause Mortality During 12-Month DB Period of APOLLO-B (Full Analysis Set)



Note: Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis.
DB=double-blind; HF=heart failure.

*6.2.8 **Exploratory Endpoints***

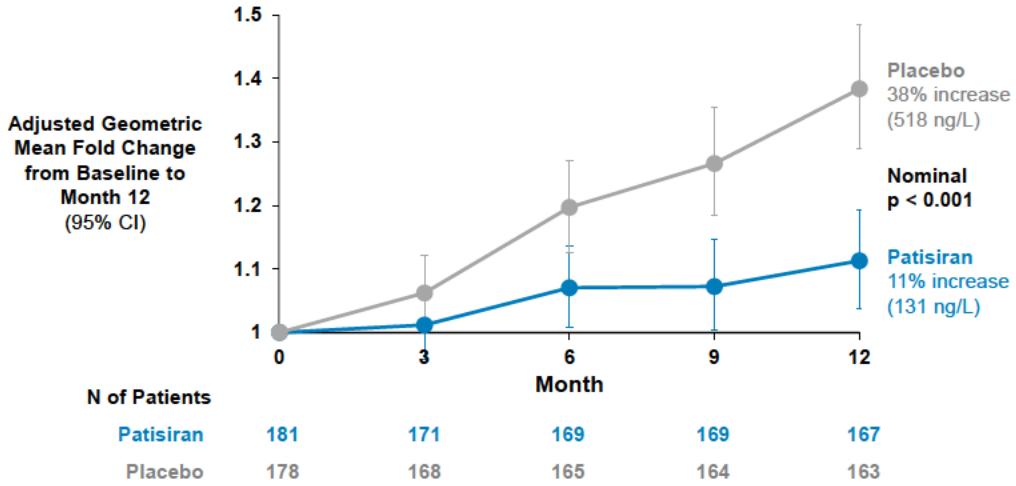
6.2.8.1 Cardiac Laboratory Parameters

Exploratory analyses of NT-proBNP and troponin I in the DB period of APOLLO-B demonstrate favorable trends for patisiran compared with placebo.

6.2.8.1.1 NT-proBNP

At Month 12, patisiran-treated patients showed a smaller increase in NT-proBNP compared with placebo (adjusted geometric mean fold change ratio [patisiran/placebo], 0.80; nominal p <0.001; Figure 27). The median increase (worsening) from baseline in NT-proBNP was larger in the placebo group (518 ng/L) compared with that in the patisiran group (131 ng/L). An effect of patisiran on NT-proBNP was observed as early as Month 6 (ratio of adjusted geometric mean fold change [patisiran/placebo] at Month 6 of 0.89; 95% CI: 0.82–0.97).

Figure 27: Change from Baseline in NT-proBNP During 12-Month DB Period in APOLLO-B (Full Analysis Set)

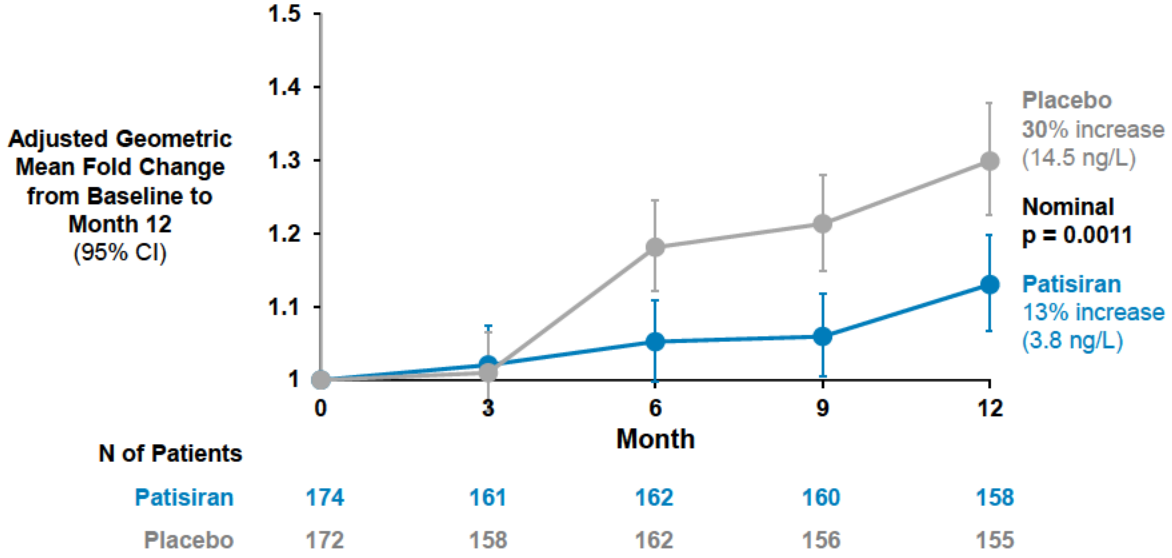


DB=double-blind; NT-proBNP=N-terminal prohormone B-type natriuretic peptide.

6.2.8.1.2 Troponin I

Similar patterns were observed with troponin I as with NT-proBNP. At Month 12, patisiran-treated patients showed a smaller increase in troponin I compared with placebo (adjusted geometric mean fold change ratio [patisiran/placebo], 0.87; nominal p=0.0011). The median increase (worsening) from baseline in troponin I was larger in the placebo group (14.5 ng/L) compared with that in the patisiran group (3.8 ng/L; Figure 28). The effect of patisiran was observed as early as Month 6 (ratio of adjusted geometric mean fold change [patisiran/placebo] at Month 6 of 0.89 (95% CI: 0.83–0.96).

Figure 28: Change from Baseline in Troponin I During 12-Month DB Period in APOLLO-B (Full Analysis Set)



DB=double-blind.

6.2.8.2 Cardiac Imaging

Exploratory analyses of cardiac imaging in the DB period of APOLLO-B included echocardiography and technetium scintigraphy.

6.2.8.2.1 Echocardiographic Parameters

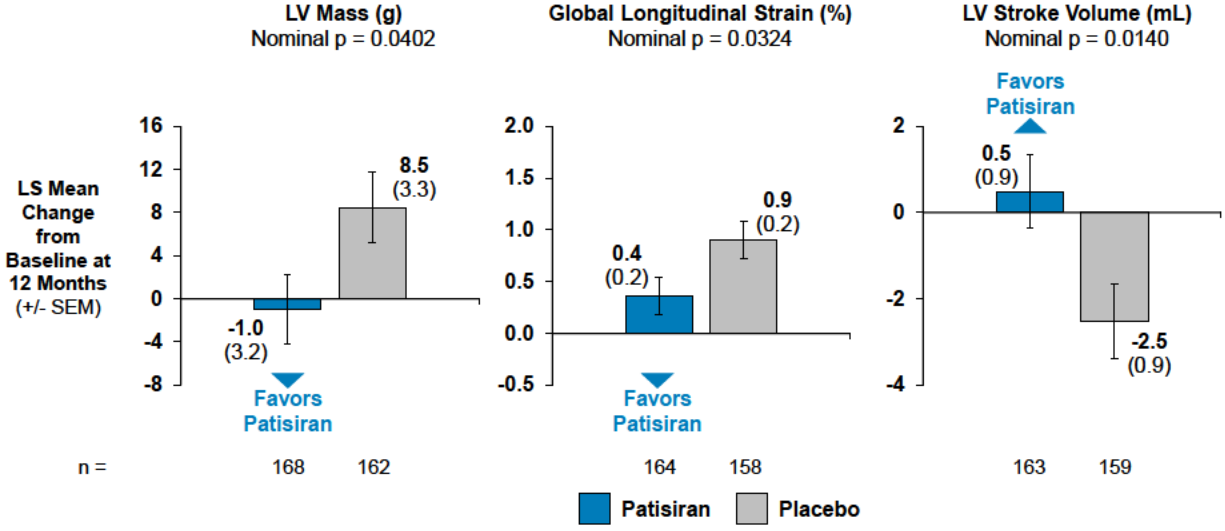
Measurement of echocardiographic parameters at baseline and Month 12 in the DB period assessed changes in cardiac structure (LV mass), systolic function (global longitudinal strain), and stroke volume. Decreases in LV mass and global LV longitudinal strain and increases in LV stroke volume represent improvements.

The results are summarized below and in Figure 29:

- LV mass increases with ongoing amyloid deposition. LV mass in patisiran-treated patients remained stable (mean change of –1.0 g [3.2]) vs increasing in placebo-treated patients (mean change of 8.5 g [3.3]; LS mean [95% CI] difference −9.5 g [−18.5, 0.4]; nominal p=0.040). The increase in LV mass in the placebo group is comparable to that reported in a natural history study of patients with ATTR-CM (Chacko et al 2020).
- Global longitudinal strain increases with disease progression. A smaller mean percent increase was observed for patisiran-treated patients (0.36% [0.18]) than for placebo-treated patients (0.90% [0.18]; LS mean [95% CI] difference -0.5% [−1.0, −0.1]; nominal p=0.032).
- LV stroke volume decreases as LV mass increases and systolic function declines, causing reduced LV end-diastolic and end-systolic volumes. At Month 12, LV stroke volume remained stable with patisiran (0.5 mL [0.9]) but declined with placebo (–2.5 mL [0.9]; LS mean [95% CI] difference 3.0 mL [0.6, 5.4]; nominal p=0.01).

The stability of LV mass in patisiran-treated patients is consistent with the suppression of ongoing amyloid deposition. In contrast, the relative worsening in the placebo- compared with patisiran-treated patients of global longitudinal strain and LV stroke volume, which measure LV function, highlights the adverse impact of the amyloid deposited in just 12 months, and links the mechanism of action of patisiran to the observed clinical benefits.

Figure 29: Change from Baseline in Echocardiographic Parameters at Month 12 in DB Period of APOLLO-B (Full Analysis Set)



DB=double-blind; LV=left ventricular.

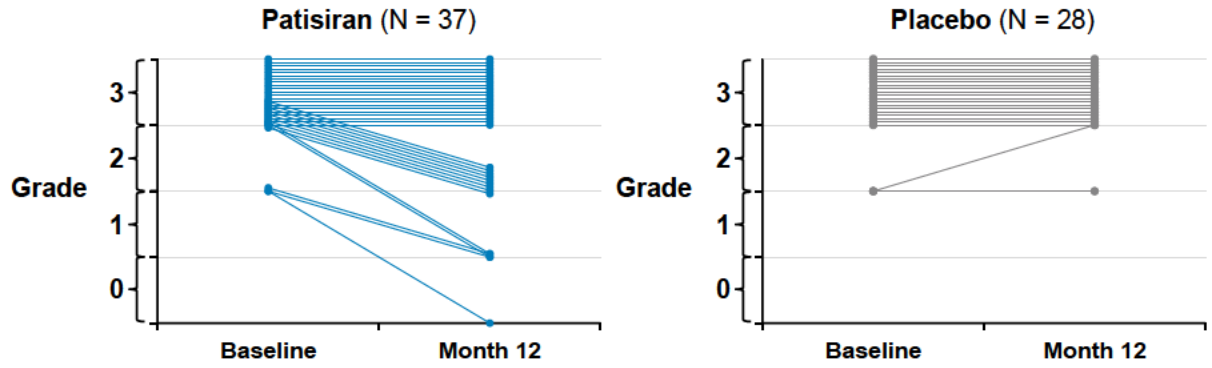
6.2.8.2.2 Technetium Scintigraphy

In a planned subset of patients in APOLLO-B (the Technetium Analysis Set; N=65 across 17 sites), cardiac technetium scintigraphy images at baseline and Month 12 were read at a central lab. Readers were blinded to treatment assignment and temporal sequence of scans.

Cardiac technetium uptake was summarized using the Perugini grading scale, a semi-quantitative, 4-point grading system based on visual assessment of technetium uptake in the myocardium compared with that in the bones as described in Section 6.2.1.2.6. Among patients in the Technetium Analysis Set, most patients (approximately 90% in both treatment groups) had Perugini Grade 3 disease at baseline, consistent with their diagnosis of ATTR-CM.

At Month 12, improvement by ≥1 grade was observed for 37.8% of evaluable patients in the patisiran group vs no patient in the placebo group (Figure 30). Notably, 5 patisiran-treated patients improved to Perugini Grade 0 or 1, i.e., below the standard threshold grade for diagnosis, with 3 patients improving by 2 grades.

Figure 30: Change from Baseline to Month 12 in Perugini Grade for Individual Patients During DB Period of APOLLO-B (Technetium Analysis Set)



Note: Perugini Grade: 0=absent cardiac uptake; 1=mild cardiac uptake less than bone; 2=moderate cardiac uptake equal to bone or with mildly attenuated bone uptake; 3=high cardiac uptake greater than bone or with marked reduction in bone uptake.
DB=double-blind.

6.2.9 Open-Label Extension

6.2.9.1 Methods

All patients who completed the 12-month DB period could enter the OLE period and receive patisiran. During the course of the sNDA review, an additional analysis of APOLLO-B was conducted after all ongoing patients had completed the Month 18 visit of the trial. Note that the number of patients who have reached visits beyond Month 18 gets smaller at each subsequent visit due to the trajectory of study enrollment, so results beyond Month 18 should be interpreted with caution. Patients are categorized by their initial randomized treatment in the DB period. Thus, the placebo group includes patients who received placebo during the 12-month DB period and then patisiran in the OLE period. The patisiran group continued to receive patisiran in the OLE period.

The blinding to patients' randomized treatment in the DB period was maintained until the last patient completed their Month 12 visit. Treatment assignments, however, were not revealed to patients or Investigators until after all patients had completed their Month 18 visit. Updates to the OLE data that include complete follow up through Month 24 will be available by 13 September 2023.

The tables and figures provide descriptive summaries of the observed data.

6.2.9.2 Disposition and Exposure

Of the 360 randomized patients, 334 patients (92.8%) entered the OLE period at Month 12. As of the data cutoff date of 19 December 2022, 299 patients (83.1%) were ongoing in the study, with the proportions being similar across the 2 initial randomized treatment groups (83.4%, patisiran group; 82.7%, placebo group). All patients remaining in the study had completed the Month 18 assessment. The proportions of patients with ongoing treatment were also similar across the 2 initial randomized treatment groups (82.9%, patisiran group; 81.6%, placebo group).

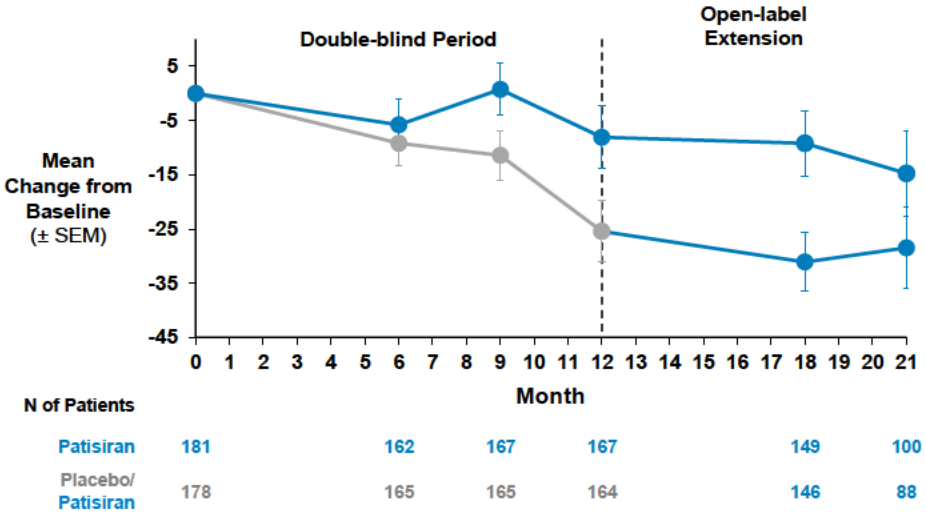
Of the 360 randomized patients, 10.6% of patients had discontinued study drug at the time of the data cutoff date (9.9%, patisiran group; 11.2% placebo group); the primary reasons for discontinuation of treatment were death (4.4% of patients), other (3.1% of patients), AE (2.5% of patients), and physician decision (0.6% of patients). A total of 347 patients received patisiran during the study, including patients initially randomized to patisiran (181 patients) and those randomized to placebo who received patisiran in the OLE period (166 patients). Overall, patients initially randomized to patisiran had received a median of 21.8 months of patisiran treatment in the study (DB + OLE periods) (range: 0.0 to 37.0 months), with a cumulative treatment exposure of 332.4 person-years. Overall, only 17.9% of patients missed more than 1 patisiran dose, and only 2.9% of patients missed at least 3 consecutive patisiran doses.

6.2.9.3 Month 18 6MWT

During the OLE period, patients randomized to patisiran in the DB period continued to demonstrate maintenance of treatment benefit on 6MWT (Figure 31). The mean decline of approximately 9 meters for the patisiran group over approximately 1.5 years of treatment in the study (DB + OLE) was consistent with the Month 12 assessment and comparable to that of healthy adults (approximately 5–6 meters/year [Enright and Sherrill 1998]), thus underscoring the meaningful slowing in the decline of functional capacity in this patient population.

For patients randomized to placebo, who experienced a steady decline in 6MWT during the DB period (a median decline of approximately 21 meters at Month 12; Section 1.6.3.2), initial evidence of a treatment effect was observed in the OLE period after initiating patisiran treatment (Figure 31).

Figure 31: Change from Baseline in 6MWT (DB+OLE) in APOLLO-B (Full Analysis Set)



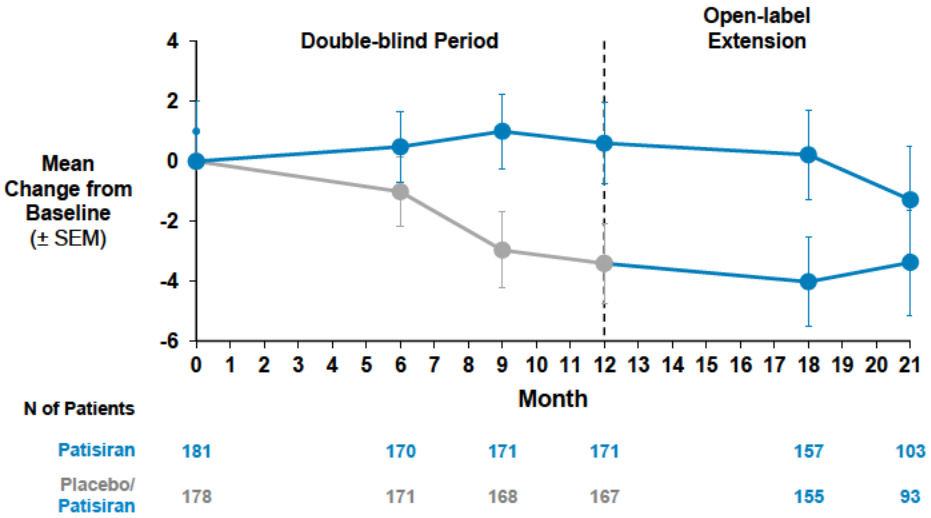
Note: The dashed line designates the Month 12 timepoint at which the placebo group crossed over to treatment with patisiran.
6MWT=6-minute walk test; DB=double-blind; OLE=open-label extension.

6.2.9.4 Month 18 KCCQ-OS

During the OLE period, patients randomized to patisiran in the DB period continued to demonstrate maintenance of treatment benefit and stability in KCCQ-OS with a mean change from baseline to Month 18 of 0.22 points (Figure 32).

For patients randomized to placebo who experienced a steady decline in KCCQ-OS during the DB period (Figure 32), initial evidence of a treatment effect was observed in the OLE period after initiating patisiran treatment.

Figure 32: Change from Baseline in KCCQ-OS (DB+OLE) in APOLLO-B (Full Analysis Set)

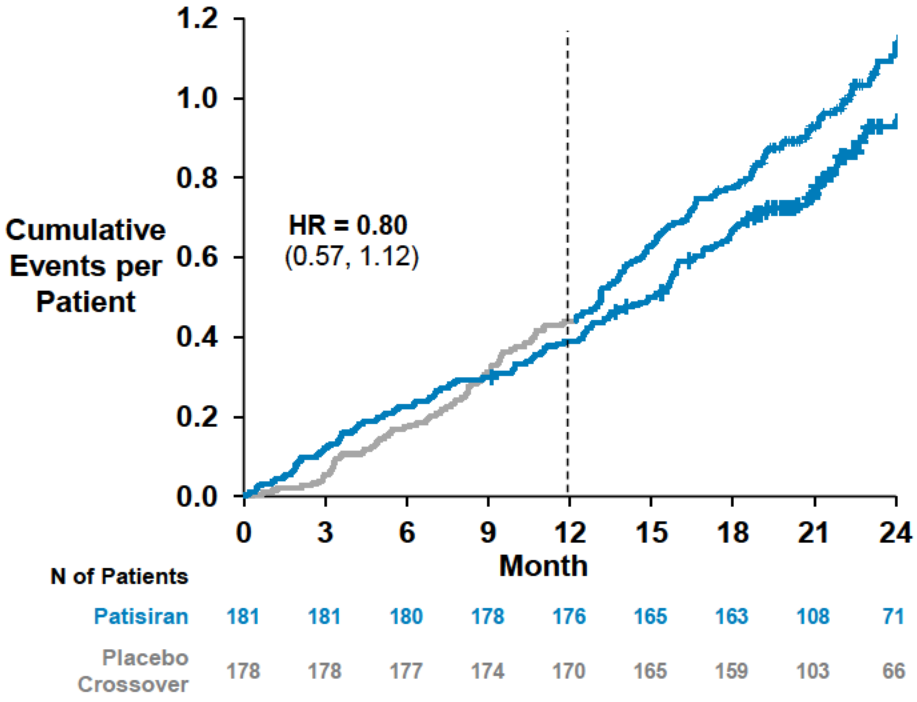


Note: The dashed line designates the Month 12 timepoint at which the placebo group crossed over to treatment with patisiran.
DB=double-blind; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; OLE=open-label extension.

6.2.9.5 Composite Endpoints

During the study (DB + OLE), for the composite of all-cause mortality and frequency of all-cause hospitalization and urgent HF visits, the point estimate of the HR was 0.80 (95% CI: 0.57–1.12; Figure 33). This HR reflects the patients' overall experience in the study, including their randomized treatment in the DB period to patisiran or placebo, plus patisiran treatment in the OLE for all patients starting at Month 12.

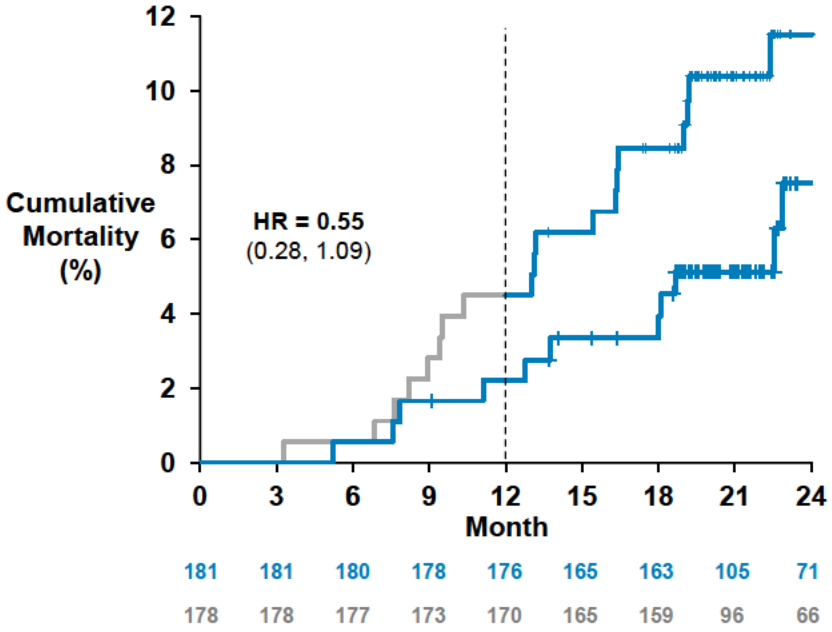
Figure 33: All-Cause Mortality, All-Cause Hospitalizations, and Urgent Heart Failure Visits (DB+OLE) During APOLLO-B (Full Analysis Set)



Note: Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis.
Note: The dashed line designates the Month 12 timepoint at which the placebo group crossed over to treatment with patisiran.
DB=double-blind; HF=heart failure; OLE=open-label extension.

All-cause mortality was a component of the composite endpoint analyses. During the study (DB + OLE periods), as of the data cutoff date of 19 December 2022, the number of deaths in the all-cause mortality efficacy analysis was 13 (7.2%) in patients randomized to patisiran and 23 (12.9%) in patients randomized to placebo (Figure 34). For all-cause mortality, the HR was 0.55 (95% CI: 0.28–1.09; Figure 34). The trend observed in the DB period continues into the OLE.

Figure 34: All-Cause Mortality (DB+OLE) During APOLLO-B (Full Analysis Set)



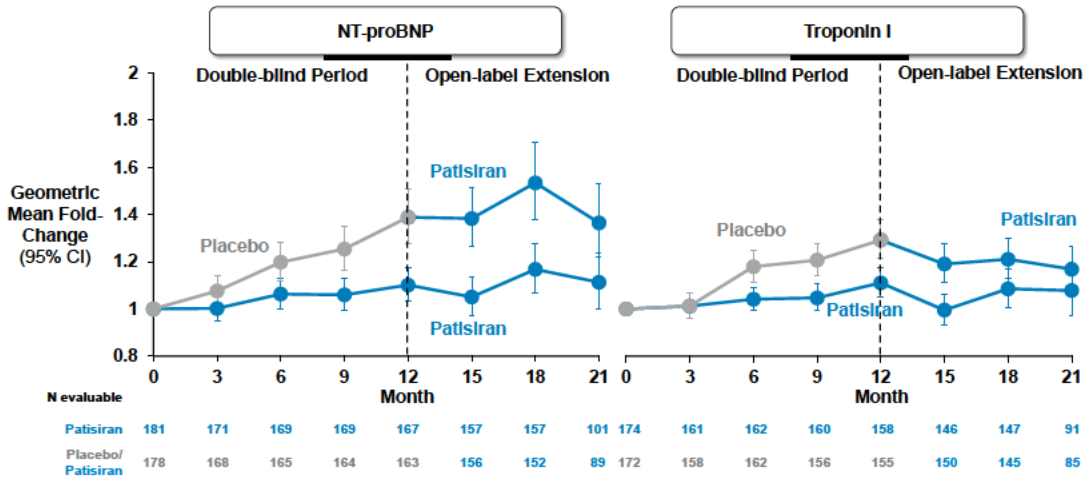
Note: Deaths due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis.
Note: The dashed line designates the Month 12 timepoint at which the placebo group crossed over to treatment with patisiran.
DB=double-blind; HF=heart failure; HR=hazard ratio; OLE=open-label extension.

6.2.9.6 Cardiac Laboratory Parameters

During the OLE period, patients randomized to patisiran continued to demonstrate relative stability in both NT-proBNP (Figure 35, left panel) and troponin I (Figure 35, right panel).

For patients randomized to placebo, who experienced a steady increase (worsening) in the levels of both laboratory parameters during the DB period (Figure 35), the steady worsening observed during the DB period appeared to slow by Month 15, within 3 months of patisiran treatment, for both NT-proBNP (Figure 35, left panel) and troponin I (Figure 35, right panel).

Figure 35: Change from Baseline in NT-proBNP and Troponin I (DB+OLE) in APOLLO-B (Full Analysis Set)



Note: The dashed line designates the Month 12 timepoint at which the placebo group crossed over to treatment with patisiran.
DB=double-blind; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; OLE=open-label extension.

6.3 Clinical Meaningfulness

APOLLO-B demonstrates the impact of continued suppression of TTR by patisiran on functional capacity and health status, symptoms, and QoL in patients with ATTR-CM. Patisiran-treated patients demonstrated relative stability in 6MWT performance comparable to what would be expected in healthy adults and stability of KCCQ-OS score over 12 months. Further analyses are described below to support the meaningfulness of the magnitude of the treatment effects observed in APOLLO-B.

6.3.1 6MWT

Although no established MCID has been reported for ATTR-CM, in order to better understand the concept of clinical meaningfulness in the 6MWT, a comprehensive, systematic PRISMA-based literature search was conducted to identify studies that reported MCID values for 6MWT derived by anchor- and distribution-based methods, across a range of disease areas. A total of 41 studies were identified for further evaluation. The literature review clearly highlighted that 6MWT MCIDs depend greatly on a number of variables including disease type, stage, treatment context, and patient characteristics. Thus, older age and lower baseline 6MWT distance are both associated with lower MCIDs, demonstrating that smaller differences are perceived as clinically meaningful by older patients who have low 6MWT distances (Bohannon and Crouch 2017; Khan et al 2023; Perera et al 2006). Based on this collective context, MCIDs must be considered in the setting of the specific disease being studied.

Accordingly, to characterize the meaningfulness of the observed 6MWT treatment effect in APOLLO-B, a post-hoc analysis was done to estimate the 6MWT MCID using the KCCQ-OS data from APOLLO-B as an anchor. The analysis followed the framework recently established in Draft Guidance (FDA 2023) and used the anchor-based CD method, the most frequently used

anchor-based statistical method for calculating the MCID (Mouelhi et al 2020). The 6MWT treatment benefit was characterized based on 3 well-established categories of KCCQ-OS change, small-to-moderate deterioration (−10 to −5 points), stable (−5 to 5 points), and small-to-moderate improvement (5 to 10 points) (Spertus et al 2020), and the associated 6MWT median within patient change from baseline to Month 12 for APOLLO-B patients in each category (Table 14). The CD MCID is calculated as the difference between the median within patient change in patients showing a small-to-moderate improvement and the median within patient change in patients who are stable, for an MCID for improvement, or the difference between the median within patient change in patients who are stable and the median within patient change in patients showing a small-to-moderate decline, for an MCID for decline. Data from placebo- and patisiran-treated patients were used. A graded relationship between the treatment effects on 6MWT and KCCQ-OS was observed, with the greatest decline and the greatest improvement in KCCQ-OS demonstrating the most substantial decline and improvement in the 6MWT change from baseline to Month 12, respectively, thus showing the internal consistency of the data. The MCID was 7.8 meters for improvement and 6.9 meters for decline (Table 14).

Table 14: Minimal Clinically Important Differences for 6MWT in APOLLO-B Anchored on KCCQ-OS (Primary)

KCCQ-OS Change Category	Median Change in 6MWT	Change Difference
Small-to-moderate decline: ≥-10 to ≤-5 (n=39)	-12.8 meters	-
MCID for decline [small-to-moderate decline minus stable]	-	-6.9 meters
Stable: >-5 to <+5 (n=103)	-5.9 meters	-
MCID for improvement [small-to-moderate improvement minus stable]	-	7.8 meters
Small-to-moderate improvement: ≥+5 to <+10 (n=28)	2 meters	-

6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; MCID=minimal clinically important difference.

As a sensitivity analysis, the MCID was also estimated using the KCCQ-PLS as the anchor. The Physical Limitations domain score of the KCCQ quantifies patient-reported limitations in activities of daily living from low (dressing yourself) to high exertion (hurrying or jogging as if to catch a bus). Following the same method, the MCID was estimated to be between 6.7 meters for improvement and 10.4 meters for decline (Table 15).

Table 15: Minimal Clinically Important Differences for 6MWT in APOLLO-B Anchored on KCCQ-PLS (Sensitivity)

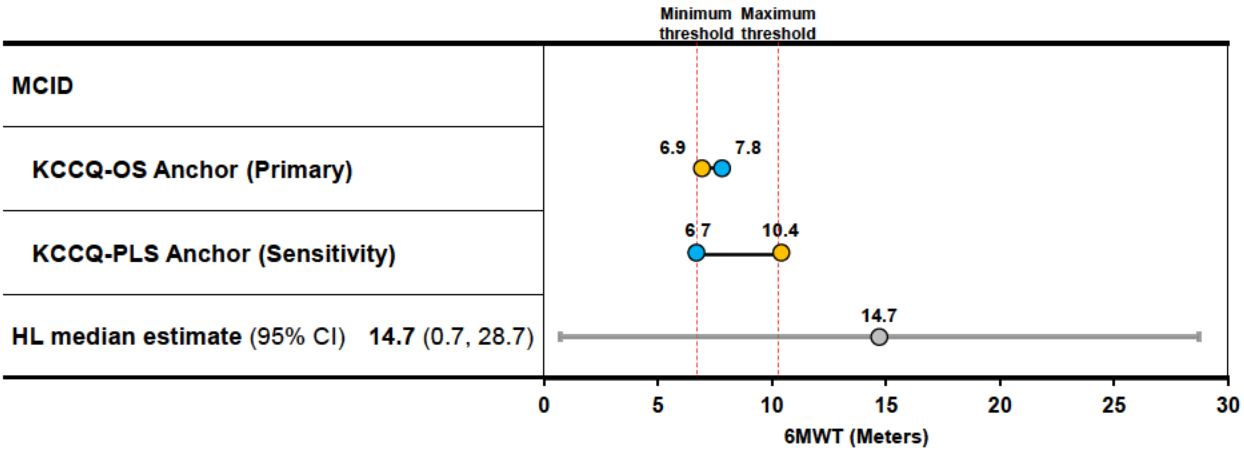
KCCQ-PLS Change Category	Median Change in 6MWT	Change Difference
Small-to-moderate decline: ≥-10 to ≤-5 (n=30)	-10.7 meters	-
MCID for decline [small-to-moderate decline minus stable]	-	-10.4 meters
Stable: >-5 to <+5 (n=112)	-0.3 meters	-
MCID for improvement [small-to-moderate improvement minus stable]	-	6.7 meters
Small-to-moderate improvement: ≥+5 to <+10 (n=19)	6.4 meters	-

6MWT=6-minute walk test; KCCQ-PLS=Kansas City Cardiomyopathy Questionnaire-Physical Limitation Score; MCID=minimal clinically important difference.

The HL median estimate of the treatment effect (14.7 meters) exceeds the MCIDs anchored on the KCCQ-OS as well as the KCCQ-PLS. The MCID analyses suggest that the 6MWT treatment effect corresponds to a difference in functional capacity that the majority of patients would consider meaningful (Figure 36).

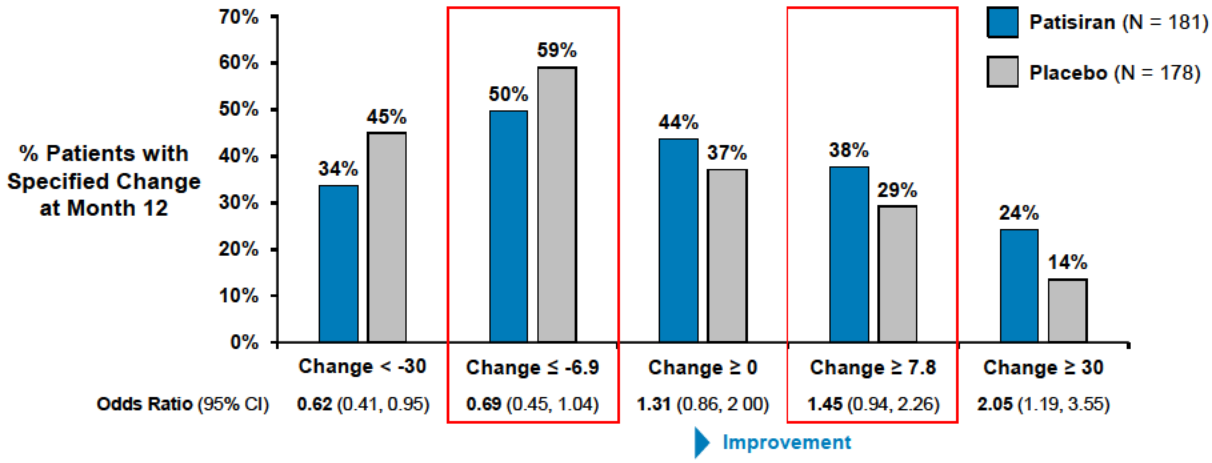
By treatment arms, a greater percentage of placebo than patisiran-treated declined more than 6.9 meters, the MCID for decline. Conversely, a greater percentage of patisiran- than placebo-treated improved more than 7.8 meters, the MCID for improvement. Across specific thresholds of change, the odds ratios for decline or improvement consistently favored patisiran-treated patients (Figure 37).

Figure 36: 6MWT Treatment Effect Corresponds to a Difference that Majority of APOLLO-B Patients Experience as Clinically Meaningful



6MWT=6-minute walk test; HL=Hodges-Lehmann; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; KCCQ-PLS=Kansas City Cardiomyopathy Questionnaire-Physical Limitation Score; MCID=minimal clinically important difference.
Note: MCID calculated using observed data.

Figure 37: Proportion of Patients Achieving 6MWT MCID Thresholds and Additional Thresholds



6MWT=6-minute walk test; MCID=minimal clinically important difference.

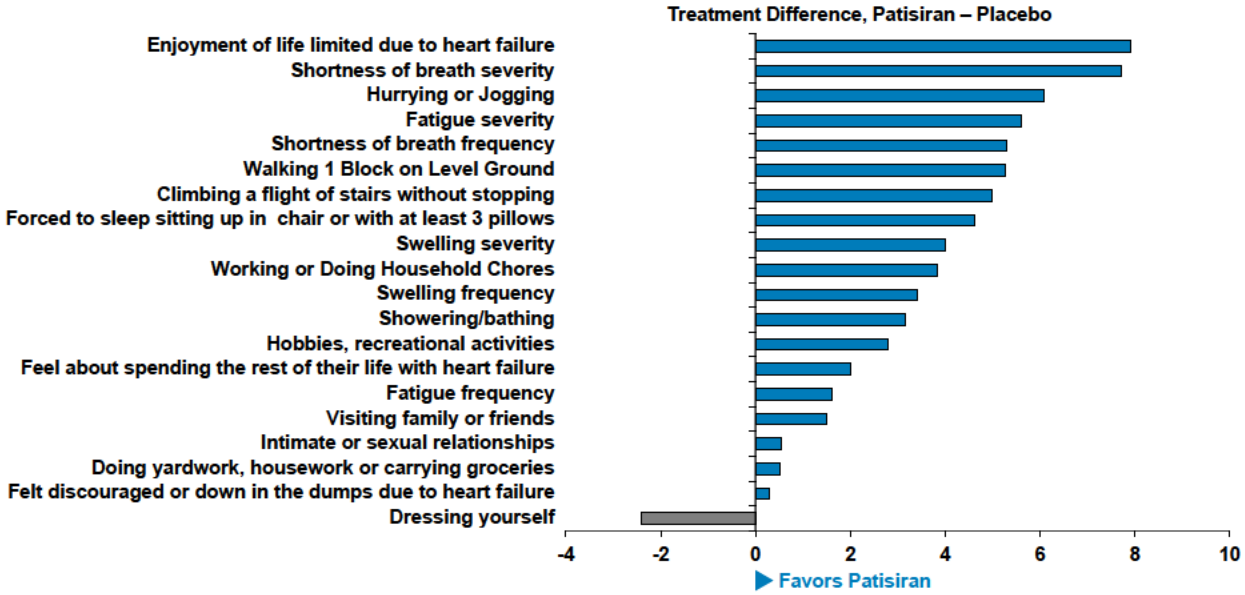
6.3.2 KCCQ-OS

The KCCQ-OS treatment effect that was measured in APOLLO-B is comparable to other HF therapies, such as sacubitril/valsartan and SGLT2 inhibitors, that improve health status and QoL (Figure 7). The responses to individual KCCQ-OS questions offer additional, valuable perspective into how patients experience the patisiran treatment effect. Treatment effects

favoring patisiran were demonstrated across 19 of the 20 questions in the four KCCQ-OS components (Figure 38). Among the largest treatment effects observed were in response to questions related to walking and demanding physical activities, such as hurrying or jogging and climbing stairs, as well as shortness of breath and fatigue that limit exertion. An effect on orthopnea suggested a benefit among patients with more severe HF.

The greatest treatment effect was observed in the question related to the impact of HF on the patient's enjoyment of life, which suggests patisiran treatment had an impact on patients HF sufficient to improve overall QoL. Furthermore, the differences between the placebo and patisiran groups in each KCCQ-OS question illustrate how the magnitude of the observed treatment effect is associated with patients experiencing beneficial impacts on their symptoms and QoL - impacts that in aggregate are reflected by the favorable results in each domain of the KCCQ-OS (Figure 22). The only question where no treatment effect was observed was for "dressing yourself," which requires minimal exertion and was not a limitation for most patients in either treatment arm at baseline or Month 12 (Figure 38).

Figure 38: Mean Treatment Difference in Change from Baseline to Month 12 in Individual KCCQ-OS Questions in APOLLO-B (Full Analysis Set)



Note: Individual KCCQ questions were scaled from 0 to 100 for analysis.
KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.

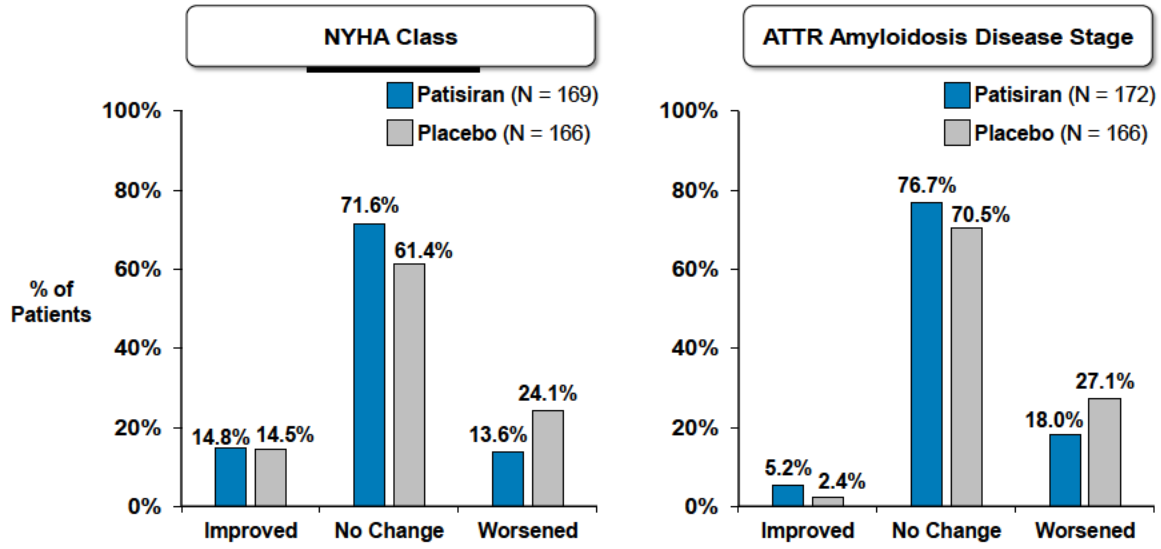
*6.3.3 **Disease Progression***

6.3.3.1 Clinical Disease Staging and Disease Progression

Exploratory analyses in APOLLO-B of NYHA class and ATTR amyloidosis disease stage (Gillmore et al 2018), both of which are used to clinically assess HF severity and progression of disease in patients with ATTR-CM are helpful to further demonstrate the clinical meaningfulness of the results at Month 12 (Figure 39). Worsening of NYHA class and ATTR amyloidosis stage from baseline to Month 12 occurred more frequently in the placebo group than in the patisiran group (Figure 39). Moreover, the likelihood of patisiran-treated patients to progress based on

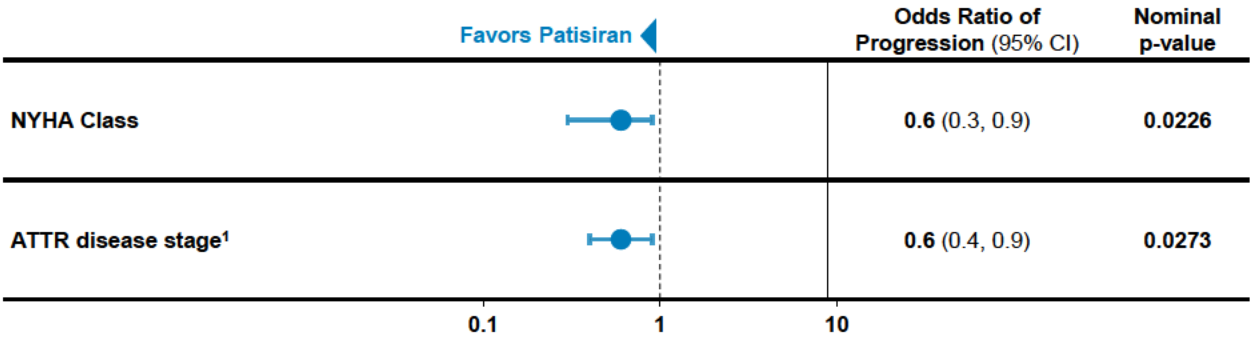
both NYHA class and ATTR amyloidosis disease stage was approximately 40% lower than placebo-treated patients (Figure 40).

Figure 39: Change from Baseline to Month 12 in NYHA Class and ATTR Amyloidosis Disease Stage in DB Period of APOLLO-B (Full Analysis Set)



Note: Patients with NYHA class III who also had ATTR amyloidosis disease Stage 3 and patients with NYHA class IV at screening were excluded from the study.
ATTR=transthyretin-mediated amyloidosis; DB=double-blind; NYHA=New York Heart Association.

Figure 40: Lower Likelihood of Disease Progression with Patisiran



1. Gillmore et al 2018.
ATTR=transthyretin-mediated amyloidosis; NYHA=Hew York Heart Association.

6.4 Patisiran Monotherapy and Background Tafamidis

6.4.1 Patisiran Monotherapy

For the most direct assessment of patisiran, the monotherapy treatment effect of patisiran was investigated in the absence of confounding effects of tafamidis. In APOLLO-B, approximately 75% of the patient population were in the monotherapy subgroup and patients were stratified by

tafamidis background use; thus, allowing for a randomized comparison in the analysis of patisiran monotherapy.

The observed median change from baseline in 6MWT in the patisiran monotherapy group at Month 12 was −8.0 meters compared with −27.8 meters in the placebo group. The HL estimate of the median difference was 21.3 meters, and LS mean difference was 26.5 meters at 12 months (nominal p=0.0045). The treatment effect of patisiran monotherapy was larger than the treatment effect in the overall population (Table 16; Table 9). On a relative basis, patisiran monotherapy resulted in a 71% reduction in the loss of functional capacity observed in the placebo group over 12 months.

Over the DB period, patients in the placebo group showed a steady decline in KCCQ-OS, with a mean change from baseline of −4.0 points. In contrast, the patisiran monotherapy group showed an increase of +0.3 points. Thus, a greater difference in KCCQ-OS at Month 12 was demonstrated with patisiran monotherapy (LS mean difference, 4.3 points; nominal p=0.0415; Table 16) compared with the overall population (Table 12).

During the DB period, the win ratio for the composite outcome of all-cause mortality, frequency of CV events and change from baseline in the 6MWT favored patisiran but was not statistically significant. The composite outcome of all-cause mortality and frequency of all-cause hospitalization was neutral (Table 16). For the all-cause mortality analysis, there were 3 deaths in the patisiran arm and 7 in the placebo. The mortality trend in favor of patisiran has continued into the OLE period (HR=0.62, 95% CI: 0.26–1.49; Appendix 12.4).

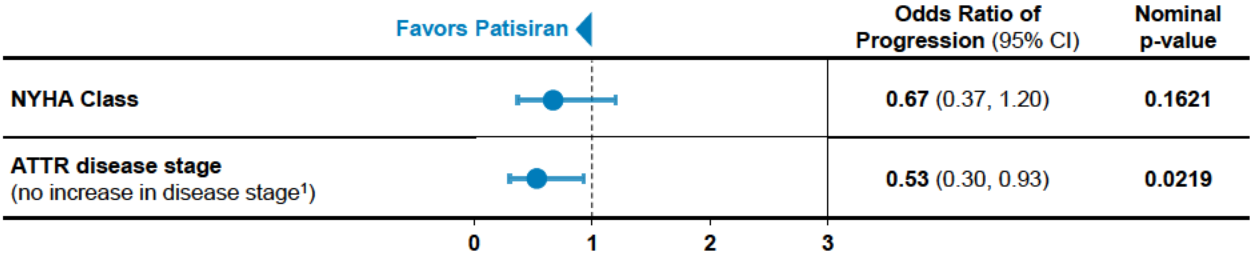
Table 16: Change from Baseline in TTR, 6MWT, and KCCQ-OS at Month 12 and Composite Outcomes in Patisiran Monotherapy Subpopulation

Endpoint at Month 12	Patisiran Monotherapy		
	Patisiran (N=135)	Placebo (N=133)	Treatment Difference (95% CI)
TTR % change, mean	-86.8	-2.2	-
6MWT, median change, meters	-8.0	-27.8	21.3 (4.7, 37.9)*
KCCQ-OS, LS mean change, points	0.3	-4.0	4.3 (0.2, 8.4)
	Composite Outcomes		
Win ratio of all-cause mortality, frequency of CV events[a] and change from baseline in 6MWT[b]	-	-	1.28 (0.97, 1.70)
Hazard ratio of all-cause mortality and frequency of all-cause hospitalization and urgent HF visits[b,c]	-	-	0.997 (0.620, 1.602)
p-value			0.9888
Hazard ratio of all-cause death[b,d]	3	7	0.40 (0.10, 1.54)

*HL median difference
a. CV events defined as CV hospitalizations and urgent HF visits.
b. Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization handled in same manner as death in analysis.
c. The hazard ratio, 95% CI and p-value were derived using an Andersen-Gill model, including treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates.
d. The hazard ratio and 95% CI were estimated using the Cox proportional hazards model with treatment group as a covariate.
6MWT=6-minute walk test; CV=cardiovascular; HF=heart failure; HL=Hodges-Lehmann; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; TTR=transthyretin.

Patients in the patisiran monotherapy group were less likely than placebo to show progression of disease based on an increase in NYHA class (OR=0.67; nominal p=0.1621) or ATTR amyloidosis disease stage (OR=0.53; nominal p=0.0219) (Figure 41).

Figure 41: Clinical and Laboratory Assessment of Progression at Month 12[a] in DB Period of APOLLO-B in Patisiran Monotherapy Subpopulation



a. Patients who are missing Month 12 due to COVID-19 are excluded from analysis. Exact confidence limits for the odds ratio are presented; nominal p-value from Fisher's exact test.
1. Gillmore et al 2018.
ATTR=transthyretin-mediated amyloidosis; DB=double-blind; NYHA=New York Heart Association.

*6.4.2 **Background Tafamidis***

Patients on background tafamidis were a small subgroup (N=91; 46 on patisiran and 45 on placebo). For the 6MWT and KCCQ-OS, a modest decline in the placebo arm over 12 months limits the ability to detect a potential treatment effect (Figure 23).

During the DB period, the composite outcomes of (1) all-cause mortality, frequency of CV events and change from baseline in the 6MWT and (2) all-cause mortality and frequency of all-cause hospitalization favor patisiran, but the win ratio and HRs are not statistically significant (Figure 17). For the all-cause mortality analysis, there was 1 death in the patisiran arm and 3 in the placebo; the latter count includes 2 placebo-treated patients who had heart transplants. The mortality trend in favor of patisiran has continued into the OLE period (HR=0.44, 95% CI: 0.15–1.29; Appendix 12.4).

As assessed by change in NYHA class or ATTR amyloidosis disease stage, patisiran treatment was associated with a numerically lower risk of disease progression (Figure 42).

Of note, patisiran suppresses TTR levels equally effectively in patients on background tafamidis (mean percentage reduction [SD] 83.7% [16.3]) or not (87.9% [12.3] at Month 12; Table 17).

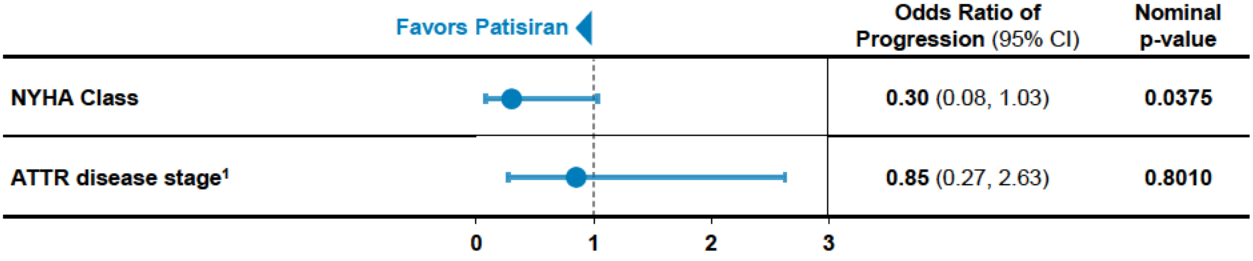
Overall, due to the small sample size and relatively modest placebo decline, the treatment effect of patisiran on background tafamidis has not been established in this study.

Table 17: Change from Baseline to Month 12 in TTR, 6MWT, and KCCQ-OS and Composite Outcomes in Background Tafamidis Subpopulation

Endpoint at Month 12	Background Tafamidis		
	Patisiran (N=46)	Placebo (N=45)	Treatment Difference (95% CI)
TTR % change, mean	-83.7	5.4	-
6MWT, median change, meters	-12.2	-7.5	-3.2 (-28.3, 21.9)*
KCCQ-OS, LS mean change, points	0.3	-1.8	2.1 (-4.9, 9.0)
	Composite Outcomes		
Win ratio of all-cause mortality, frequency of CV events[a] and change from baseline in 6MWT[b]	-	-	1.22 (0.76, 1.95)
Hazard ratio of all-cause mortality and frequency of all-cause hospitalization and urgent HF visits[b,c]	-	-	0.633 (0.240, 1.666)
p-value			0.3539
Hazard ratio of all-cause death[b,d]	1	3	0.30 (0.03, 2.86)

*HL median difference
a. CV events defined as CV hospitalizations and urgent HF visits.
b. Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization handled in same manner as death in analysis.
c. The hazard ratio, 95% CI and p-value were derived using an Andersen-Gill model, including treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates.
d. The hazard ratio and 95% CI were estimated using the Cox proportional hazards model with treatment group as a covariate.
6MWT=6-minute walk test; CV=cardiovascular; HF=heart failure; HL=Hodges-Lehmann; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; TTR=transthyretin.

Figure 42: Clinical and Laboratory Assessment of Progression at Month 12[a] in DB Period of APOLLO-B in Background Tafamidis Subpopulation



a. Patients who are missing Month 12 due to COVID-19 are excluded from analysis. Exact confidence limits for the odds ratio are presented; nominal p-value from Fisher's exact test.
1. Gillmore et al 2018.
ATTR=transthyretin-mediated amyloidosis; DB=double-blind; NYHA=New York Heart Association.

6.5 Efficacy Conclusions

Efficacy of patisiran for the treatment of ATTR-CM is supported by evidence from two independent sources, one is the pivotal APOLLO-B study, and the second is confirmatory data from the hATTR-PN study APOLLO including data from the cardiac subgroup in this study.

The APOLLO-B study has shown TTR reduction in ATTR-CM patients leading to statistically significant and clinically relevant improvements in functional capacity and health status and QoL compared to placebo.

- The magnitude of decline in functional capacity observed in patisiran-treated patients after 12 months of treatment was comparable to the expected annual age-related decline in healthy adults, and more than 60% less than that of placebo-treated patients.
    - The patisiran treatment effect in functional capacity exceeds the estimated study-derived MCID, suggesting that the treatment effect observed in APOLLO-B corresponds to a difference in functional capacity that the majority of patients would consider meaningful.
    - Changes in functional capacity favored patisiran over placebo across all response thresholds. Patisiran patients were 45% more likely than placebo patients to experience a gain in functional capacity greater than 7.8 meters (the study-derived MCID for improvement), and nearly 30% less likely to experience a decline in functional capacity more than 6.9 meters (the study-derived MCID for decline). Similar trends favoring patisiran on both ends of the response spectrum were observed at changes ≥30m from baseline (OR=2.05) and at changes <−30m from baseline (OR=0.62).
- In health function and QoL as measured by KCCQ-OS, patisiran-treated patients remained stable for 12 months compared to a clinically relevant decline in placebo-treated patients. The LS mean treatment difference is small but meaningful and is consistent with the treatment effect observed in other HF medications.
    - Like the effect observed in functional capacity, patisiran-treated patients experienced an improvement across all response thresholds compared to placebo.
    - The effects observed on KCCQ showed a high degree of internal consistency with 19 of 20 individual KCCQ-OS questions favoring patisiran and effects in each of the four KCCQ-OS scales favoring patisiran. Notably, the greatest differences between patisiran and placebo were in questions related to the cardinal symptoms of ATTR-CM and physical limitations corresponding to activities associated with high metabolic demand.
- Clinical disease assessment and staging showed reduced rates of disease progression.
    - Patisiran treated patients were 40% less likely to progress in either NYHA class or ATTR amyloidosis disease stage compared to placebo.
- Exploratory endpoints of prognostic clinical laboratory parameters (NT-proBNP, troponin I) and cardiac imaging provide further evidence of a beneficial treatment effect.

- Statistical significance was not met for the secondary endpoints of composite outcomes. However, the overall results from the analyses of composite outcomes and of all-cause mortality were numerically in favor of patisiran, suggesting no harmful effects.
- Efficacy was consistent across most major subgroups.
    - For patients on background tafamidis, due to the small sample size and relatively modest placebo decline, the treatment effect of patisiran on background tafamidis was not established in this study.
    - For patients in the patisiran monotherapy subgroup, patisiran showed a greater effect on 6MWT and KCCQ-OS, compared with patients in the overall population.
- The treatment effect of patisiran was maintained across endpoints with ongoing treatment in the OLE through at least Month 18.

Further confirmatory data are provided by the APOLLO study in patients with hATTR-PN including data from a pre-specified subgroup of patients with cardiac amyloidosis. In this subgroup, TTR lowering was associated with improvements in cardiac structure and function, and NT-proBNP.

The results from APOLLO-B and the totality of evidence from the patisiran development program, indicate that patisiran has a meaningful benefit in delaying disease progression in ATTR-CM, and support the approval of the proposed indication for the treatment of cardiomyopathy of wt or hATTR amyloidosis in adults to slow the decline in functional capacity and reduce symptoms.

7 CLINICAL SAFETY

Summary

- The safety profile of patisiran has been well characterized in the clinical and post-marketing setting.
  - Primary safety considerations are IRRs and reductions in serum vitamin A levels.
  - The safety profile of patisiran in patients with ATTR-CM is consistent with the established safety profile in the polyneuropathy indication with no new or unexpected safety concerns.
- In the APOLLO-B study, most AEs were mild to moderate in severity.
  - AEs observed in 5% or more of patisiran-treated patients and at a greater frequency than placebo (≥3%) are known adverse drug reactions (ADRs) of patisiran: IRRs (12.2% vs 9.0%), arthralgia (7.7% vs 4.5%), and muscle spasms (6.6% vs 2.2%).
- Most AEs were non-serious and consistent with those expected in this patient population.
- The patisiran and placebo groups had the same proportion of patients experiencing an AE leading to study treatment discontinuation (2.8%).
- During the DB period, 5 patients (2.8%) in the patisiran group and 9 patients (5.1%) in the placebo group died. None of the deaths were considered related to study drug by the Investigators.
- No new safety concerns were raised regarding cardiac events with patisiran. For cardiac events, no clinically relevant differences were noted between the patisiran and placebo treatment groups and the frequencies of cardiac failure and arrythmia were similar or lower in the patisiran group. Overall, the types of cardiac events observed in the DB period were consistent with the natural history of the disease.
- The safety profile of patisiran was consistent across subgroups, including background tafamidis use.
- The overall safety results of the OLE period were consistent with the DB period.
- Since the completion of APOLLO-B, 200 patients in the US with ATTR-CM, who have had an inadequate response to or cannot tolerate standard of care, received patisiran through an EAP. The safety profile has been consistent with clinical trials and post-marketing use. No new safety concerns were identified.

7.1 Overview of Safety Program

The safety profile of patisiran has been well established in the clinical trial setting (hATTR-PN and ATTR-CM) and post-marketing experience in hATTR-PN, with over 8,500 patient-years of exposure; some patients have received patisiran for over 7 years. To date, ONPATTRO® (patisiran) has been approved in more than 35 countries. The primary safety considerations are IRRs and reduction in serum vitamin A levels, each of which are reflected in the approved

prescribing information in the Warnings and Precautions section. IRRs are mostly mild, abate with time and rarely lead to dose interruption or discontinuation. Patients receive pre-medication with a corticosteroid, acetaminophen, and antihistamines to reduce the risk of IRRs. The risk of serum vitamin A reduction was evaluated extensively in APOLLO and no cases of night blindness or other serious ocular events were identified. This risk is mitigated by the recommended daily allowance supplementation of vitamin A during treatment with patisiran.

The safety profile of patisiran in patients with ATTR-CM is primarily based on results from the pivotal Phase 3 APOLLO-B study. Overall, the safety profile of patisiran in APOLLO-B was consistent with the known and established safety profile of patisiran in hATTR-PN.

The presentation of safety results in the following sections will focus on the placebo-controlled, DB period of APOLLO-B (data cutoff: 20 June 2022). Results for the All Patisiran Treated Set, which includes all patients who received ≥1 dose of patisiran in APOLLO-B (data cutoff: 19 December 2022), including patients treated with patisiran during the DB period will be presented briefly, as these results are generally consistent with the results observed in the placebo-controlled period (Section 7.2.2).

7.2 Treatment Exposure

7.2.1 ***Double-Blind Period of APOLLO-B***

During the DB period of APOLLO-B, 181 patients were treated with patisiran, and 178 patients were treated with placebo. At the time of data cutoff, all active patients had completed the Month 12 visit.

The median treatment duration in the patisiran group was 12.4 months (range: 0.0–14.0 months), with a cumulative treatment exposure of 180.7 patient-years (Table 18).

Table 18: Patisiran and Placebo Exposure in DB Period of APOLLO-B (Safety Analysis Set)

	Double-Blind Period	
	Patisiran (N=181) n (%)	**Placebo (N=178) n (%)**
Cumulative treatment exposure, patient-years[a]	180.7	178.8
Median treatment duration (cumulative months), (range)	12.4 (0–14.0)	12.4 (0–13.2)
≥3 months, n (%)	177 (97.8)	175 (98.3)
≥6 months, n (%)	173 (95.6)	175 (98.3)
≥9 months, n (%)	170 (93.9)	168 (94.4)
≥12 months, n (%)	169 (93.4)	166 (93.3)
Total number of doses received		
Mean (SD)	16.9 (3.0)	16.9 (2.5)
Cumulative doses received	3054	3015

a. Individual duration of exposure (in days) was calculated as the earliest date of (the end of study, data cutoff date, 20 days after the last dose of study drug, or date of first dose of patisiran in OLE Period-1), minus the date of the first dose of study drug plus 1.
DB=double-blind; OLE=open-label extension.

7.2.2 Open-Label Extension of APOLLO-B

As of the data cutoff date of 19 December 2022, 347 patients have received patisiran treatment during the OLE period: 181 patients in the patisiran/patisiran group and 166 patients in the placebo/patisiran group (Table 19). The overall median duration of patisiran exposure for the All Patisiran Treated Set was 18.4 months (range: 0.0–37.0 months), with a cumulative treatment exposure of 482 patient-years.

Table 19: Patisiran Treatment Exposure (DB+OLE) in APOLLO-B (All Patisiran Treated Set)

	Double-Blind + Open-Label Extension (N=347)
Cumulative treatment exposure, patient-years	482.0
Median treatment duration, months (range)	18.4 (0.0–37.0)
Treatment duration (cumulative, months), n (%)	
≥12 months	227 (65.4)
≥18 months	176 (50.7)
≥24 months	71 (20.5)
≥30 months	16 (4.6)
≥33 months	11 (3.2)

DB=double-blind; OLE=open-label extension.

7.3 Overview of Safety

In APOLLO-B, the incidence, nature, and severity of AEs, SAEs, and AEs leading to discontinuation were similar between the patisiran and placebo groups (Table 20).

A total of 14 patients died during the DB period: 5 patients (2.8%) in the patisiran group and 9 patients (5.1%) in the placebo group. None of the deaths were considered related to study drug. Additional details on deaths are provided in Section 7.8.

Table 20: Overview of Safety in DB Period of APOLLO-B (Safety Analysis Set)

	Double-Blind Period	
	Patisiran (N=181) n (%)	Placebo (N=178) n (%)
AE	165 (91.2)	168 (94.4)
SAE	61 (33.7)	63 (35.4)
Severe AE	47 (26.0)	52 (29.2)
AE leading to study drug interruption	20 (11.0)	23 (12.9)
AE leading to study drug discontinuation	5 (2.8)	5 (2.8)
Deaths[a]	5 (2.8)	9 (5.1)

a. Safety analysis includes deaths on-study and after withdrawal from the study. One placebo patient stopped study participation during the DB period and died after the pre-specified window for the statistical analysis of deaths during the DB period.
AE=adverse event; DB=double-blind; SAE=serious adverse event.

7.4 Common Adverse Events

AEs that were reported in ≥5% of patients in either group in the DB period of the APOLLO-B study are presented in Table 21. Cardiac failure was the most frequently reported AE, consistent with the patient population in APOLLO-B; although, there were no clinically relevant differences observed between the groups, the incidence of cardiac failure events trended lower in patients treated with patisiran. Other cardiac symptoms consistent with ATTR amyloidosis included atrial fibrillation and orthostatic hypotension, which also trended lower in the patisiran group. As expected, AEs of IRRs and those that are associated symptoms of IRRs occurred at a higher incidence in patisiran-treated patients. AEs observed in at least 5% of patisiran-treated patients and more frequently (≥3%) in patisiran-treated patients than placebo included: IRRs (12.2% vs 9.0%), arthralgia (7.7% vs 4.5%), and muscle spasms (6.6% vs 2.2%), which are known ADRs of patisiran.

Table 21: Adverse Events in ≥5% of Patients in Either Treatment Group in DB Period of APOLLO-B (Safety Analysis Set)

	Double-Blind Period	
	Patisiran (N=181) n (%)	Placebo (N=178) n (%)
Any AE	165 (91.2)	168 (94.4)
Cardiac failure	54 (29.8)	68 (38.2)
Infusion-related reaction	22 (12.2)	16 (9.0)
Constipation	20 (11.0)	19 (10.7)
Atrial fibrillation	16 (8.8)	26 (14.6)
Diarrhea	15 (8.3)	14 (7.9)
COVID-19	14 (7.7)	25 (14.0)
Arthralgia	14 (7.7)	8 (4.5)
Fatigue	12 (6.6)	15 (8.4)
Back pain	12 (6.6)	12 (6.7)
Muscle spasms	12 (6.6)	4 (2.2)
Gout	11 (6.1)	12 (6.7)
Fall	10 (5.5)	15 (8.4)
Nasopharyngitis	10 (5.5)	12 (6.7)
Insomnia	10 (5.5)	11 (6.2)
Pain in extremity	10 (5.5)	5 (2.8)
Dizziness	9 (5.0)	15 (8.4)
Dyspnea	9 (5.0)	7 (3.9)
Syncope	8 (4.4)	13 (7.3)
Nausea	8 (4.4)	9 (5.1)
Headache	6 (3.3)	11 (6.2)
Orthostatic hypotension	3 (1.7)	9 (5.1)

AE=adverse event; DB=double-blind.

7.5 Adverse Events Leading to Treatment Discontinuation

There were no AEs leading to treatment discontinuation that were reported in ≥2 patients in the patisiran group. AEs leading to treatment discontinuation that were reported in ≥2 patients in the placebo group were cardiac failure (2 patients, 1.1%) and amyloidosis (2 patients, 1.1%). One patient (0.6%) in the patisiran group discontinued treatment due to a mild AE of IRR that was considered to be related to study drug by the Investigator.

7.6 Serious Adverse Events

In the DB period of APOLLO-B, similar proportions of patients experienced an SAE in the patisiran (33.7%) and placebo (35.4%) groups. The events were consistent with those expected

in the study population. SAEs reported in ≥2% of patients in either treatment group included cardiac failure, atrial fibrillation, AV block complete, amyloidosis, and syncope (Table 22). There were no SAEs of anaphylaxis, anaphylactoid, or severe hypersensitivity reactions in the study.

SAEs considered related to study drug by the Investigator were reported in 2 patients (1.1%) in the patisiran group and 1 patient (0.6%) in the placebo group. In the patisiran group, 1 patient was hospitalized for an infusion site phlebitis that resolved after treatment with antibiotics; and 1 patient had an SAE of hepatic enzymes increased (alanine aminotransferase [ALT] 2x upper limit of normal [ULN]; aspartate aminotransferase [AST] 3x ULN) that was considered medically significant by the Investigator and was not associated with elevation of total bilirubin. Study drug was interrupted, the event resolved, and the patient resumed dosing of patisiran without reoccurrence of the event. In the placebo group, 1 patient was hospitalized for a functional GI disorder.

Table 22: Serious Adverse Events in ≥2% of Patients in Either Treatment Group in DB Period of APOLLO-B (Safety Analysis Set)

	Double-Blind Period	
	Patisiran (N=181) n (%)	**Placebo (N=178) n (%)**
Any SAE	61 (33.7)	63 (35.4)
Cardiac failure	15 (8.3)	13 (7.3)
Atrial fibrillation	5 (2.8)	4 (2.2)
Atrioventricular block complete	2 (1.1)	4 (2.2)
Syncope	2 (1.1)	4 (2.2)
Amyloidosis	1 (0.6)	4 (2.2)

DB=double-blind; SAE=serious adverse event.

7.7 Severity of Adverse Events

The majority of AEs were mild to moderate in severity. Severe AEs reported in ≥2% of patients in either group included cardiac failure, atrial fibrillation, and amyloidosis (Table 23).

Severe AEs considered related to study drug were reported in 1.1% of patients in the patisiran group and 1.1% of patients in the placebo group. Severe AEs considered related to study drug included infusion site reaction (1 patient [0.6%]; 1 event) and hepatic enzyme increased (1 patient [0.6%]; 1 event) in the patisiran group; and functional GI disorder (1 patient [0.6%]; 1 event) and cough (1 patient [0.6%]; 1 event) in the placebo group.

Table 23: Severe Adverse Events in ≥2% of Patients in Either Treatment Group in DB of APOLLO-B (Safety Analysis Set)

	Double-Blind Period	
	Patisiran (N=181) n (%)	Placebo (N=178) n (%)
Any severe AE	47 (26.0)	52 (29.2)
Cardiac failure	10 (5.5)	7 (3.9)
Atrial fibrillation	4 (2.2)	1 (0.6)
Amyloidosis	1 (0.6)	4 (2.2)

AE=adverse event; DB=double-blind.

7.8 Deaths

During the DB period, 14 patients died: 5 patients (2.8%) in the patisiran group and 9 patients (5.1%) in the placebo group. One patient in the patisiran group and 4 patients in the placebo group died after having been off treatment for >28 days after the last dose of study drug and having stopped study participation. None of the deaths were considered related to study drug by the Investigators. One placebo patient stopped study participation on Study Day 270 during the DB period and died on Day 447, which was after the pre-specified window in the statistical analysis plan for the analysis of deaths during the DB period (additional details for all deaths are provided in Table 24).

The deaths were evaluated by an external, independent adjudication committee to classify whether they were of CV or non-CV origin. Of the 5 deaths in the patisiran group, 2 were adjudicated as CV deaths (1 sudden cardiac death and 1 death due to cardiac failure) and 3 deaths were classified as non-CV deaths (1 COVID-19, 1 pancreatitis, and 1 undetermined). Of the 9 deaths in the placebo group, 4 were classified as CV deaths (all due to cardiac failure), and 5 were classified as non-CV deaths (infection, cholangitis, and pancreatic cancer [1 each]); 2 undetermined).

Table 24: Summary of Deaths in DB Period of APOLLO-B (Safety Analysis Set)

ATTR Amyloidosis Type	Age/Sex	Background Tafamidis	SAE(s) Reported as Fatal	Adjudicated Cause of Death	Study Day of Death[a]	Days Since Last Dose[b]
Patisiran						
Hereditary	73/M	Yes	Cardiac arrest	Sudden Cardiac Death (CV Death)	230	19
Wild-type	82/M	No	Pancreatitis	Pancreatitis (Non-CV Death)	159	33
Wild-type	83/M	No	Cardiac amyloidosis	Heart Failure (CV Death)	339	88
Wild-type	78/M	No	COVID-19	COVID-19 (Non-CV Death)	277	25
Wild-type	76/M	No	NA[c]	Undetermined (Undetermined Death)	239	239
Placebo						
Wild-type	73/M	No	Cholangitis	Cholangitis (Non-CV Death)	100	30
Hereditary	72/M	No	Cardiac failure	Heart Failure (CV Death)	287	35
Hereditary	77/F	No	Cardiac failure	Heart Failure (CV Death)	249	38
Wild-type	73/M	No	Hypertensive heart disease, Chronic kidney disease	Undetermined (Undetermined Death)	315	85
Wild-type	84/M	No	NA[c]	Heart Failure (CV Death)	272	36
Wild-type	80/M	No	NA[c]	Pancreatic cancer (Non-CV Death)	209	41
Wild-type	86/M	Yes	NA[c]	Infection (Non-CV Death)	400	43
Wild-type	82/M	No	NA[c]	Undetermined (Undetermined Death)	396	396
Wild-type	80/M	Yes	NA[c]	Heart Failure (CV Death)	447[d]	195

a. Study day is relative to the first dose of study medication in the 12-month DB period.
b. Study day is relative to the last dose of study medication in the study.
c. Death occurred after patient had stopped study participation.
d. Patient in the placebo group stopped study participation on Study Day 270 during the DB period and died on Day 447, which was after the pre-specified window in the statistical analysis plan for the analysis of deaths during the DB period.

ATTR=transthyretin-mediated amyloidosis; CV=cardiovascular; DB=double-blind; F=Female; M=Male; NA=not applicable; SAE=serious adverse event.

7.9 Safety Topics of Interest

To characterize the safety profile of patisiran for ATTR-CM, careful review of all available safety data was performed including patients' vital signs, laboratory data, and evaluation of all AEs.

Based on the therapeutic class and mechanism of action of patisiran, observations from nonclinical studies, route of administration, and disease-related pathophysiology of ATTR amyloidosis with cardiomyopathy, several potential areas of interest were evaluated in depth, including cardiac events, IRRs, hepatic events, and ocular events (due to role of TTR in vitamin A circulation).

*7.9.1 **Cardiac Events***

The type and nature of cardiac events were consistent with those expected in the patient population. No clinically relevant imbalances in cardiac events were noted between the patisiran and placebo treatment groups. Events in the cardiac Standardized Medical Dictionary for Regulatory Activities Queries (SMQs) and FDA medical queries (FMQs) evaluated were less frequent in patisiran patients than in patients treated with placebo.

During the DB period, AEs in the Cardiac disorders SOC were reported in 45.3% of patients in the patisiran group and 56.2% of patients in the placebo group (Table 25). Cardiac AEs reported in ≥5% of patients in the either group were cardiac failure (29.8% patisiran, 38.2% placebo) and atrial fibrillation (8.8% patisiran, 14.6% placebo). One patient in the patisiran group had a mild non-serious AE of cardiac failure that was considered related to the study drug.

The frequency of SAEs in the Cardiac disorders SOC was similar across both treatment groups. Cardiac SAEs reported in ≥2% of patients in either group were cardiac failure (8.3% patisiran, 7.3% placebo), atrial fibrillation (2.8% patisiran, 2.2% placebo), and AV block complete (1.1% patisiran, 2.2% placebo); none were related to study drug.

Table 25: Summary of Cardiac Events in DB Period of APOLLO-B (Safety Analysis Set)

Type of AE	Double-Blind Period	
	Patisiran (N=181) n (%)	Placebo (N=178) n (%)
AEs in the Cardiac disorders SOC	82 (45.3)	100 (56.2)
SAEs in the Cardiac disorders SOC	32 (17.7)	28 (15.7)
Cardiac Failure SMQ (narrow) AEs	65 (35.9)	78 (43.8)
Cardiac Failure SMQ (broad and narrow) AEs	69 (38.1)	84 (47.2)
Cardiac arrhythmia HLGT AEs	35 (19.3)	48 (27.0)
Cardiac conduction disorders HLT	8 (4.4)	10 (5.6)
Rate and rhythm disorders NEC HLT	5 (2.8)	4 (2.2)
Supraventricular arrhythmias HLT	24 (13.3)	36 (20.2)
Ventricular arrhythmias and cardiac arrest HLT	5 (2.8)	8 (4.5)
Torsade de Pointes[a]/QT Prolongation SMQ AEs	12 (6.6)	18 (10.1)
Heart Failure FMQ (narrow) AEs	65 (35.9)	78 (43.8)
Arrhythmia FMQ (narrow) AEs	28 (15.5)	43 (24.2)
Cardiac conduction disturbance FMQ (narrow) AEs	9 (5.0)	11 (6.2)

a. No confirmed events of Torsade de pointes were reported.
AE=adverse event; DB=double-blind; FMQ=Food and Drug Administration Medical Query; HLGT=high-level group term; HLT=high-level term; NEC=not elsewhere classified; SMQ=standardized Medical Dictionary for Regulatory Activities query; SOC=System Organ Class.

7.9.2 Infusion-Related Reactions

Across patisiran clinical studies, all patients received a pre-medication regimen of oral steroids, antihistamines, and acetaminophen to reduce the potential risk of IRRs. When IRRs have occurred, they have generally been mild or moderate in severity and can be readily managed by slowing or stopping the infusion, and providing additional symptomatic treatment as medically indicated. Few IRRs (<1%) have led to treatment discontinuation.

Within the DB period of APOLLO-B, 22 (12.2%) patients in the patisiran group and 16 (9.0%) patients in the placebo group reported ≥1 IRR. All IRRs were mild or moderate in severity, and none were reported as SAEs. One patient (0.6%) in the patisiran group had a mild IRR that resulted in discontinuation of study treatment.

IRR signs and symptoms reported in ≥2% of patients in the patisiran group were back pain (4.4%) and flushing (2.2%). IRR signs and symptoms reported in the placebo group were reported for ≤2 patients (1.1%) each. Back pain, dyspnea, hiccups, and flushing occurred in both groups.

*7.9.3 **Hepatic Events***

As patisiran is directed to the liver, the frequency of hepatic events was evaluated by performing an analysis of AEs mapping to the SMQ Drug-related Hepatic Disorders – Comprehensive Search.

Hepatic AEs were reported for 14 patients (7.7%) in the patisiran group and 7 patients (3.9%) in the placebo group. Two patients, 1 in the patisiran group (0.6%) and 1 in the placebo group (0.6%), had severe hepatic SAEs. The rest of the hepatic AEs were non-serious and either mild or moderate in severity. None of the hepatic AEs led to discontinuation of study drug. Two patients, 1 in the patisiran group (0.6%) and 1 in the placebo group (0.6%), had hepatic AEs that were considered related to study drug by the Investigator. The majority of patients had ALT and AST within normal ranges. No confirmed cases of Hy's law or Drug Induced Liver Injury (DILI) were identified. Details on patients with hepatic events that were serious, severe, or related are provided in Appendix 12.10.

*7.9.4 **Ocular Events***

By reducing serum TTR protein, patisiran treatment leads to a decrease in serum vitamin A (retinol) levels. Therefore, ocular events were closely monitored during APOLLO-B. Oral supplementation with a daily dose of vitamin A is recommended in patients receiving patisiran to reduce the potential risk of ocular toxicity due to vitamin A deficiency.

Extensive evaluations of ocular safety were carried out during APOLLO and no confirmed cases of night blindness were identified. During the DB period of APOLLO-B, 17.1% of patients in the patisiran group and 11.8% of patients in the placebo group had AEs in the Eye disorders SOC. Ocular events reported in ≥2% of patients in either group included conjunctival hemorrhage (patisiran 3.9%, placebo 0), vision blurred (patisiran 3.3%, placebo 2.2%), and cataract (patisiran 2.2%, placebo 1.1%). All AEs in the Eye disorders SOC were mild or moderate in severity. None of the AEs were severe or serious. There were 4 patients (2.2%) in the patisiran group with AEs in the Eye disorders SOC that were considered related to study drug by the Investigator; 2 patients with vision blurred and 1 patient each with night blindness and retinal tear. The AE of night blindness (reported as reduction in night vision) in the patisiran group was reported on Study Day 11 and was recovering/resolving at the time of reporting. Based on the early timing of the event and resolving nature, it was not suggestive of vitamin A deficiency. In APOLLO-B, none of the AEs in the Eye disorders SOC were considered related to study drug in the placebo group. One patient in the placebo group had an AE of night blindness (reported as impaired vision at night while driving) that was considered not related to study drug and consistent with advanced age and early-stage cataract.

7.10 Additional Safety Topics

Additional safety analyses were done for extravasation or other infusion site complications, renal events, hypothyroidism, and immunogenicity.

*7.10.1 **Extravasation or Other Infusion Site Complications***

Two patients in the patisiran group had an AE that was potentially associated with or had possible symptoms of extravasation.

One patient in the placebo group had a mild AE of infusion site extravasation during the tenth dose of placebo (Study Day 190) that led to interruption of the infusion. One patient in the patisiran group had an infusion interruption due to an extravasation that was not considered an AE. The infusion was restarted, and the patient received the full dose.

Overall, events of extravasation or potential events of extravasation were reported in <0.1% of infusions (2 events in 3,054 administrations) in patients dosed with patisiran during the DB period.

*7.10.2 **Renal Events***

As patients with ATTR amyloidosis often have renal involvement as a component of their disease that can result in renal failure and end-stage renal disease, an analysis of renal events mapping to the Acute Renal Failure SMQ was performed.

During the DB period of APOLLO-B, 15 (8.3%) patients in the patisiran group and 12 (6.7%) patients in the placebo group had AEs in the SMQ Acute renal failure. Renal events reported in ≥2% of patients in either group included acute kidney injury (patisiran 3.3%, placebo 1.1%), renal impairment (patisiran 3.3%, placebo 2.2%), and renal failure (patisiran 1.7%, placebo 2.8%).

Two patients in the patisiran group had severe SAEs of acute kidney injury that were considered not related to study drug. For 1 patient, the event occurred after a fall that resulted in rhabdomyolysis; the event resolved. For the other patient, the event occurred during a prolonged hospitalization for pancreatitis complicated by paralytic ileus and bacterial sepsis; subsequently, the patient entered hospice and died due to pancreatitis.

The rest of the renal AEs were non-serious and either mild or moderate in severity; none were considered related to study drug by the Investigator, and none of the events resulted in discontinuation of study treatment.

Mean absolute values and change from baseline in eGFR and creatinine were similar in the patisiran and placebo groups. Shifts from baseline to worst post-baseline for eGFR were comparable in the two groups and none of the shifts were related to study drug. In the patisiran group, 9 patients (5.0%) had a worst post-baseline eGFR of <30 mL/min/1.73 m^2; and 11 patients (6.2%) in the placebo group had a worst post-baseline eGFR of <30 mL/min/1.73 m^2; no patients in either group had shifts in eGFR to <15 mL/min/1.73 m^2.

*7.10.3 **Hypothyroidism***

Transthyretin is a minor transporter of thyroxine in humans. No clinically meaningful difference of AEs of hypothyroidism has been observed with patisiran treatment compared with placebo. All events were non-serious and considered not related to study drug. In the pooled safety data

across the polyneuropathy and cardiomyopathy studies, the frequency of hypothyroidism remained low (2.4%) and did not increase over time.

7.10.4 ***Immunogenicity***

ADA against patisiran were assessed over the course of the DB period of the APOLLO-B study. One patient (1/175; 0.6%) in the patisiran group and 3 patients (3/177; 1.7%) in the placebo group had confirmed treatment-emergent ADA; the titers were low and were not treatment boosted. Overall, there was no pattern of AEs in patients with positive ADA status to suggest an impact of ADA on the safety profile of patisiran.

7.11 Overall Safety of Patisiran During the Double-Blind and Open-Label Extension Periods

As of the data cutoff date of 19 December 2022, the safety profile of patisiran in patients who received patisiran at any time in APOLLO-B was consistent with that seen during the DB period. In the All Patisiran Treated Set, 95.1% of patients reported ≥1 AE. The majority of AEs were mild or moderate in severity. The most common AEs reported in ≥10% of patients were cardiac failure (32.3%), COVID-19 (26.8%), IRR (14.4%), atrial fibrillation (14.1%), constipation (13.5%), and fall (11.0%). Severe AEs were reported by 37.8% of patients and 49.6% of patients reported SAEs. Cumulatively, SAEs reported in ≥2% of patients included cardiac failure (11.2%), atrial fibrillation (4.3%), pneumonia (2.3%), cardiac failure acute (2.0%), and sepsis (2.0%). The proportion of patients with an AE leading to discontinuation of study treatment was 5.8%, of which 3 events (0.9%) were considered related to study drug.

As of the data cutoff date, a total of 27 patients in the All Patisiran Treated Set have died, including the 5 patients from the DB period (described in Sections 1.6.6.2 and 7.8) and 22 patients from the OLE period (details for these deaths are provided in Appendix 12.11). During the OLE period, 1 death was considered related to study drug. An 86-year-old patient with a history of ATTR-CM, hypercholesterolemia, paroxysmal atrial fibrillation, and congestive heart failure died from a related SAE of sudden death during the infusion. The infusion was close to completion and the patient did not show any signs or symptoms of distress during the infusion. The patient had previously received 33 patisiran infusions and had no prior infusion reactions.

For the All Patisiran Treated Set, not including deaths due to COVID-19, the follow-up time adjusted all-cause mortality rate was 5.28 per 100 patient-years (95% CI: 3.596–7.756) based on 26 deaths observed over 492.34 patient-years. Among published studies in patients with ATTR amyloidosis with sufficient information to estimate a mortality rate, the estimated mortality rate ranges from 6.8 to 29 deaths per 100 patient-years (Arruda-Olson et al 2013; Berk et al 2013; Maurer et al 2018; Ruberg et al 2012; Sattianayagam et al 2012).

7.12 Safety in Subgroups

An evaluation of the safety profile of patisiran in subgroups, including analyses by intrinsic and extrinsic factors pertinent to patient management, was performed. Intrinsic factors included age, sex, race, baseline weight category, ATTR amyloidosis type, NYHA class, PND Score, baseline 6MWT, and use of background tafamidis. Extrinsic factors included geographic region.

Overall, there was no consistent pattern of risk associated with any of these intrinsic or extrinsic factors and treatment with patisiran. Importantly, the types and frequencies of AEs, including deaths, SAEs, and other significant AEs, were similar between patients who were or were not taking background tafamidis.

7.13 Safety Conclusions

Overall, the safety profile of patisiran in patients with ATTR-CM was consistent with that previously observed in the patisiran clinical studies and post-marketing experience in patients with hATTR-PN. No new safety signals or changes were observed in APOLLO-B (DB + OLE).

Patisiran treatment is associated with IRRs, which were reported in 14.4% of patients and were mostly mild or moderate in severity. IRRs, when they occurred, were readily managed and a total of 2 patients (0.6%) discontinued study treatment due to IRR.

Collectively, the data support an acceptable safety profile for patisiran with no cardiac safety concerns in patients with ATTR-CM.

8 EXPANDED ACCESS PROGRAM

A patisiran EAP for patients with ATTR-CM who, at baseline, have an inadequate response to or cannot tolerate standard of care (tafamidis) was initiated in August 2022. Common cardiac signs and symptoms among patients on tafamidis that are prompting enrollment in the patisiran EAP include shortness of breath, atrial fibrillation, increased diuretic use, decreased exercise tolerance, and increased CV laboratory parameters. The EAP has finished enrolling the target number of patients (N=200) in less than a year of initiation across 20 centers in the US. The willingness of patients and their physicians to enroll in a study with an IV therapy further highlights the high unmet need in this patient population. No new safety concerns have been identified to date via routine safety monitoring activities including review of individual and aggregate case reviews.

9 POST-MARKETING EXPERIENCE

Patisiran was first approved in the US in 2018 for the treatment of the polyneuropathy of hATTR-PN. Since then, patisiran has been approved in more than 35 countries. To date, there are over 8,500 patient-years of exposure to patisiran worldwide. The Sponsor continues to review the safety of patisiran, including all reports of adverse experiences. The post-marketing experience with patisiran has been consistent with the safety profile from the clinical studies (ONPATTRO USPI; Appendix 12.12), with no new risks or safety concerns identified.

As part of the Sponsor's continued evaluation of the safety of patisiran, the company has an ongoing, prospective, global, multicenter, long-term observational study (Study ALN-TTR02-013 hereafter referred to as ConTTRibute) designed to document the natural history and clinical outcomes of patients with ATTR amyloidosis, and the safety of patisiran (ONPATTRO®) as a part of routine clinical practice in the real-world clinical setting.

10 BENEFIT-RISK CONCLUSIONS

ATTR amyloidosis is a rare, serious, debilitating, and ultimately fatal disease. The unrelenting disease progression that characterizes both wt and hATTR amyloidosis is driven by the ongoing, infiltrative deposition of circulating TTR as amyloid. Deposition in the peripheral nerves or heart causes polyneuropathy, cardiomyopathy, or both, resulting in irreversible loss of functional capacity, worsening health status and QoL, and high mortality. The widespread adoption of non-invasive technetium scintigraphy has driven a dramatic shift toward diagnosis of patients with less advanced disease, thus providing the opportunity to treat patients before there is substantial, irreversible loss of functional capacity and QoL. Currently, there is only one approved treatment option for ATTR-CM and disease progression is commonly observed despite the availability of tafamidis, leaving a significant unmet need in a life-limiting disease.

The unique mechanism of action of patisiran specifically targets the production of TTR, the pathogenic substrate for amyloid deposition, at its source. The therapeutic hypothesis is that substantial and sustained TTR reduction will slow or effectively stop ongoing amyloid formation, significantly slowing and possibly stabilizing the rate of disease progression.

APOLLO-B was a robust and well-conducted clinical trial that met its primary and key secondary endpoint with statistically persuasive results. The results were also clinically meaningful. During the DB period, the placebo arm showed worsening across multiple measures, consistent with the known pathophysiology and natural history of disease progression resulting from ongoing amyloid deposition. In contrast the median decline in 6MWT observed on the patisiran arm was similar to that of natural aging, suggesting relative stability in functional capacity for many patients in the study. On a relative basis, patisiran slowed the decline of functional capacity by 62% compared with placebo. In health status and QoL (KCCQ-OS), patisiran-treated patients remained stable for 12 months compared to a clinically relevant decline in placebo-treated patients. The KCCQ-OS changes in APOLLO-B are comparable to or exceed changes observed for therapies approved for use in other forms of HF. The results also show that across all response thresholds for both 6MWT and KCCQ, patisiran-treated patients consistently fared better than those on placebo; including at thresholds of commonly accepted or established clinically meaningful changes. Results from the OLE, in which both treatment arms received patisiran, further corroborated the primary analysis, with continued efficacy in patisiran treated patients.

The clinical meaningfulness of the primary efficacy results has been corroborated by multiple findings. First, an MCID for change in 6MWT in the APOLLO-B patient population was derived using an anchor-based method based on patient-reported health status and QoL. The median treatment effect of APOLLO-B exceeded the study-derived MCID, and the results suggest that the observed treatment effect corresponds to a difference in functional capacity that the majority of patients would find clinically meaningful. When considering the derived MCID as a threshold of change, compared to placebo, after 12 months of treatment patients on patisiran had a lower likelihood of experiencing a meaningful decline (OR=0.69; 95% CI: 0.45–1.04) and a higher likelihood of experiencing a meaningful improvement (OR=1.45; 95% CI: 0.94–2.26). Second, patisiran-treated patients demonstrated favorable changes compared to placebo in health status

and QoL for 19 of 20 individual questions in the KCCQ reflecting heart failure symptoms, physical limitations, and QoL. The greatest changes favoring patisiran-treated patients were seen in questions related to the cardinal symptoms of ATTR-CM and in physical limitations corresponding to activities requiring increasing levels of exertion. Third, analyses of disease progression as measured by increase in NYHA class and ATTR amyloidosis disease stage showed that the risk of progression in each of these clinically important parameters was reduced by 40% in patisiran-treated patients compared to placebo. These findings are further supported by changes in imaging assessments of cardiac structure and function and important clinical cardiac laboratory parameters that are all consistent with reduced disease progression and the expected mechanism of action of patisiran.

Patients on patisiran monotherapy demonstrated a greater treatment effect on patient function and health status and QoL than the overall population. Approximately 75% of the patient population were in the patisiran monotherapy subgroup, which in the absence of confounding effects of tafamidis allowed for a clearer assessment of patisiran treatment effect in this patient population. For patients on background tafamidis, due to the small sample size and relatively modest placebo decline over 12 months, the treatment effect of patisiran on background tafamidis is uncertain and was not established in this study.

Notably, the reduction in TTR is consistent across all subgroups suggesting all patients receive a beneficial PD effect.

In addition to the data from APOLLO-B, overall, the efficacy of patisiran in ATTR-CM is supported by the following lines of confirmatory evidence. First is highly persuasive PD data providing a strong biologic rationale for the drug's mechanism of action. Patisiran treatment has resulted in rapid and sustained knock-down of circulating TTR ≥85% leading to improvements compared to placebo in important cardiac laboratory measures (NT-proBNP, troponin I), echocardiographic measures of cardiac structure and function, and technetium scintigraphy imaging. These data are corroborated by evidence of an effect of patisiran on echocardiographic parameters and NT-proBNP observed in the pre-specified sub-population of patients with evidence of cardiac amyloid involvement at baseline from APOLLO (56% of the overall population; Solomon et al 2019). Patisiran was also shown to be highly effective in patients with hATTR-PN; the APOLLO study demonstrated that patisiran is disease-modifying in this related patient population.

The risks of patisiran are well-characterized. The majority of AEs in APOLLO-B were mild or moderate in severity. The AEs noted to be more frequent in the patisiran than placebo group – IRRs, muscle spasm, and arthralgia – are known ADRs and already listed in the approved labeling. The favorable safety profile observed on APOLLO-B is consistent with the known safety profile of patisiran, as outlined in the ONPATTRO US prescribing information, and post-marketing data. Patisiran has been approved in multiple regions for the treatment of hATTR-PN; its first approval occurred in 2018 in the US. Patisiran has been administered to 633 patients in clinical studies. An estimated 2,564 patients worldwide in at more than 35 countries have received patisiran, and 377 patients have received treatment via early access and compassionate

use programs. Overall, there are over 8,500 patient-years of experience with patisiran in clinical trials and the post-marketing setting.

In APOLLO-B, analyses of outcomes data including both analysis of the composite of all-cause mortality and all-cause hospitalization and urgent HF visits, as well as analysis of all-cause mortality, demonstrate numerical trends favoring patisiran and are reassuring in indicating no harmful effects. The favorable safety and outcomes data (post-hoc) from APOLLO (Adams et al 2018; Solomon et al 2019; Adams et al 2021) provide further evidence to rule out harm.

In summary, the results from APOLLO-B demonstrate that by lowering levels of the pathogenic protein, patisiran addresses ATTR-CM patients' important need for therapies that can delay disease progression, including functional decline, and improve HF symptoms. These results, along with confirmatory evidence from APOLLO support a favorable benefit-risk profile for patients with cardiomyopathy due to wtATTR or hATTR amyloidosis. The uncertainty of the effect of patisiran on background tafamidis should be clearly reflected in the prescribing information. Taken together, these data support the expansion of the approved indication for patisiran to include treatment of ATTR-CM to slow the decline in functional capacity and reduce symptoms.

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12 APPENDICES

12.1 APOLLO-B Study Eligibility Criteria

12.1.1 ***Inclusion Criteria***

For inclusion into the APOLLO-B study, patients were required to fulfill all of the following criteria. Patients must have had/been:

1. Age 18 (or age of legal consent, whichever was older) to 85 years, inclusive.
2. Documented diagnosis of transthyretin-mediated amyloidosis (ATTR) with cardiomyopathy, classified as either hereditary transthyretin-mediated amyloidosis (hATTR) amyloidosis with cardiomyopathy or wild-type (wt)ATTR amyloidosis with cardiomyopathy:

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

   a. Transthyretin (TTR) pathogenic mutation consistent with hATTR.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at screening).
   c. Amyloid deposits in cardiac or noncardiac tissue (e.g., fat pad aspirate, salivary gland, median nerve connective sheath) confirmed by Congo Red (or equivalent) staining or technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc], or ^{99m}Tchydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) had been excluded.
   d. If MGUS, confirmed TTR protein in tissue with immunohistochemistry (IHC) or mass spectrometry.

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

   a. Absence of pathogenic TTR mutation.
   b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at screening).
   c. Amyloid deposits in cardiac tissue with TTR precursor identification by IHC, mass spectrometry, or technetium (^{99m}Tc) scintigraphy (DPD-Tc, PYP-Tc, or HMDP) with Grade 2 or 3 cardiac uptake, if MGUS had been excluded.

d. If MGUS, confirmed TTR protein in cardiac tissue with IHC or mass spectrometry.

3. Medical history of heart failure (HF) with ≥1 prior hospitalization for HF (not due to arrhythmia or a conduction system disturbance treated with a permanent pacemaker) or clinical evidence of HF (with or without hospitalization) manifested by signs and symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that currently required treatment with a diuretic.
4. Met one of the following criteria:
    a. Tafamidis naïve; in addition to patients who have never taken tafamidis, those who had been on tafamidis for ≤30 days total and had not received any tafamidis in the 6 months prior to baseline were considered tafamidis naïve and may qualify for the study.
    b. Currently on tafamidis (for ≥6 months) and had demonstrated disease progression, as determined by the Investigator. (At the time of study entry, tafamidis treatment must have been on-label use of commercial tafamidis for the treatment of ATTR amyloidosis with cardiomyopathy at the approved dose in the country of use.)
5. Clinically stable, with no cardiovascular (CV)-related hospitalizations within 6 weeks prior to randomization, as assessed by the Investigator.
6. Able to complete ≥150 meters on the 6-minute walk test (6MWT) at screening.
7. Screening N-terminal prohormone B-type natriuretic peptide (NT-proBNP) >300 ng/L and <8500 ng/L; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP >600 ng/L and <8500 ng/L.
8. Able to understand and was willing and able to comply with the study requirements and to provide written informed consent; and patient agreed to sign the medical records release form for collection of vital status.

*12.1.2 **Exclusion Criteria***

The following was regarded as criterion for exclusion from the APOLLO-B study. Patients must not have had/been:

1. Known primary amyloid light chain (AL) amyloidosis or leptomeningeal amyloidosis.
2. New York Heart Association (NYHA) class III and ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3000 ng/L and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2) (Gillmore et al 2018).
3. NYHA class IV at the screening visit.
4. A polyneuropathy disability (PND) score IIIa, IIIb, or IV (requires cane or stick to walk, or is wheelchair bound) at the screening visit.

5. Any of the following laboratory parameter assessments at screening:
    a. Aspartate transaminase (AST) or alanine transaminase (ALT) levels >2.0x the upper limit of normal (ULN).
    b. Total bilirubin >2x ULN.
    c. International normalized ratio (INR) >1.5 (unless patient is on anticoagulant therapy, in which case excluded if INR >3.5).
6. eGFR <30 mL/min/1.73 m^2 (using the modification of diet in renal disease formula).
7. Known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.
8. Tafamidis naïve (at baseline) for whom the Investigator actively planned or anticipated commencing treatment with tafamidis during the 12-month double-blind period, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
9. Taking diflunisal; if previously on this agent, must have had at least a 30-day washout prior to dosing (Day 1).
10. Taking doxycycline, ursodeoxycholic acid, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 30-day washout prior to dosing (Day 1).
11. Received prior TTR-lowering treatment (including patisiran) or participated in a gene therapy trial for hATTR amyloidosis.
12. Participated or future participation in another investigational device or drug study, scheduled to occur during this study, or had received an investigational agent or device within 30 days (or 5 half-lives of the investigational drug, whichever was longer) prior to dosing (Day 1). In the case of investigational TTR stabilizer drugs, washout for 6 months prior to dosing (Day 1) was required; this did not apply to patients who were on tafamidis at baseline (per inclusion Criterion 4).
13. Required chronic treatment with non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem).
14. Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease (e.g., prior myocardial infarction with documented history of cardiac enzymes and electrocardiogram [ECG] changes).
15. Non-amyloid disease affecting exercise testing (e.g., severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation).
16. Recent or planned orthopedic procedure during the double-blind period (e.g., lower extremity or back surgery) that could impact 6MWT.
17. Unstable congestive heart failure (CHF) (e.g., no adjustment of diuretics at time of screening required to achieve optimal treatment of CHF).

18. Acute coronary syndrome or unstable angina within the past 3 months.
19. History of sustained ventricular tachycardia or aborted ventricular fibrillation.
20. History of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
21. Persistent elevation of systolic (>180 mmHg) and diastolic (>100 mmHg) blood pressure that was considered uncontrolled by physician.
22. Untreated hypo- or hyperthyroidism.
23. Prior or planned heart, liver, or other organ transplant.
24. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that had been successfully treated.
25. Other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient.
26. A history of severe hypersensitivity (e.g., anaphylaxis) to any of the excipients in patisiran. Also see exclusion Criterion 11, which excludes all patients with prior TTR-lowering treatment including patisiran.
27. Not willing to comply with the contraceptive requirements during the study period,
28. Female patient that was pregnant or breast-feeding.
29. A known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (for females, >14 units of alcohol/week; for males, >21 units of alcohol/week [unit: 1 glass of wine [125 mL]=1 measure of spirits=½ pint of beer]).
30. History of illicit drug abuse within the past 5 years that in the opinion of the Investigator would interfere with compliance with study procedures or follow-up visits.

12.2 United States Baseline Demographics and Baseline Disease Characteristics in APOLLO-B

Table 26: Baseline Demographics in APOLLO-B (United States Population)

Characteristic	Patisiran (N=45)	Placebo (N=52)
Median age at screening, years (min, max)	77 (55, 85)	76 (59, 85)
≥75 years old, n (%)	29 (64.4)	30 (57.7)
Male	43 (95.6)	47 (90.4)
Race		
White	38 (84.4)	43 (82.7)
Asian	1 (2.2)	0
Black or African American	6 (13.3)	9 (17.3)
Other or Not reported	0	0
Ethnicity		
Not Hispanic or Latino	44 (97.8)	52 (100.0)
Unknown	1 (2.2)	0

Table 27: Baseline Disease Characteristics in APOLLO-B (United States Population)

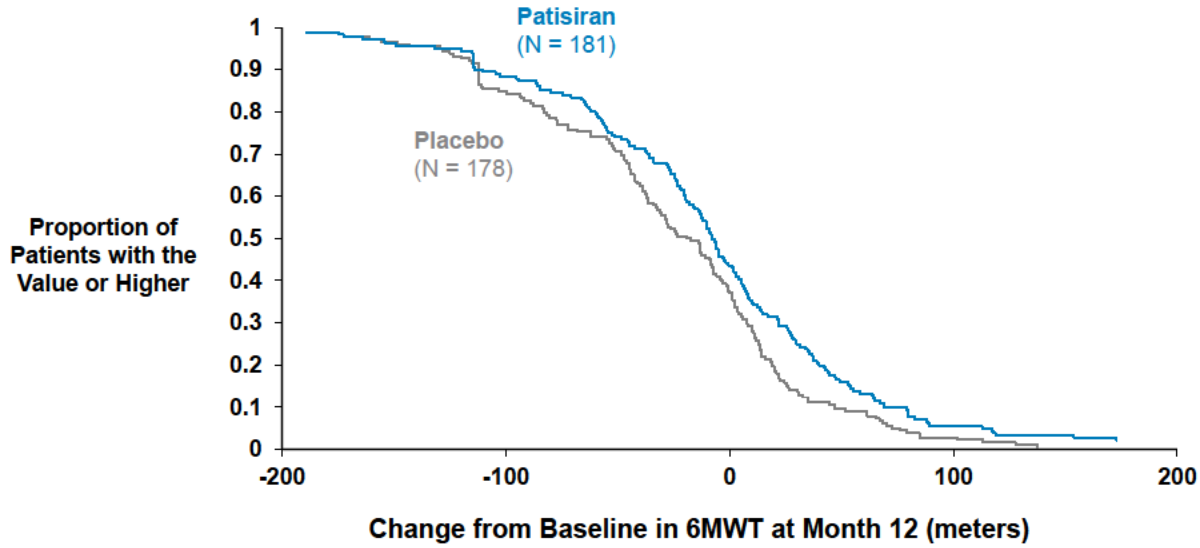
Characteristic	Patisiran (N=45)	Placebo (N=52)
ATTR amyloidosis type, n (%)		
wtATTR	39 (86.7)	43 (82.7)
hATTR	6 (13.3)	9 (17.3)
Time since diagnosis (years), median (min, max)	2.0 (0, 5)	1.4 (0, 10)
Background tafamidis use, n (%) No Yes	 8 (17.8) 37 (82.2)	 12 (23.1) 40 (76.9)
NYHA class, n (%)		
Class I	4 (8.9)	6 (11.5)
Class II	33 (73.3)	40 (76.9)
Class III	8 (17.8)	6 (11.5)
NT-proBNP level (ng/L), median (min, max)	1948.0 (288, 8530)	1946.0 (273, 7285)
ATTR amyloidosis stage[a], n (%)		
Stage 1	34 (75.6)	33 (63.5)
Stage 2	7 (15.6)	16 (30.8)
Stage 3	4 (8.9)	3 (5.8)
6MWT (m), median (min, max)	360 (175, 551)	374 (166, 740)
KCCQ-OS score, median (min, max)	79 (30, 100)	79 (30, 98)

a. ATTR amyloidosis disease stage is defined by a combination of NT-proBNP and eGFR thresholds (Gillmore et al 2018).
6MWT=6-minute walk test; ATTR=transthyretin-mediated amyloidosis; eGFR=estimated glomerular filtration rate; h=hereditary; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; wt=wild-type.

12.3 Cumulative Distribution Function Figures for Primary and First Secondary Endpoints at Month 12 in APOLLO-B

Cumulative distribution curves show separation between the patisiran and placebo groups for change in 6MWT at 12-months across a broad range of response thresholds (Figure 43), further supporting the robustness of the effect.

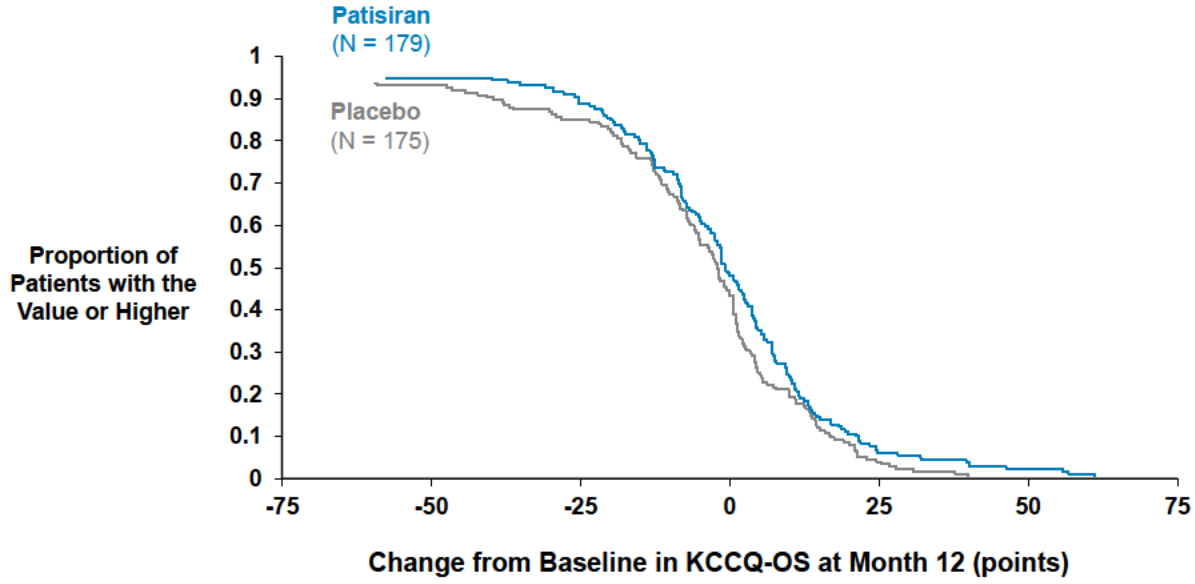
Figure 43: Cumulative Distribution Function of Change From Baseline in 6MWT at Month 12 (Full Analysis Set)



Note: Figure presents observed 6MWT data and the imputed values; for each patient, the change from baseline is averaged across 100 complete datasets.
Note: Cumulative distribution functions of change from baseline from -200 to 200 are presented.
Note: Patients who died (not due to COVID-19) or were unable to walk due to amyloidosis were imputed with the worst 10th percentile change from baseline value (-115 meters).
6MWT=6-minute walk test.

Cumulative distribution curves show separation between the patisiran and placebo groups for change in KCCQ-OS at 12-months across a broad range of response thresholds (Figure 44), further supporting the robustness of the effect.

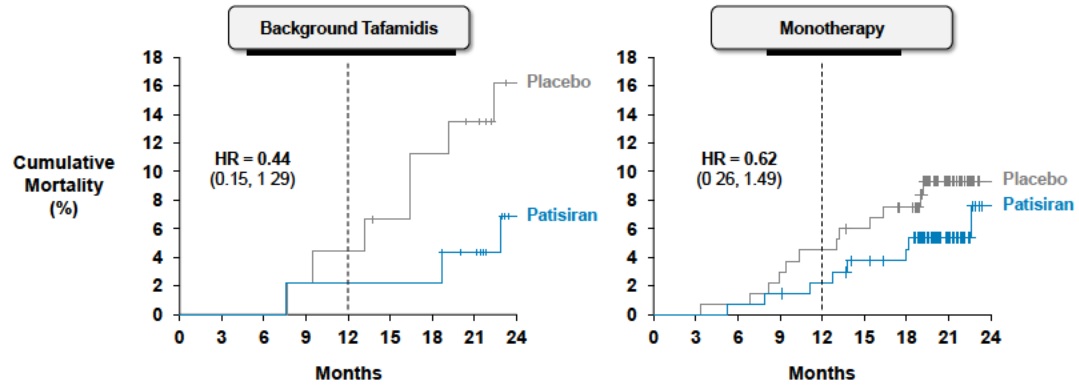
Figure 44: Cumulative Distribution Function of Change From Baseline in KCCQ-OS at Month 12 (Full Analysis Set)



Note: Figure presents observed KCCQ-OS data.
Note: Patients who had their Month 12 assessment on or after a serious COVID-19 adverse event are excluded from the analysis.
KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.

12.4 All-Cause Mortality for Background Tafamidis or Patisiran Monotherapy Subgroups

Figure 45: All-Cause Mortality During APOLLO-B for Background Tafamidis (Left Panel) and Patisiran Monotherapy (Right Panel) Subgroups (Full Analysis Set)



Note: The dashed lines designate the Month 12 timepoint at which the placebo group crossed over to treatment with patisiran.
HR=hazard ratio.

12.5 Pharmacokinetics

12.5.1 ***Distribution, Metabolism, and Excretion***

Patisiran drug product includes the drug substance patisiran combined with lipid excipients and cholesterol to form an ionizable lipid nanoparticle (LNP). Once delivered to the cytoplasm of hepatocytes, patisiran is metabolized by nucleases to nucleotides of various lengths. Patisiran shows low plasma protein binding. Furthermore, <1% of patisiran is excreted unchanged in the urine, which demonstrates that the kidney does not play a major role in patisiran clearance. The absorption, distribution, metabolism, elimination properties are expected to be consistent across several patient populations, including patients with mild or moderate renal impairment, patients with mild hepatic impairment, and hATTR amyloidosis patients that have progressed and require liver transplant, and indications including treatment of adult patients with hATTR-PN and treatment of cardiomyopathy in adults with wild-type or hATTR amyloidosis. Patisiran has not been studied in patients with moderate or severe hepatic impairment, severe renal impairment, or end-stage renal disease.

12.6 Population Pharmacokinetics

Covariate analysis indicated that the effects of baseline age, sex, race (white vs all other races), renal function (mild and moderate impairment), hepatic function (mild impairment), Japanese or Hispanic ethnicity, anti-drug antibody (ADA), and NYHA class did not have a meaningful impact on pharmacokinetics (PKs) of patisiran, lipid excipients DLin-MC3-DMA or PEG_{2000}-C-DMG, or on inter-participant variability in plasma PK. Body weight was found to be a significant covariate in population PK models, although it was not a significant covariate in the PK/pharmacodynamic (PD) model, consistent with similar TTR reduction observed across body weight categories. Additional significant covariates included health status (healthy participants or ATTR amyloidosis patients with cardiomyopathy) for patisiran, concomitant use of tafamidis for DLin-MC3-DMA, and ATTR amyloidosis disease stage and type of amyloidosis (wild-type or hereditary ATTR amyloidosis [wt or hATTR]) for PEG_{2000}-C-DMG. These covariates were all found to have minimal impact on PK exposure and were not considered to be clinically meaningful. No difference in PK exposure was observed in patients with mild to moderate renal impairment or in patients with mild hepatic impairment.

Population PK analysis supports the adequacy of the proposed dosing regimen of 0.3 mg/kg patisiran intravenously (IV) once every 3 weeks (q3W) in patients with transthyretin-mediated amyloidosis with cardiomyopathy (ATTR-CM) since none of the covariates analyzed appear to impact the PK of patisiran.

12.7 Population Pharmacokinetic/Pharmacodynamic Modeling

Population PK/PD modeling was performed to characterize the relationship between patisiran plasma concentrations and serum TTR reduction in healthy participants (from Studies 001 and 005) and patients with ATTR-CM (from APOLLO-B), as well as to evaluate the impact of demographic and baseline characteristics (age, body weight, Hispanic ethnicity, race, Japanese patients, renal function, hepatic function, baseline TTR, type of amyloidosis [hATTR vs

wtATTR], background use of tafamidis or prior use of other TTR stabilizers, NYHA class, and baseline NT-proBNP) as covariates on intra- and inter-individual variability on serum TTR measures. Another objective of population PK/PD modeling was to confirm the adequacy of the proposed patisiran dose for patients with ATTR-CM.

A population PK/PD model was developed to describe the exposure-response relationship of patisiran plasma concentrations and serum TTR reduction in patients with ATTR-CM. The model adequately characterized serum TTR concentration data in both placebo and patisiran treatment groups. The model predicted median steady-state peak, trough, and average TTR reduction of 89.5%, 83.5%, and 87.4%, respectively, confirming sustained TTR reduction with minimal peak-to-trough variability across the dosing interval with 0.3 mg/kg patisiran administered q3W. Covariate analysis indicated similar TTR reduction across extrinsic and intrinsic factors, with no clinically relevant differences. The model also supported the use of 0.3 mg/kg patisiran administered q3W (fixed dose of 30 mg q3W in patients weighing >100 kg) for all patients with ATTR-CM.

Overall, the population PK/PD model supports the use of 0.3 mg/kg patisiran IV q3W.

12.8 Pharmacokinetic/Pharmacodynamic Development Program for Patisiran

Phase	Study Number (Type)	Study Design	Number of Patients Enrolled	Status
PK, PD, and safety studies in healthy volunteers				
Phase 1	ALN-TTR02-001 (SAD)	Single-Blind, Placebo-Controlled, SAD, Safety, Tolerability and PK/PD Study	17	Complete
Phase 1	ALN-TTR02-005 (SAD in Japanese Healthy volunteers in the UK)	Randomized, DB, Placebo-Controlled, SAD, Safety, Tolerability and PK/PD Study	12	Complete

PD=pharmacodynamic; PK=pharmacokinetic; SAD=single ascending dose; United Kingdom.

12.9 Intercurrent Event and Handling Strategies

Table 28: Intercurrent Event Strategies for the Primary Analysis of 6MWT

Intercurrent Event	Handling Strategy
Treatment discontinuation (not due to death)	Treatment policy strategy: Intercurrent event is ignored; 6MWT assessments obtained after treatment discontinuation will be included in analysis.
Serious COVID-19 AE	Hypothetical strategy: Assessments obtained on or after the onset of a serious COVID-19 AE will be treated as missing and will be assumed as MAR. The goal is to estimate the scheduled visit values as if the patient had not been infected with COVD-19.
Tafamidis drop-in (i.e., taking tafamidis for more than 28 days after randomization) in the subgroup of patients who were not on background tafamidis	Treatment policy strategy: Intercurrent event is ignored; 6MWT assessments obtained after tafamidis drop-in will be included in analysis.
Missing dose(s) due to COVID-19	Treatment policy strategy: Intercurrent event is ignored; 6MWT assessments obtained after missing dose(s) due to COVID-19 will be included in analysis.
Inability to walk due to progression of ATTR amyloidosis (including patients who are unable to walk due to hospitalization related to progression of ATTR amyloidosis)	Composite variable strategy: For patients who die (not due to COVID-19), the missing Month 12 6MWT change from baseline will be imputed as the worst 10th percentile change observed across all patients in the 12m-DB period, capped by the worst possible change for the patient (i,e, 0 minus baseline 6MWT).
Death (including heart transplant and ventricular assist device placement) not due to COVID-19	Composite variable strategy: For patients who die (not due to COVID-19), have a heart transplant, or ventricular assist device placement, the missing Month 12 6MWT change from baseline will be imputed as the worst 10th percentile change observed across all patients in the 12m-DB period, capped by the worst possible change for the patient (i.e., 0 minus baseline 6MWT).
Death due to COVID-19	Hypothetical strategy: Missing data due to COVID-19 death will be assumed as MAR.

6MWT=6-minute walk test; AE=adverse event; ATTR=transthyretin-mediated amyloidosis; DB=double-blind; HL=Hodges-Lehmann; m=month; MAR=missing at random.

Table 29: Intercurrent Event Strategies for the Secondary Analysis of KCCQ-OS

Intercurrent Event	Handling Strategy
Treatment discontinuation (not due to death)	Treatment policy strategy: Intercurrent event is ignored; assessments obtained after treatment discontinuation will be included in analysis.
Serious COVID-19 AE	Hypothetical strategy: Assessments obtained on or after the onset of a serious COVID-19 AE will be treated as missing and will be assumed as MAR. The goal is to estimate the scheduled visit values as if the patient had not been infected with COVID-19.
Tafamidis drop-in (i.e., taking tafamidis for more than 28 days after randomization) in the subgroup of patients who were not on background tafamidis	Treatment policy strategy: Intercurrent event is ignored; assessments obtained after tafamidis drop-in will be included in analysis.
Missing dose(s) due to COVID-19	Treatment policy strategy: Intercurrent event is ignored; assessments obtained after missing dose(s) due to COVID-19 will be included in analysis.
Death	Hypothetical strategy: Missing data due to death will be assumed as MAR.

AE=adverse event; KCCQ=OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; MAR=missing at random.

12.10 Additional Details of Serious, Severe, or Related Hepatic Adverse Events (Safety Analysis Set)

The patients with hepatic AEs that were serious, severe, or related are described below:

- A 69-year-old male in the patisiran group, had a severe serious adverse event (SAE) of hepatic enzyme increased on Study Day 170 (AST 2.0×ULN, ALT 1.8x ULN, and total bilirubin 0.5x ULN) that was considered medically significant by the Investigator. During the event, on Study Day 176, the patient had an AST 3.2× ULN, ALT 2.2× ULN, and total bilirubin 0.4× ULN on local laboratory testing. Study drug was interrupted, and the event resolved. The Investigator considered the event related to study drug.
- A 79-year-old male in the placebo group had a severe hepatic SAE of hepatocellular carcinoma on Study Day 335. The event was not considered related to study drug. The event was not recovered.
- A 73-year-old male in the placebo group had a mild AE of transaminases increased on Study Day 110 that was considered related to study drug by the Investigator. During the event, the patient had an ALT and AST value >3× ULN associated with a concurrent elevation of total bilirubin >2× ULN. Study drug was interrupted, and the event resolved.

In addition, one patient in the patisiran group had a moderate AE of cholestasis that occurred during a concurrent SAE of cardiac failure on Study Day 278. During the event, the patient had an ALT and AST value >3× ULN associated with a concurrent elevation of total bilirubin >2× ULN on local laboratory testing. The event was considered not related to study drug.

12.11 Details of Deaths Reported in the APOLLO-B Open-Label Extension Period

As of the data cutoff date, a total of 27 patients in the All Patisiran Treated Set have died, including 5 patients in the DB period (described in Section 1.6.6.2 and 7.8) and 22 patients from the OLE period, described in the table below.

Table 30: Summary of Deaths as of 19 December 2022 in OLE Period of APOLLO-B

ATTR Amyloidosis Type	Age/ Sex	Background Tafamidis	SAE(s) Reported as Fatal	Primary Cause of Death (Primary Adjudication)	Study Day of Death/ OLE Study Day[a]	Days Since Last Dose[b]
Patisiran/Patisiran						
Wild-type	85/M	No	Cardiac arrest	Sudden Cardiac Death (CV Death)	551/173	5
Hereditary	69/M	No	Cardiac failure	Death due to HF (CV Death)	389/11	11
Hereditary	65/M	No	Chronic kidney disease	Kidney Death (Non-CV Death)	687/309	36
Wild-type	82/M	Yes	N/A[c]	Metastatic pancreatic cancer (Non-CV Death)	568/188	63
Hereditary	85/M	Yes	Sudden death (verbatim: sudden death during infusion)	Sudden cardiac death[f] (CV Death)	696/318	1
Wild-type	65/M	No	Cardiac failure	Cardiogenic shock; amyloidosis (Undetermined Death)	419/42	21
Hereditary	69/M	No	Septic shock	Death due to HF (CV Death)[e]	498/99	36
Wild-type	84/M	No	N/A[c]	Unknown[c] (Non-CV Death) Other: infection	699/316	131[d]
Hereditary	74/M	Yes	Cardiac failure	Death due to HF (CV Death)	742/365	25
Wild-type	74/M	Yes	Cardiac failure, Cardiogenic shock	-	1072/694	24
Hereditary	77/F	No	Cardiac failure	Death due to HF (CV Death)	548/169	85
Placebo/Patisiran						
Hereditary	61/M	No	Cardiac failure; Septic shock	Sepsis: pyelonephritis (Non-CV Death)	578/200	32
Wild-type	75/M	No	Cardiac failure	Death due to HF (CV Death)	497/112	35

ATTR Amyloidosis Type	Age/ Sex	Background Tafamidis	SAE(s) Reported as Fatal	Primary Cause of Death (Primary Adjudication)	Study Day of Death/ OLE Study Day[a]	Days Since Last Dose[b]
Placebo/Patisiran						
Wild-type	83/M	Yes	Hypotension	Death due to HF (CV Death)	908/531	48
Wild-type	67/M	No	Cardiac failure	Death due to HF (CV Death)	470/93	68
Wild-type	83/M	Yes	N/A[c]	Death due to HF (CV Death)	582/204	78
Hereditary	78/M	No	Cardiac failure	Death due to HF (CV Death)	401/31	31
Wild-type	76/M	Yes	Arthritis bacterial, septic shock	Sepsis (Non-CV Death)	736/357	23
Wild-type	80/M	Yes	Fluid overload, Cardiogenic shock[c]	Death due to HF (CV Death)	738/363	48
Wild-type	76/M	Yes	Unknown[c]	-	826/449	92[d]
Wild-type	76/M	No	Multiple organ failure dysfunction syndrome/ Obstructive shock/ Fulminant hepatitis	-	783/402	45
Wild-type	69/M	No	Undetermined death	- (Undetermined Death)	585/207	17

a. Study day of death is relative to the first dose of patisiran or placebo in the DB period. OLE study day is the study day in the OLE period.
b. Study day relative to last dose of study medication in the study.
c. Death occurred after patient had stopped study medication in the study.
d. Patient's death occurred >90 days after the last dose of study drug.
e. Patient had COVID-19 infection at the time of death.
f. Death assessed as related to study drug (see Section 7.11).
Note: Deaths due to COVID-19 were excluded from efficacy analyses of composite endpoints that include all-cause mortality or of all-cause mortality alone (Sections 1.6.3.5, 1.6.4, 6.2.7, and 6.2.9.5).
ATTR=transthyretin-mediated amyloidosis; CV=cardiovascular; F=female; HF=heart failure; M=male; OLE=open-label extension; SAE=serious adverse event; N/A=not applicable.

12.12 Current Approved Prescribing Label for Patisiran

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ONPATTRO® safely and effectively. See full prescribing information for ONPATTRO.

ONPATTRO (patisiran) lipid complex injection, for intravenous use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ONPATTRO contains a transthyretin-directed small interfering RNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg every 3 weeks by intravenous infusion. For patients weighing 100 kg or more, the recommended dosage is 30 mg (2.1)
- Premedicate with a corticosteroid, acetaminophen, and antihistamines (2.2)
- Filter and dilute prior to administration (2.3)
- Infuse over approximately 80 minutes (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Infusion-related reactions: Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs (5.1)
- Reduced serum vitamin A levels and recommended supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur (5.2)

----------ADVERSE REACTIONS----------
The most frequently reported adverse reactions (that occurred in at least 10% of ONPATTRO-treated patients and at least 3% more frequently than on placebo) were upper respiratory tract infections and infusion-related reactions (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alnylam Pharmaceuticals at 1-877-256-9526 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

ONPATTRO should be administered by a healthcare professional.

ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight.

For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks.

For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

Missed Dose

If a dose is missed, administer ONPATTRO as soon as possible.

- If ONPATTRO is administered within 3 days of the missed dose, continue dosing according to the patient's original schedule.
- If ONPATTRO is administered more than 3 days after the missed dose, continue dosing every 3 weeks thereafter.

2.2 Required Premedication

All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs) *[see Warnings and Precautions (5.1)]*. Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)
- Oral acetaminophen (500 mg)
- Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs *[see Warnings and Precautions (5.1)]*.

2.3 Preparation Instructions

ONPATTRO must be filtered and diluted prior to intravenous infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- Remove ONPATTRO from the refrigerator and allow to warm to room temperature. Do not shake or vortex.
- Inspect visually for particulate matter and discoloration. Do not use if discoloration or foreign particles are present. ONPATTRO is a white to off-white, opalescent, homogeneous solution. A white to off-white coating may be observed on the inner surface of the vial, typically at the liquid-headspace interface. Product quality is not impacted by presence of the white to off-white coating.
- Calculate the required dose of ONPATTRO based on the recommended weight-based dosage *[see Dosage and Administration (2.1)]*.
- Withdraw the entire contents of one or more vials into a single sterile syringe.
- Filter ONPATTRO through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.
- Withdraw the required volume of filtered ONPATTRO from the sterile container using a sterile syringe.
- Dilute the required volume of filtered ONPATTRO into an infusion bag containing 0.9% Sodium Chloride Injection, USP for a total volume of 200 mL. Use infusion bags that are di(2-ethylhexyl)phthalate-free (DEHP-free).
- Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.
- Discard any unused portion of ONPATTRO.
- ONPATTRO does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time). Do not freeze.

2.4 Infusion Instructions

- Use a dedicated line with an infusion set containing a 1.2 micron polyethersulfone (PES) in-line infusion filter. Use infusion sets and lines that are DEHP-free.
- Infuse the diluted solution of ONPATTRO intravenously, via an ambulatory infusion pump, over approximately 80 minutes, at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, then increase to approximately 3 mL/min for the remainder of the infusion. The duration of infusion may be extended in the event of an IRR *[see Warnings and Precautions (5.1)]*.
- Administer only through a free-flowing venous access line. Monitor the infusion site for possible infiltration during drug administration. Suspected extravasation should be managed according to local standard practice for non-vesicants.
- Observe the patient during the infusion and, if clinically indicated, following the infusion *[see Warnings and Precautions (5.1)]*.
- After completion of the infusion, flush the intravenous administration set with 0.9% Sodium Chloride Injection, USP to ensure that all ONPATTRO has been administered.

3 DOSAGE FORMS AND STRENGTHS

Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) white to off-white, opalescent, homogeneous solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs led to infusion interruption in 5% of patients. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies. Across clinical studies, the most common symptoms (reported in greater than 2% of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache *[see Adverse Reactions (6.1)]*. Severe hypotension and syncope have been reported as symptoms of IRRs in the expanded access program and postmarketing setting.

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion *[see Dosage and Administration (2.2)]*. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs *[see Dosage and Administration (2.2)]*.

5.2 Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking ONPATTRO. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion-Related Reactions *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of ONPATTRO cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

A total of 224 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received ONPATTRO in the placebo-controlled and open-label clinical studies, including 186 patients exposed for at least 1 year, 137 patients exposed for at least 2 years, and 52 patients exposed for at least 3 years. In the placebo-controlled study, 148 patients received ONPATTRO for up to 18 months (mean exposure 17.7 months). Baseline demographic and disease characteristics were generally similar between treatment groups. The median age of study patients was 62 years and 74% were male. Seventy-two percent of study patients were Caucasian, 23% were Asian, 2% were Black, and 2% were reported as other. At baseline, 46% of patients were in Stage 1 of the disease and 53% were in Stage 2. Forty-three percent of patients had Val30Met mutations in the transthyretin gene; the remaining patients had 38 other point mutations. Sixty-two percent of ONPATTRO-treated patients had non-Val30Met mutations, compared to 48% of the placebo-treated patients.

Upper respiratory tract infections and infusion-related reactions were the most common adverse reactions. One patient (0.7%) discontinued ONPATTRO because of an infusion-related reaction.

Patients were instructed to take the recommended daily allowance of vitamin A *[see Warnings and Precautions (5.2)]*. Sixty-four percent of patients treated with ONPATTRO had normal vitamin A levels at baseline, and 99% of those with a normal baseline developed low vitamin A levels. In one case, the decreased vitamin A level was reported as an adverse reaction.

Table 1 lists the adverse reactions that occurred in at least 5% of patients in the ONPATTRO-treated group and that occurred at least 3% more frequently than in the placebo-treated group in the randomized controlled clinical trial.

Table 1: Adverse Reactions from the Placebo-Controlled Trial that Occurred in at Least 5% of ONPATTRO-treated Patients and at Least 3% More Frequently than in Placebo-treated Patients

Adverse Reaction	ONPATTRO N=148 %	Placebo N=77 %
Upper respiratory tract infections [a]	29	21
Infusion-related reaction [b]	19	9
Dyspepsia	8	4
Dyspnea [c, d]	8	0
Muscle spasms [c]	8	1
Arthralgia [c]	7	0
Erythema [c]	7	3
Bronchitis [e]	7	3
Vertigo	5	1

[a] Includes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, pharyngitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.
[b] Infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.

[c] Not part of an infusion-related reaction.
[d] Includes dyspnea and exertional dyspnea.
[e] Includes bronchitis, bronchiolitis, bronchitis viral, lower respiratory tract infection, lung infection.

Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Ocular adverse reactions that occurred in 5% or less of ONPATTRO-treated patients in the controlled clinical trial, but in at least 2% of ONPATTRO-treated patients, and more frequently than on placebo, include dry eye (5% vs. 3%), blurred vision (3% vs. 1%), and vitreous floaters (2% vs. 1%).

Extravasation was observed in less than 0.5% of infusions in clinical studies, including cases that were reported as serious. Signs and symptoms included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema or injection site redness, burning sensation, or injection site pain.

6.2 Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ONPATTRO in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies to ONPATTRO were evaluated by measuring antibodies specific to PEG_{2000}-C-DMG, a lipid component exposed on the surface of ONPATTRO. In the placebo-controlled and open-label clinical studies, 7 of 194 (3.6%) patients with hATTR amyloidosis developed anti-drug antibodies during treatment with ONPATTRO. One additional patient had pre-existing anti-drug antibodies. There was no evidence of an effect of anti-drug antibodies on clinical efficacy, safety, or the pharmacokinetic or pharmacodynamic profiles of ONPATTRO. Although these data do not demonstrate an impact of anti-drug antibody development on the efficacy or safety of ONPATTRO in these patients, the available data are too limited to make definitive conclusions.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ONPATTRO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Symptoms of infusion-related reactions have included syncope *[see Warnings and Precautions (5.1)]* and pruritus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ONPATTRO during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the program by calling 1-877-256-9526 or by contacting alnylampregnancyprogram@iqvia.com.

Risk Summary

There are no available data on ONPATTRO use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. ONPATTRO treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking ONPATTRO. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by ONPATTRO and of vitamin A supplementation are unknown *[see Clinical Pharmacology (12.2), Warnings and Precautions (5.2)]*.

In animal studies, intravenous administration of patisiran lipid complex (patisiran-LC) to pregnant rabbits resulted in developmental toxicity (embryofetal mortality and reduced fetal body weight) at doses that were also associated with maternal toxicity. No adverse developmental effects were observed when patisiran-LC or a rodent-specific (pharmacologically active) surrogate were administered to pregnant rats (see *Data*).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Intravenous administration of patisiran LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (1.5 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or embryofetal development.

Intravenous administration of patisiran-LC (0, 0.1, 0.3, or 0.6 mg/kg) to pregnant rabbits every week during the period of organogenesis produced no adverse effects on embryofetal development. In a separate study, patisiran-LC (0, 0.3, 1, or 2 mg/kg), administered to pregnant rabbits every week during the period of organogenesis, resulted in embryofetal mortality and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific surrogate (1.5 mg/kg) to pregnant rats every week throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ONPATTRO in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ONPATTRO and any potential adverse effects on the breastfed infant from ONPATTRO or from the underlying maternal condition.

In lactating rats, patisiran was not detected in milk; however, the lipid components (DLin-MC3-DMA and PEG_{2000}-C-DMG) were present in milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No dose adjustment is required in patients ≥65 years old *[see Clinical Pharmacology (12.3)]*. A total of 62 patients ≥65 years of age, including 9 patients ≥75 years of age, received ONPATTRO in the placebo-controlled study. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤1 x ULN and AST >1 x ULN, or bilirubin >1.0 to 1.5 x ULN) *[see Clinical Pharmacology (12.3)]*. ONPATTRO has not been studied in patients with moderate or severe hepatic impairment.

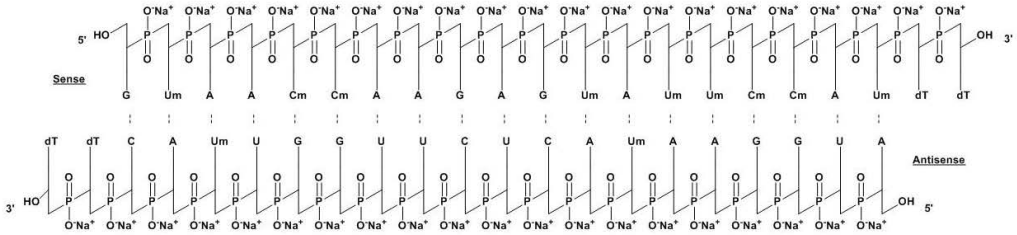
8.7 Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/min/1.73m^2) *[see Clinical Pharmacology (12.3)]*. ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

11 DESCRIPTION

ONPATTRO contains patisiran, a double-stranded small interfering ribonucleic acid (siRNA), formulated as a lipid complex for delivery to hepatocytes. Patisiran specifically binds to a genetically conserved sequence in the 3' untranslated region (3'UTR) of mutant and wild-type transthyretin (TTR) messenger RNA (mRNA).

The structural formula is:



A, adenosine; C, cytidine; G, guanosine; U, uridine; Cm, 2'-*O*-methylcytidine; Um, 2'-*O*-methyluridine; dT, thymidine

ONPATTRO is supplied as a sterile, preservative-free, white to off-white, opalescent, homogeneous solution for intravenous infusion in a single-dose glass vial. Each 1 mL of solution contains 2 mg of patisiran (equivalent to 2.1 mg of patisiran sodium). Each 1 mL also contains 6.2 mg cholesterol USP, 13.0 mg (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA), 3.3 mg 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1.6 mg α-(3'-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene (PEG_{2000}-C-DMG), 0.2 mg potassium phosphate monobasic anhydrous NF, 8.8 mg sodium chloride USP, 2.3 mg sodium phosphate dibasic heptahydrate USP, and Water for Injection USP. The pH is ~7.0.

The molecular formula of patisiran sodium is $C_{412}H_{480}N_{148}Na_{40}O_{290}P_{40}$ and the molecular weight is 14304 Da.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Patisiran is a double-stranded siRNA that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.

12.2 Pharmacodynamics

The pharmacodynamic effects of ONPATTRO were evaluated in hATTR amyloidosis patients treated with 0.3 mg/kg ONPATTRO via intravenous infusion once every 3 weeks.

Mean serum TTR was reduced by approximately 80% within 10 to 14 days after a single dose. With repeat dosing every 3 weeks, mean reductions of serum TTR after 9 and 18 months of treatment were 83% and 84%, respectively. The mean maximum reduction of serum TTR over 18 months was 88%. Similar TTR reductions were observed regardless of TTR mutation, sex, age, race, or prior liver transplantation. In a dose-ranging study, greater TTR reduction was maintained over the dosing interval with the recommended dosing regimen of 0.3 mg/kg every 3 weeks compared to 0.3 mg/kg every 4 weeks.

Serum TTR is a carrier of retinol binding protein, which is involved in the transport of vitamin A in the blood. Mean reductions in serum retinol binding protein of 45% and serum vitamin A of 62% were observed over 18 months *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Following a single intravenous administration, systemic exposure to patisiran increases in a linear and dose-proportional manner over the range of 0.01 to 0.5 mg/kg. Greater than 95% of patisiran in the circulation is associated with the lipid complex. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, steady state is reached by 24 weeks of treatment. The estimated mean ± SD steady state peak concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_τ) were 7.15 ± 2.14 µg/mL, 0.021 ± 0.044 µg/mL, and 184 ± 159 µg·h/mL, respectively. The accumulation of AUC_τ was 3.2-fold at steady state, compared to the first dose. In the placebo-controlled study, inter-patient variability in patisiran exposure did not result in differences in clinical efficacy (mNIS+7 change from baseline) or safety (adverse events, serious adverse events).

Distribution

Plasma protein binding of ONPATTRO is low, with ≤2.1% binding observed *in vitro* with human serum albumin and human α1-acid glycoprotein. ONPATTRO distributes primarily to the liver. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, the mean ± SD steady state volume of distribution of patisiran (V_{ss}) was 0.26 ± 0.20 L/kg.

Elimination

The terminal elimination half-life (mean ± SD) of patisiran is 3.2 ± 1.8 days. Patisiran is mainly cleared through metabolism, and the total body clearance (mean ± SD) at steady state (CL_{ss}) is 3.0 ± 2.5 mL/h/kg.

Metabolism

Patisiran is metabolized by nucleases to nucleotides of various lengths.

Excretion

Less than 1% of the administered dose of patisiran is excreted unchanged into urine.

Specific Populations

Age, race (non-Caucasian vs. Caucasian), sex, and prior liver transplantation had no impact on the steady state pharmacokinetics of patisiran or TTR reduction. Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR ≥30 to <90 mL/min/1.73m^2) or mild hepatic impairment (bilirubin ≤1 x ULN and AST >1 x ULN, or bilirubin >1.0 to 1.5 x ULN) on patisiran exposure or TTR reduction. ONPATTRO has not been studied in patients with severe renal impairment, end-stage renal disease, or moderate or severe hepatic impairment.

Drug Interaction Studies

No formal clinical drug interaction studies have been performed. The components of ONPATTRO are not inhibitors or inducers of cytochrome P450 enzymes or transporters at clinically relevant plasma concentrations. Patisiran is not a substrate of cytochrome P450 enzymes. In a population pharmacokinetic analysis, concomitant use of strong or moderate CYP3A inducers and inhibitors did not impact the pharmacokinetic parameters of patisiran. ONPATTRO is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Patisiran-LC was not carcinogenic in TgRasH2 mice when administered at intravenous (IV) doses of 0, 0.5, 2, or 6 mg/kg every two weeks for 26 weeks.

Mutagenesis

Patisiran-LC was negative for genotoxicity in *in vitro* (bacterial mutagenicity assay, chromosomal aberration assay in human peripheral blood lymphocytes) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Intravenous (IV) administration of patisiran-LC (0, 0.03, 0.1, or 0.3 mg/kg) or a rodent-specific (pharmacologically active) surrogate (0.1 mg/kg) to male rats every two weeks prior to and throughout mating to untreated females produced no adverse effects on fertility.

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (1.5 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or on embryofetal development.

Intravenous administration of patisiran-LC (0, 0.3, 1, or 2 mg/kg) to adult monkeys every three weeks for 39 weeks produced no adverse effects on male reproductive organs or on sperm morphology or count.

14 CLINICAL STUDIES

The efficacy of ONPATTRO was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis (NCT 01960348). Patients were randomized in a 2:1 ratio to receive ONPATTRO 0.3 mg/kg (N=148) or placebo (N=77), respectively, via intravenous infusion once every 3 weeks for 18 months. All patients received premedication with a corticosteroid, acetaminophen, and H1 and H2

blockers. Ninety-three percent of ONPATTRO-treated patients and 62% of placebo-treated patients completed 18 months of the assigned treatment.

The primary efficacy endpoint was the change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7). The mNIS+7 is an objective assessment of neuropathy and comprises the NIS and Modified +7 (+7) composite scores. In the version of the mNIS+7 used in the trial, the NIS objectively measures deficits in cranial nerve function, muscle strength, and reflexes, and the +7 assesses postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology. The maximum possible score was 304 points, with higher scores representing a greater severity of disease.

The clinical meaningfulness of effects on the mNIS+7 was assessed by the change from baseline to Month 18 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The version of the Norfolk QoL-DN that was used in the trial had a total score range from -4 to 136, with higher scores representing greater impairment.

The changes from baseline to Month 18 on both the mNIS+7 and the Norfolk QoL-DN significantly favored ONPATTRO (Table 2, Figure 1 and Figure 3). The distributions of changes in mNIS+7 and Norfolk QoL-DN scores from baseline to Month 18 by percent of patients are shown in Figure 2 and Figure 4, respectively.

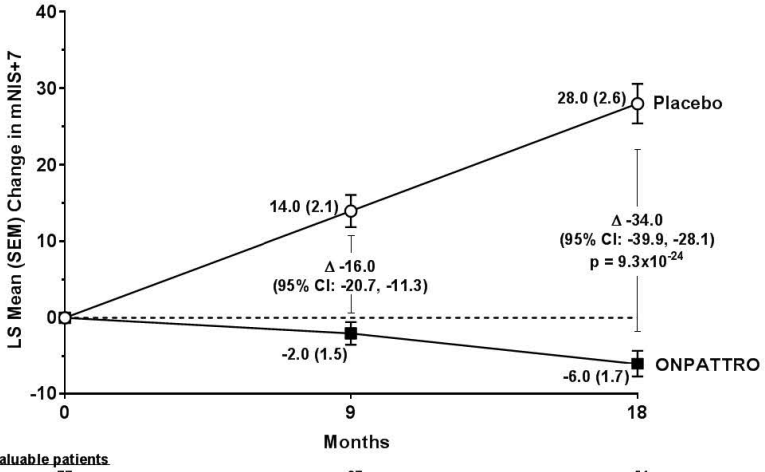
The changes from baseline to Month 18 in modified body mass index (mBMI) and gait speed (10-meter walk test) significantly favored ONPATTRO (Table 2).

Table 2: Clinical Efficacy Results from the Placebo-Controlled Study

Endpoint[a]	Baseline, Mean (SD)		Change from Baseline to Month 18, LS Mean (SEM)		ONPATTRO-Placebo Treatment Difference, LS Mean (95% CI)	*p*-value
	ONPATTRO N=148	Placebo N=77	ONPATTRO	Placebo		
Primary						
mNIS+7 [b]	80.9 (41.5)	74.6 (37.0)	-6.0 (1.7)	28.0 (2.6)	-34.0 (-39.9, -28.1)	$p<0.001$
Secondary						
Norfolk QoL-DN [b]	59.6 (28.2)	55.5 (24.3)	-6.7 (1.8)	14.4 (2.7)	-21.1 (-27.2, -15.0)	$p<0.001$
10-meter walk test (m/sec) [c]	0.80 (0.40)	0.79 (0.32)	0.08 (0.02)	-0.24 (0.04)	0.31 (0.23, 0.39)	$p<0.001$
mBMI [d]	970 (210)	990 (214)	-3.7 (9.6)	-119 (14.5)	116 (82, 149)	$p<0.001$

CI, confidence interval; LS, least squares; mBMI, modified body mass index; mNIS, modified Neuropathy Impairment Score; QoL-DN, Quality of Life – Diabetic Neuropathy; SD, standard deviation; SEM, standard error of the mean
[a] All endpoints analyzed using the mixed-effect model repeated measures (MMRM) method.
[b] A lower value indicates less impairment/fewer symptoms.
[c] A higher number indicates less disability/less impairment.
[d] mBMI: body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L); a higher number indicates better nutritional status.

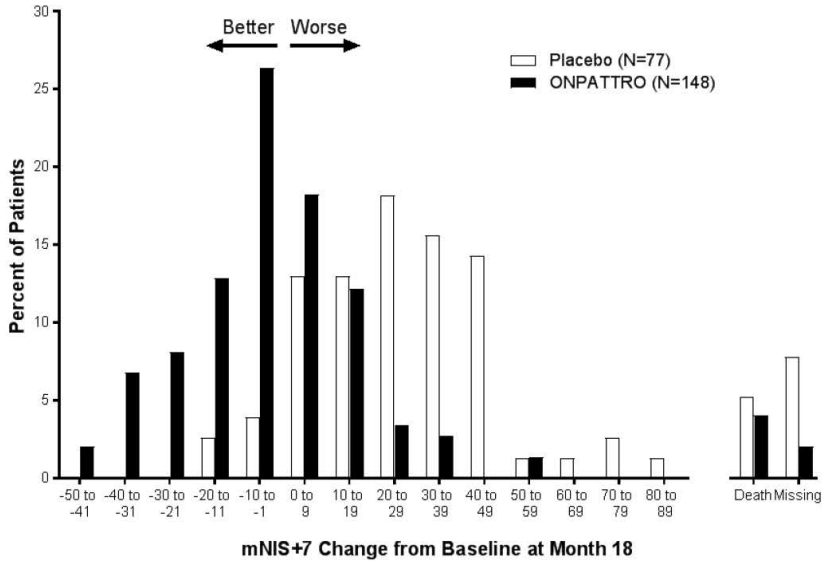
Figure 1: Change from Baseline in mNIS+7



N of evaluable patients			
Placebo	77	67	51
ONPATTRO	148	141	137

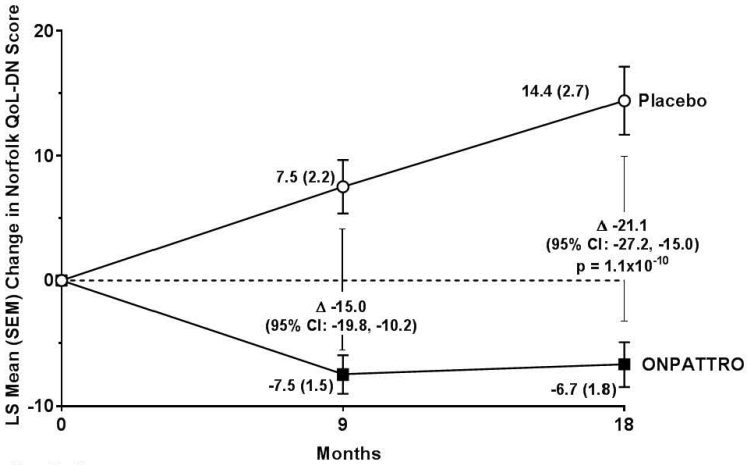
A decrease in mNIS+7 indicates improvement.
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for ONPATTRO – placebo.

Figure 2: Histogram of mNIS+7 Change from Baseline at Month 18



mNIS+7 change scores are rounded to the nearest whole number; last available post-baseline scores were used.
Categories are mutually exclusive; patients who died before 18 months are summarized in the "Death" category only.

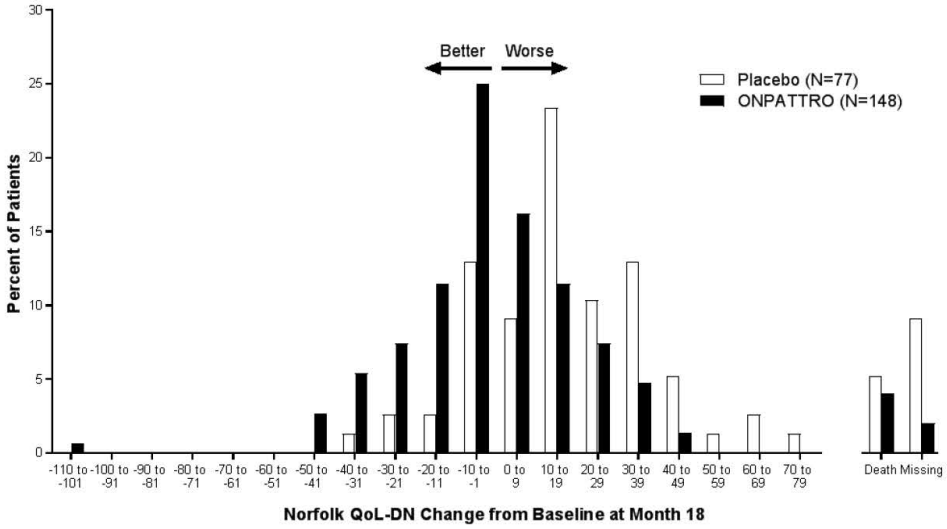
Figure 3: Change from Baseline in Norfolk QoL-DN Score



N of evaluable patients			
Placebo	76	65	48
ONPATTRO	148	141	136

A decrease in Norfolk QoL-DN score indicates improvement.
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for ONPATTRO – placebo.

Figure 4: Histogram of Norfolk QoL-DN Change from Baseline at Month 18



Norfolk QoL-DN change scores are rounded to the nearest whole number; last available post-baseline scores were used.
Categories are mutually exclusive; patients who died before 18 months are summarized in the "Death" category only.

Patients receiving ONPATTRO experienced similar improvements relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, Val30Met mutation status, and disease stage.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ONPATTRO is a sterile, preservative-free, white to off-white, opalescent, homogeneous solution for intravenous infusion supplied as a 10 mg/5 mL (2 mg/mL) solution in a single-dose glass vial. The vial stopper is not made with natural rubber latex. ONPATTRO is available in cartons containing one single-dose vial each.

The NDC is: 71336-1000-1.

16.2 Storage and Handling

Store at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard vial if it has been frozen.

If refrigeration is not available, ONPATTRO can be stored at room temperature up to 25°C (up to 77°F) for up to 14 days.

For storage conditions of ONPATTRO after dilution in the infusion bag, see Dosage and Administration (2.3).

17 PATIENT COUNSELING INFORMATION

Infusion-Related Reactions

Inform patients about the signs and symptoms of infusion-related reactions (e.g., flushing, dyspnea, chest pain, syncope, rash, increased heart rate, facial edema). Advise patients to contact their healthcare provider immediately if they experience signs and symptoms of infusion-related reactions *[see Warnings and Precautions (5.1)]*.

Recommended Vitamin A Supplementation

Inform patients that ONPATTRO treatment leads to a decrease in vitamin A levels measured in the serum. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) and refer them to an ophthalmologist if they develop these symptoms *[see Warnings and Precautions (5.2)]*.

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking ONPATTRO they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus. Encourage patients to enroll in the ONPATTRO pregnancy exposure registry if they become pregnant while taking ONPATTRO *[see Use in Specific Populations (8.1)]*.

Manufactured for: Alnylam Pharmaceuticals, Inc.
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11040 Roselle Street, San Diego, CA 92121

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