FDA Briefing Document

sNDA 210922/015

Drug name: patisiran

Applicant: Alnylam Pharmaceuticals, Inc.

Cardiovascular and Renal Products Advisory Committee Meeting

09/13/2023

Division of Cardiology and Nephrology, Office of Cardiology, Hematology, Endocrinology and Nephrology

Division of Biometrics II, Division of Biometrics III, Division of Analytics and Informatics, Office of Biostatistics

Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought concerns to the Advisory Committee regarding the clinical meaningfulness of a small treatment effect in a single pivotal trial upon which the efficacy of patisiran for the treatment of cardiomyopathy of wild type or inherited transthyretin amyloidosis (ATTR) is based. We wish to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

6MWT	6-minute walk test
AC	Advisory Committee
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloidosis cardiomyopathy
ATTRv	hereditary transthyretin-mediated amyloidosis
ATTRwt	wild-type transthyretin-mediated amyloidosis
CI	confidence interval
CV	cardiovascular
DCN	Division of Cardiology and Nephrology
DNP	Division of Neurology Products
FDA	Food and Drug Administration (alternatively, *the Agency*)
HF	heart failure
HL	Hodges-Lehmann
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire Overall Summary Score
LV	left ventricle
MAR	missing at random
MI	multiple imputation
MMRM	mixed-effects model repeated measures
mNIS+7	modified Neuropathy Impairment Score +7
NYHA	New York Heart Association
SAE	serious adverse event
SAP	Statistical Analysis Plan
siRNA	small interfering ribonucleic acid
sNDA	supplemental New Drug Application
TTR	transthyretin
wATTR	wild-type transthyretin-mediated amyloidosis

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss:

- Whether Onpattro (patisiran) has clinically meaningful benefits for the treatment of cardiomyopathy of wild-type transthyretin mediated (ATTRwt) or hereditary transthyretin-mediated (ATTRv) amyloidosis.

1.2 Context for Issues to Be Discussed at the AC

Transthyretin amyloidosis (ATTR) is a rare, underrecognized and progressively debilitating systemic disease caused by the deposition of toxic misfolded amyloid fibrils in various organs altering structural integrity and function and increasing morbidity and mortality. Increased awareness and advancements in diagnostic modalities have resulted in patients being diagnosed earlier. However, despite earlier diagnosis, cardiac involvement is associated with worse prognosis (median survival of 2 to 5 years)(Ioannou et al. 2022).

Cardiomyopathy is a common manifestation of ATTR (ATTR-CM) with structural changes and physiologic derangements resulting in arrhythmias, conduction abnormalities, and decompensated heart failure. Tafamadis is the only FDA-approved treatment for ATTR-CM and is indicated to reduce cardiovascular mortality and cardiovascular-related hospitalization. The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Guideline for the Management of Heart Failure recommends the use of tafamidis in patients with ATTRwt or ATTRv and NYHA class I to III heart failure symptoms to reduce cardiovascular morbidity and mortality (Class of Recommendation 1a)(Heidenreich et al. 2022).

Patisiran is already approved for the treatment of polyneuropathy of ATTRv. This supplemental marketing application is seeking to expand the approval of patrisiran to patients with cardiomyopathy of ATTRwt or ATTRv based on one phase 3 trial (APOLLO-B).

1.3 Brief Description of Issues for Discussion at the AC

APOLLO-B is a multicenter, randomized, double blind, placebo-controlled trial in adults with ATTR-CM. The trial randomized 360 patients in a (1:1) ratio to patisiran 0.3 mg/kg dose administered intravenously (capped at 30 mg for patients weighing 100 kg or more) every 3 weeks (181 patients) or placebo (179 patients). This is the same dose approved for the polyneuropathy indication. Twenty-five percent of the subjects were on background treatment with tafamidis, which became available in the United States 4 months before APOLLO-B was initated and 6 months before the first subject was enrolled. The trial appears to have been well-conducted.

The primary efficacy endpoint was the change from baseline in the 6-minute walk test (6MWT) at Month 12 in patisiran-treated patients compared to placebo. The first secondary endpoint was the change from baseline at Month-12 in the Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS).

Other secondary endpoints were a composite endpoint of all-cause mortality, frequency of cardiovascular (CV) events (CV hospitalizations and urgent heart failure [HF] visits) and change from baseline in 6MWT; a composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the double-blind period in patients not on tafamidis at baseline, and a composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the double-blind period in the overall population. The trial was not powered for a mortality endpoint.

The 6MWT, a performance outcome (PerfO), is a practical simple test that measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise. The results of the APOLLO-B trial showed a statistically significant but small treatment effect for the primary efficacy endpoint. Subjects treated with patisiran experienced an average decrease in their 6MWD of 13 m at Month 12 from an average 6MWD of 361 m at baseline, while subjects in the placebo arm experienced an average decrease in their 6MWD of 31 m at Month 12 from an average 6MWD of 375 m at baseline. The change from baseline at Month 12 in 6MWT (Hodges-Lehmann [HL] estimate of median difference) for patisiran vs. placebo was 14.7 m (95% confidence interval [CI] 0.7, 28.7; p-value 0.04). Literature has reported a range of meaningful differences (22 to 90 m) reflective of the heterogeneity in cardiomyopathy patients (Mathai et al. 2012; Shoemaker et al. 2012)..

The KCCQ, a patient-reported outcome (PRO) and a disease-specific measure for HF, is a 23-item self-administered questionnaire developed to measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how heart failure impacts their quality of life (QOL) within a 2-week recall period. The KCCQ-OSS has a 0-100 transformed score range where higher scores reflect better health status (based on the Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life and Social Limitations Domain Scores). In the APOLLO-B trial,the treatment effect for the first secondary efficacy endpoint, change from baseline at Month 12 in KCCQ-OSS was small (3.7 points on a 0 to 100 transformed score range; 95% CI 0.2, 7.2; p-value 0.04). On average, subjects treated with patisiran had an increase in KCCQ-OSS of 0.3 points at Month 12 from the average baseline score of 69.8 points, while subjects in the placebo arm had a decrease in KCCQ-OSS of 3.4 points at Month 12 from the average baseline score of 70.3 points.

FDA guidances[1] recommend the use of anchor-based methods[2] to directly incorporate subjects' perspectives to help interpret the clinical meaningfulness of clinical outcome assessment (COA) based endpoints. Other methods, such as qualitative exit interviews or surveys[3], can be used in addition to or instead of anchor-based methods (e.g., when appropriate anchors do not exist). However, approaches such as distribution-based methods using an effect size or a standard deviation, or model-based approaches, are inappropriate as a primary method to determine clinical meaningfulness as they do not

[1] FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, December 2009; FDA Draft Guidance for Industry, Food and Drug Administration Staff and Other Stakeholders, Patient-Focused Drug Development: Incorportaing Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making, April 2023

[2] An anchor scale is some external variable, not derived from the COA whose scores require interpretation, for which meaningful differences are directly interpratble or already known.

[3] FDA Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders, Patient-Focused Drug Development: Methods to Identify What Is Important to Patients, February 2022

directly take into account the subject's perspective. In the APOLLO-B trial, there were neither appropriate anchor scales administered nor qualitative data collected to aid in the evaluation of the clinical meaningfulness of the treatment effects of the 6MWT or the KCCQ-OSS, from the perspective of subjects.

In a prespecified subgroup analysis by background tafamidis use, there was no evidence of a treatment effect in subjects on background tafamidis. The HL median difference between patisiran and placebo in change from baseline at Month 12 in 6MWT was -4.2 m (95% CI -29.0, 20.5) for the subjects on background tafamidis compared to 20.4 m (95% CI 4.1, 36.8) for the subjects not on background tafamidis therapy. A difference in the size of treatment effect was also observed in the change from baseline at Month 12 in KCCQ-OSS. The LS mean difference between patisiran and placebo was 2.1 points (95% CI -4.9, 9.0) in subjects on background tafamidis compared to 4.3 points (95% CI 0.2, 8.4) in subjects not on background tafamidis therapy.

The safety profile of patisiran was adequately characterized in the APOLLO-B trial and was supported by the safety data from APOLLO (the trial that led to the approval of patisiran for the polyneuropathy indication in the ATTRv patient population) and HELIOS-A data (study of vutrisiran in patients with ATTRv amyloidosis with polyneuropathy, where patisiran was used as a reference comparator arm). The main side effects were infusion-related reactions, lowered vitamin A levels (that can be treated with vitamin A supplementation), myalgias and arthralgias.

In summary, APOLLO-B was a well-designed and executed clinical trial meeting its pre-specified objectives. Although the primary efficacy endpoint of 6MWT and key secondary endpoint of KCCQ-OSS were statistically significant, the effects of patisiran compared to placebo on both endpoints were small, of questionable clinical meaningfulness, and may not be detectable by patients . Moreover, the effects of patisiran compared to placebo on 6MWT appeared confined to patients not on background therapy with tafamidis.

1.4 Draft Points for Consideration

We ask the AC to opine on the following issues raised during the review of the APOLLO-B trial, stated here:

- The review team believes that there are no fundamental problems with the conduct of the APOLLO-B trial. Does the Advisory committee agree?
- The review team believes that the safety profile of patisiran for the treatment of ATTR-CM has been adequately characterized. Does the Advisory committee agree?
- Do the results of the APOLLO-B trial show evidence of a clinically meaningful treatment effect of patisiran in patients with ATTR-CM?
- Is there a population of patients for which the results of APOLLO-B trial support use of patisiran as monotherapy or in combination with tafamidis for the treatment of ATTR-CM?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Transthyretin amyloidosis (ATTR) is an underrecognized, progressively debilitating, and life-threatening infiltrative systemic disease caused by the deposition of misfolded transthyretin (TTR) tetramer proteins

into unstable and insoluble monomers with amyloiogenic properties. ATTR can be acquired (wild-type; ATTRwt), commonly seen in older patients, or inherited (ATTRv) in an autosomal dominant pattern with variable penetrance. Mutations in the *TTR* gene or aging promote proteolytic remodeling and dissociation of transthyretin tetramers into monomers. These subsequently misfold and aggregate to form amyloid fibrils, which are deposited in tissues of various organs, altering their structural integrity and, over time, their functions. ATTR is associated with increased morbidity and mortality(Gonzalez-Lopez et al. 2015).

While the true prevalence of ATTRwt is unknown, autopsy case series have identified amyloid fibrils in 25% of adults over the age of 80 years. It has been estimated that ATTRwt accounts for up to 13% of patients diagnosed with heart failure (HF) with preserved ejection fraction, 16% of patients undergoing percutaneous aortic valve replacement, and up to 5% of patients with presumed hypertrophic cardiomyopathy (Maurer et al. 2018). While the diagnosis of ATTRwt can often be missed due to the heterogeneity of its presentation, improvements in noninvasive imaging techniques have enhanced the ability to correctly diagnose ATTR when tissue procurement is not feasible (Damy et al. 2016; Castano et al. 2017; Witteles et al. 2019). The global prevalence of ATTRv is estimated to be 40,000 to 50,000 patients (Hawkins et al. 2015).

While amyloid fibrils can deposit in any structure, involvement of the heart, kidneys, liver, nerves, gastrointestinal tract, lungs, muscles, and/or skin is typical. Cardiomyopathy is a common manifestation of ATTR (ATTR-CM) caused by deposition of misfolded amyloid fibrils in the myocardial extracellular space, resulting in increased wall thickness, biatrial enlargement, impaired ventricle relaxation, and elevated filling pressures.

Patients typically present with progressively worsening symptoms of decompensated HF, elevated cardiac biomarkers out of proportion to symptoms, arrhythmias, and conduction abnormalities. Cardiac involvement is associated with a worse prognosis (median survival of 2 to 5 years). Certain inherited mutations present predominantly with cardiomyopathy (Val122Ile) or can overlap with polyneuropathy (Thr60Ala). In patients with ATTR-CM, as the disease progresses, adverse remodeling of the ventricle from the toxic effects of the amyloid fibrils results in systolic dysfunction, low cardiac output, and pulmonary and systemic congestion. These effects manifest as fatigue, impaired gait and balance, limited mobility, inability to perform activities of daily living, and recurrent hospitalizations for HF, infections, falls, or embolic events. Death in most cases is cardiac (sudden death and HF).

Tafamidis meglumine is the only drug approved in the United States for the treatment of patients with ATTR-CM. Its approval was based on data from the ATTR-ACT study—a randomized, double-blind, placebo-controlled, phase 3 study involving adults with ATTR-CM (wild-type or inherited)(Maurer et al. 2018). Tafamidis is a transthyretin tetramer stabilizer. It binds to one of the two T4 binding sites on the tranthyretin tetramer, thereby stabilizing the tetramer and preventing its dissociation into monomers. Compared to placebo, tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations, slowed the decline in functional capacity as assessed using 6-minute walk test, and slowed the decline in Kansas City Cardiomyopathy Questionnaire scores[4] . The safety profile for Tafamidis was similar to placebo.

[4] The KCCQ, a disease-specific measure for HF, is a 23-item self-administered questionnaire developed to measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QOL) within a 2 week recall period.

Prior to the availability of other less-invasive therapies for patients with ATTRv, organ transplantation was once the only intervention available to improve the outcomes of patients with ATTRv. Orthotopic liver transplantation from a non-ATTR donor suppresses production of the mutated transthyretin protein and prevents disease progression. Unfortunately, the disease can still progress and liver transplantation does not prevent extrahepatic TTR production in the choroid plexus and progression of central nervous system (CNS) or ocular disease. While uncommon, dual organ transplantation (heart-liver) has been performed in patients with hereditary ATTR-CM. However, due to the limited donor pool from which to select and the patient selection variables (age, number and extent of disease with organ involvement, and overall prognosis) this option may only be available to few patients. In patients with cardiomyopathy-predominant inherited ATTR-CM, such as those with Val122Ile, this option is more feasible. Patients with ATTRwt with cardiomyopathy tend to be older, with multiple comorbid conditions; organ transplant is not commonly performed in such individuals (Muchtar et al. 2021).

Small interfering RNA (siRNA) therapies have been approved for the treatment of patients with polyneuropathy of ATTRv. Currently, two products are approved in the United States (patisiran and vutrisiran). These share a mechanism of action—cleavage and degradation of the transthyretin mRNA in the cytoplasm of hepatocytes, thereby suppressing the production of the wild-type and variant TTR protein. There are no approved siRNA therapies for ATTR-CM.

Antisense oligonucleotides are another class of drugs approved for the treatment of patients with polyneuropathy of ATTRv. Inotersen (Tegsedi™) is the only antisense oligonucleotide currently approved in the United States for the treatment of patients with ATTR amyloidosis. Inotersen binds to TTR mRNAs and degrades the mRNA transcripts via the RNAseH pathway, thereby halting TTR production. The safety profile of this drug was concerning for thrombocytopenia and glomerulonephritis, resulting in the implementation of enhanced monitoring with use. Antisense oligonucleotides are not approved for the treatment of ATTR-CM.

Diflunisal is a nonsteroidal anti-inflammatory drug that binds and stabilizes transthyretin protein, thereby inhibiting tetrameric TTR dissociation and suppressing amyloidogenesis. The efficacy of diflunisal has been tested in animal and small-scale human studies. Concerns for the safety profile of diflunisal in patients with cardiovascular disease and renal dysfunction, have limited further development of this therapy but it is used off-label in patients with ATTR-CM without access to or unable to afford tafamidis (Lohrmann et al. 2020).

Tafamidis was the first FDA approved therapy for treatment of patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) on May 3, 2019. Tafamidis is a small molecule stabilizer of the transthyretin (TTR) tetramer that prevents TTR from dissociating into amyloidogenic monomers. The approval of tafamidis transformed the treatment landscape for patients with ATTR-CM (wild-type and variant), and it is now considered the standard of care. While tafamidis targets pre-existing wild-type or variant transthyretin protein before its dissociation and aggregation into amyloidogenic monomers, it does not affect amyloid fibrils deposited in tissue or their production in the liver. Therapies that target transthyretin synthesis could show synergism when combined with tafamidis by reducing amyloid fibril production by another mechanism.

2.2 Pertinent Drug Development and Regulatory History

Patisiran is currently approved in the United States for the treatment of polyneuropathy (PN) of ATTRv amyloidosis in adults based on the results of APOLLO, an 18-month, randomized, double-blind, placebo-

controlled study involving adults with ATTRv-PN. The APOLLO study compared a 0.3 mg/kg dose of patisiran administered intravenously (IV) every 3 weeks to placebo on the change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7)[5] (primary efficacy endpoint) and the Norfolk-Quality of Life-Diabetic Neuropathy Scale score[6] (key secondary endpoint). The APOLLO study demonstrated a statistically significant and clinically meaningful treatment effect on the mNIS+7 score (LS mean difference -34 points [p<0.001]) and the Norfolk-Quality of Life-Diabetic Neuropathy Scale (LS mean difference -21 points [p<0.001]). Patisiran administration also resulted in a rapid and sustained reduction in TTR level (mean percentage change from baseline) as early as 3 weeks (75%), which persisted at Month 12 (87%).

Exploratory endpoints assessed in the APOLLO study included cardiac structure and function indices based on echocardiograms and levels of cardiac biomarkers (troponin I and NTproBNP). Other variables assessed by echocardiography under the exploratory endpoint included the left ventricle (LV) wall thickness, LV mass, global longitudinal strain, LV ejection fraction, diastolic function, and LV end-diastolic volume. These assessments were performed in the cardiac subpopulation (90 of the patisiran-treated subjects and 36 of those on placebo) at baseline and at 9 and 18 months.

The Division of Cardiology and Nephrology (DCN) evaluated the cardiac data from the APOLLO trial and concluded that there was no substantial evidence of a cardiac treatment effect. Post hoc cardiovascular (CV) outcome analyses from APOLLO showed trends favoring patisiran in subjects with polyneuropathy-predominant ATTR (APOLLO excluded subjects who were NYHA class III or IV). DCN concluded that a new trial in patients with ATTR-CM would be needed to support a cardiomyopathy claim. This new trial – APOLLO-B – is the focus of the advisory committee meeting.

Relevant Regulatory History for the Cardiac Indication

June 14, 2012

- Patisiran received orphan drug designation status

December 11, 2018

- Discussions between the Agency and the Applicant on endpoints for a cardiomyopathy claim:
  - The study should demonstrate a meaningful improvement in a clinical outcome such as cardiovascular death and hospitalization for HF. Alternatively, meaningful improvements in functional testing or quality-of-life assessments could suffice if a predetermined level of harm with respect to death and hospitalization could be excluded.

[5] The mNIS+7 is an objective assessment of neuropathy that objectively measures deficits in cranial nerve function, muscle strength, reflexes, 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.

[6] 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 Applicant expressed concerns that in the polyneuropathy-predominant population of ATTR amyloidosis, it is difficult to separate functional improvement that is due to neurological improvement from functional improvement due to cardiac improvement.
- The Agency provided the following guidance to the Applicant:
  - *If you believe that your post hoc assessment of death and hospitalization from APOLLO is real in its magnitude and reproducible in subjects with cardiac involvement, we strongly encourage you to incorporate a death and hospitalization composite endpoint into your alpha-conserving analysis plan…among subjects with scintigraphy or endomyocardial biopsy-proven cardiac involvement. Alternatively, improved functional testing or quality of life could be assessed in a separate trial of ATTR-CM predominant subjects…with coprimary endpoints of 6-minute walk distance and TTR (change from baseline to Month 18).*

- The Applicant engaged DCN on the approach to address study design if another tetramer stabilizer is approved in the United States subsequent to initiation of the APOLLO-B study. The Applicant agreed that it will be necessary to reconsent previously enrolled subjects.

March 9, 2019

- Follow-up discussions to address the addition of tafamidis to the APOLLO-B study:
  - DCN indicated that a placebo-controlled clinical study would need to be reconsented if another drug were approved with morbidity or mortality claims applicable to the population under study.
  - DCN did not agree with the Applicant's proposal to interpolate the 6-month 6-minute walk test (6MWT) results for subjects who chose to start tafamidis more than 1.5 months before Month 6 because it might attribute to patisiran beneficial effects on the 6MWT results that were due to exposure to tafamidis (which has been shown to positively affect such results). The Division required all tafamidis drop-ins to undergo 6MWT at the time of tafamidis drop-in.
  - The Applicant was advised to consider imputation methods for missing data for 6MWT and the KCCQ endpoints.

On December 8, 2022, Alnylam Pharmaceuticals, Inc. (Alnylam) submitted an efficacy supplement to NDA 210922 (patisiran) with the results from APOLLO-B for the proposed indication to treat the cardiomyopathy of ATTRwt or ATTRv amyloidosis in adults.

3 Summary of Issues for the AC

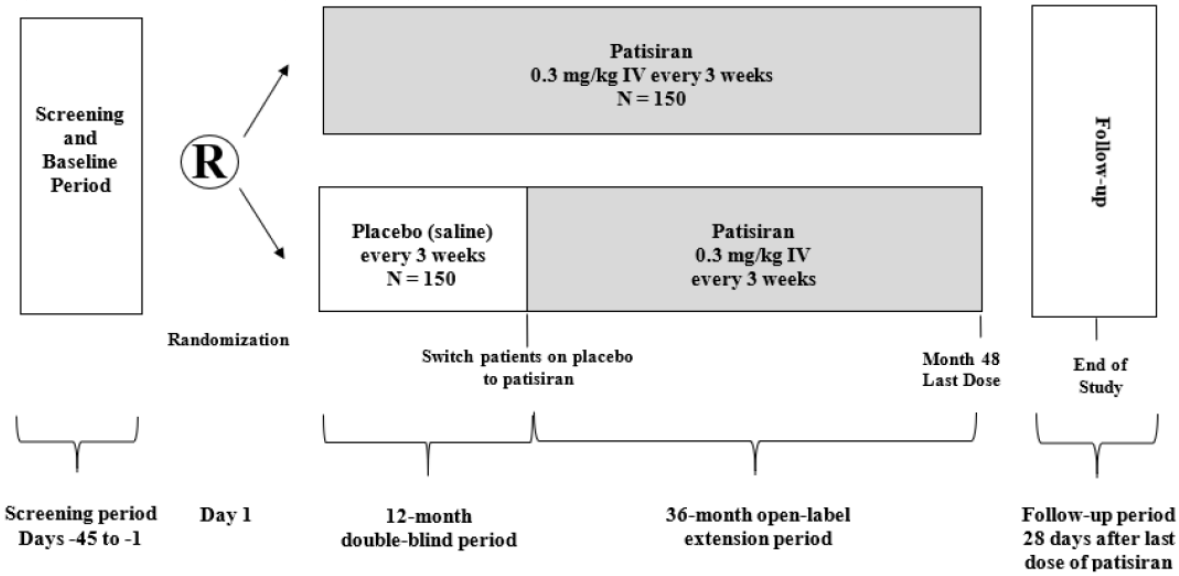
3.1 Efficacy Issues

The main issue is whether the treatment effects in APOLLO-B are clinically meaningful for the ATTR-CM population.

3.1.1 Sources of Data for Efficacy

APOLLO-B (Study 011) randomized a total of 360 subjects (181 to patisiran and 179 to placebo). Randomization was stratified by (1) use of tafamidis (yes versus no), (2) genotype (ATTRv versus wtATTR), and (3) NYHA Class I or II and age <75 years (yes versus no). The study design of APOLLO-B is shown in Figure 1.

Figure 1. APOLLO-B (Study 011) Study Design



Source: Figure 1 of the Clinical Study Report
Abbreviations: IV, intravenously; N, number of subjects

The overall Type I error for the study was 0.05 for two-sided testing. The primary and secondary endpoints were tested in the following prespecified hierarchical order, with testing stopped if the findings on one of these endpoints were not statistically significant:

(1) (Primary) 6MWT change from baseline at Month 12.
(2) KCCQ-OSS[7] change from baseline at Month 12.
(3) 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 double-blind period.
(4) Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month double-blind period in subjects not on tafamidis at baseline.
(5) Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the 12-month double-blind period in the overall population.

There was no multiplicity adjustment for exploratory endpoints. Note that the study was powered to assess the primary endpoint and the KCCQ-OSS secondary endpoint, but not the other secondary endpoints.

All efficacy analyses were performed on the modified intent-to-treatment population, which included all randomized subjects who received any amount of study drug. This consisted of 359 subjects (181 in the patisiran arm and 178 in the placebo arm). Efficacy analyses were performed according to the treatment to which the subjects were randomized. All safety analyses were performed on the safety analysis population, which comprised all randomized subjects who received any amount of study drug, and analyses were performed according to the treatment received.

[7] The KCCQ-OSS has a 0-100 transformed score range, where higher scores reflect better health status (based on the Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life and Social Limitations Domain Scores).

3.1.2 Efficacy Summary

Subject Disposition

A total of 360 subjects were randomized into the trial (Table 1). A total of 359 subjects were included in the efficacy and safety analyses. One subject randomized to placebo was not treated. About 7% of the randomized subjects discontinued the study during the 12-month double-blind period. The primary reasons for study discontinuation were death, subject withdrawal, adverse event, and physician decision.

Table 1. Subject Disposition During the 12-Month Double-Blind Period, APOLLO-B

Disposition	Patisiran N (%)	Placebo N (%)
Randomized	181	179
Treated	181 (100.0%)	178 (99.4%)
Discontinued treatment	12 (6.6%)	13 (7.3%)
Primary reason for treatment discontinuation		
Adverse event	3 (1.7%)	5 (2.8%)
Death	3 (1.7%)	3 (1.7%)
Other	6 (3.3%)	4 (2.2%)
Physician decision	0	1 (0.6%)
Discontinued study	11 (6.1%)	13 (7.3%)
Primary reason for study discontinuation		
Adverse event	1 (0.6%)	4 (2.2%)
Death	4 (2.2%)	4 (2.2%)
Physician decision	0	2 (1.1%)
Withdrawal by subject	6 (3.3%)	3 (1.7%)

Source: Statistical Reviewer
Percentages in parentheses are relative to the total number of subjects randomized.
Abbreviation: N, number of subjects

Baseline Demographics and Disease Characteristics

Baseline demographic and disease characteristics were similar between the study arms (Table 2). The mean age of the study population was 75 years (range 41 to 85 years), 77% were white, 84% were non-Hispanic or Latino, and 89% were male. A total of 27% of the subjects were from the United States.

Of the subjects, 80% had wtATTR amyloidosis and 20% had ATTRv amyloidosis. The mean age at ATTR amyloidosis diagnosis was 74 years (range 41 to 85 years), 25% of subjects were on tafamidis at baseline, 85% had NYHA Class II HF, 68% had ATTR amyloidosis disease stage 1, and 25% had ATTR amyloidosis disease stage 2.

Table 2. Baseline Demographic and Disease Characteristics, APOLLO-B

Characteristic	Patisiran N=181	Placebo N=178
Sex, n (%)		
Female	20 (11.0)	18 (10.1)
Male	161 (89.0)	160 (89.9)
Age at screening (years)		
Mean (SD)	75.3 (6.5)	74.2 (7.8)
Median	76.0	76.0
Minimum, maximum	47.0, 85.0	41.0, 85.0

Characteristic	Patisiran N=181	Placebo N=178
Age group, n (%) (years)		
<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)
Race, n (%)		
Asian	23 (12.7)	15 (8.4)
Black or African American	16 (8.8)	15 (8.4)
Not reported	1 (<1)	4 (2.2)
Other	3 (1.7)	4 (2.2)
White	138 (76.2)	140 (78.7)
Ethnicity, n (%)		
Hispanic or Latino	21 (11.6)	20 (11.2)
Not Hispanic or Latino	153 (84.5)	150 (84.3)
Not reported	5 (2.8)	4 (2.2)
Unknown	2 (1.1)	4 (2.2)
Region, n (%)		
North America	45 (24.9)	52 (29.2)
Rest of World	66 (36.5)	59 (33.1)
Western Europe	70 (38.7)	67 (37.6)
Country, n (%)		
Other	136 (75.1)	126 (70.8)
United States	45 (24.9)	52 (29.2)
ATTR amyloidosis type, n (%)		
ATTRv	37 (20.4)	34 (19.1)
wtATTR	144 (79.6)	144 (80.9)
Time since ATTR amyloidosis diagnosis (years)		
Mean (SD)	1.5 (1.6)	1.1 (1.5)
Median	0.8	0.4
Minimum, maximum	0.0, 6.4	0.0, 9.7
Age at ATTR diagnosis (years)		
Mean (SD)	74.2 (6.7)	73.5 (8.0)
Median	75.0	75.0
Minimum, maximum	47.0, 85.0	41.0, 85.0
Baseline tafamidis use, n (%)		
No	135 (74.6)	133 (74.7)
Yes	46 (25.4)	45 (25.3)
ATTR amyloidosis disease stage, n (%)		
Stage 1 (lower risk)	124 (68.5)	120 (67.4)
Stage 2 (intermediate risk)	46 (25.4)	45 (25.3)
Stage 3 (higher risk)	11 (6.1)	13 (7.3)

Characteristic	Patisiran N=181	Placebo N=178
NYHA class, n (%)		
I	10 (5.5)	15 (8.4)
II	156 (86.2)	150 (84.3)
III	15 (8.3)	13 (7.3)
NT-proBNP (ng/L)		
Mean (SD)	2390 (1742)	2289 (1841)
Median	2008	1813
Minimum, maximum	288, 8530	273, 12234
PND score, n (%)		
0	96 (53.0)	109 (61.2)
1	63 (34.8)	55 (30.9)
2	22 (12.2)	14 (7.9)

Source: Statistical Reviewer

Abbreviations: ATTR, transthyretin-mediated amyloidosis; ATTRv, hereditary ATTR; N, number of subjects; n, number of subjects with specific characteristic; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; SD, standard deviation; wtATTR, wild-type ATTR

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline at Month 12 in 6MWT distance. Availability of the 6MWT data at Month 12 is summarized in Table 3. There were 166 (92%) patisiran-treated subjects and 161 (90%) placebo-treated subjects with neither missing nor censored assessments (treated as missing). Month 12 assessments were missing in four (2%) patisiran-treated subjects and eight (5%) placebo-treated subjects due to non-coronavirus disease 2019 (non-COVID-19) death and in one (0.6%) subject in each arm due to inability to walk. There were four (2%) patisiran-treated subjects and three (2%) placebo-treated subjects with censored Month 12 assessments. The main reason for censoring was that the assessment occurred on or after the onset of a COVID-19 serious adverse event (SAE) (two [1.1%] patisiran-treated and three [1.7%] placebo-treated subjects).

Table 3. Missing Data Summary for 6MWT at Month 12

Statistic	Patisiran N=181 n (%)	Placebo N=178 n (%)
Nonmissing, uncensored Month 12	166 (91.7)	161 (90.4)
Missing Month 12	11 (6.1)	14 (7.9)
Due to COVID-19	1 (0.6)	0
Due to non-COVID-19 death	4 (2.2)	8 (4.5)
Inability to walk due to progression of ATTR amyloidosis	1 (0.6)	1 (0.6)
Other	5 (2.8)	5 (2.8)

Statistic	Patisiran N=181 n (%)	Placebo N=178 n (%)
Censored Month 12	4 (2.2)	3 (1.7)
Assessment occurred on or after onset of COVID-19 SAE[1]	2 (1.1)	3 (1.7)
Timer stopped after ≤4 minutes	1 (0.6)	0
Unapproved walking aid	1 (0.6)	0

Source: Statistical Reviewer

Abbreviations: ATTR, transthyretin-mediated amyloidosis; AE, adverse event; COVID-19, coronavirus disease 2019; N, number of subjects; n, number of subjects with specific statistic; SAE, severe adverse event; 6MWT, 6-minute walking test

[1]If a subject experienced a COVID SAE after baseline and before the 6-month 6MWT assessment, the 6MWT assessments at months 6, 9, and 12 would be considered missing.

In the prespecified primary analysis method, missing due to non-COVID-19 death or unable to walk due to progression of ATTR amyloidosis was single-imputed as the worst 10th percentile change observed among all subjects in the 12-month double-blind period, capped by the worst possible change for the subject (0-baseline 6MWT). Cases of missing due to other reasons or censored data were multiply imputed assuming missing at random (MAR). The multiple imputation (MI) was conducted separately by treatment arm and baseline tafamidis use, including type of amyloidosis (ATTRv versus wATTR), NYHA class (I/II versus III), age at randomization (<75 versus ≥75 years), baseline NT-proBNP (≤3000 ng/L versus >3000 ng/L), baseline 6MWT, and change from baseline in 6MWT at Month 6, Month 9, and Month 12 in the model. The treatment effect was estimated by the stratified Hodges-Lehmann (HL) method (stratified by baseline tafamidis use) of the median difference between patisiran and placebo. The stratified HL was an estimate of the median value of all paired differences between observations in the patisiran versus placebo groups accounting for baseline tafamidis use, calculated using 100 imputed datasets.

We have moved away from using single imputation to address missing data in the primary analysis because doing so typically underestimates variability. Instead, MI is now recommended to quantify uncertainty when estimating missing values. Our preference for imputing values missing due to non-COVID-19 death or inability to walk due to progression of ARRT amyloidosis is MI. However, in cases where the numbers imputed are small, such as here, the differences in results will be minimal.

The placebo-treated subjects had slightly higher baseline 6MWT values (median 368 m) than those who received Patisiran (median 358 m). From baseline to Month 12, both patisiran- and placebo-treated subjects showed declines in 6MWT. Using the Applicant's prespecified method with censored and imputed data in the primary analysis, patisiran demonstrated a statistically significantly smaller decline from baseline in 6MWT at Month 12 compared to placebo (HL estimate of median difference 14.7 m; (95% CI 0.7, 28.7; p-value=0.04) (Table 4). We evaluated the primary analysis using our preferred multiple imputation of missing data instead of single imputation, that is missing data due to non-COVID-19 death or inability to walk were multiply imputed with the worst 10th percentile change, capped by 0-baseline 6MWT. The results were not meaningfully different: the HL estimate of the median difference was 14.4 m (95% CI 0.4, 28.3).

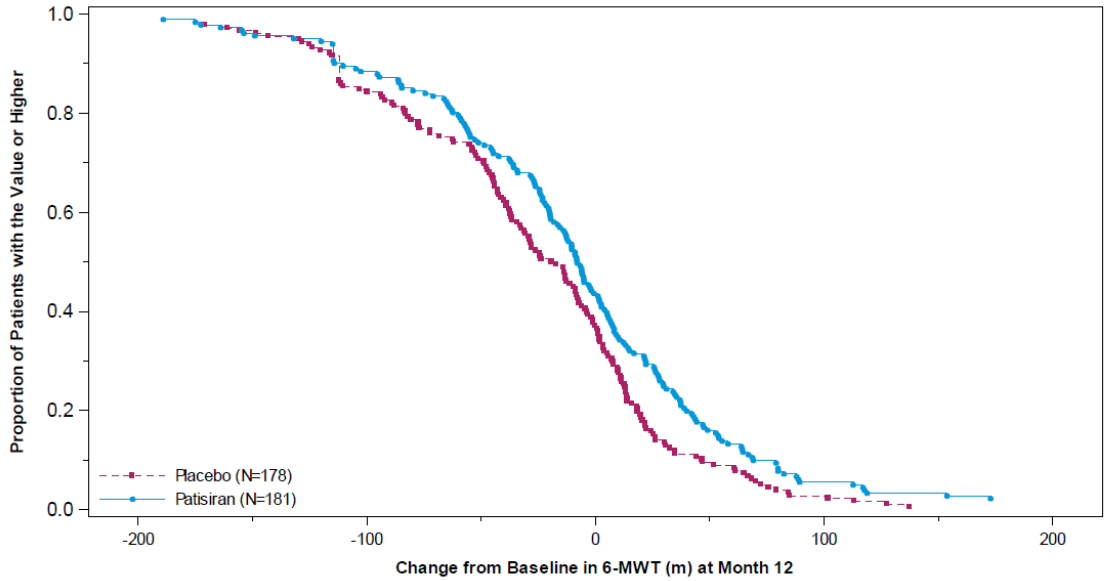
Table 4. Change From Baseline at Month 12 in 6MWT With Applicant-Defined Missing Data Imputation Method in the Primary Analysis

Statistic	Patisiran N=181	Placebo N=178
Baseline (meters)		
n	181	178
Mean (SE)	360.5 (7.6)	374.6 (7.7)
Median (Q1, Q3)	358.0 (295.0, 420.0)	367.7 (300.0, 444.3)
Change from Baseline at Month 12 with imputed values of missing data (meters)		
Mean (SE)	-13.0 (6.2)	-30.7 (5.5)
Median (Q1, Q3)	-8.1 (-54.7, 29.5)	-21.3 (-68.3, 12.8)
HL estimate of median difference (patisiran − placebo) (95% CI)	14.7 (0.7, 28.7)	
p-value	0.04	

Source: Statistical Reviewer
In the summary of change from baseline with imputed values, for each patient, the change from baseline is averaged across 100 complete datasets.
HL estimate and 95% CI were performed on the 100 multiply imputed datasets. The HL estimate (95% CI) stratified by baseline tafamidis use is presented. p-value was calculated using HL method based on the 100 multiply imputed datasets.
Abbreviations: 6MWT, 6-minute walking test; CI, confidence interval; HL, Hodges-Lehmann; N, number of subjects; n, number of subjects with statistic; Q, quartile; SE, standard error

Despite achievement of statistical significance, the change from baseline at Month 12 in 6MWT was small, as evidenced by the minimal separation observed between the treatment arms in the empirical cumulative distribution function curves (Figure 2).

Figure 2. Empirical Cumulative Distribution Function Plot of Change From Baseline at Month 12 in 6MWT



Source: Applicant's figure in Clinical Study Report ALN-TTR02-011, Figure 14.2.2.2
Abbreviation: 6MWT, 6-minute walk test

Sensitivity analyses were conducted on the primary endpoint to assess the robustness of the primary analysis result (Table 5). For these sensitivity analyses, we included all 6MWT assessments (not treating one patisiran-treated and three placebo-treated subjects who underwent assessments on or after the onset of a COVID-19 SAE as missing). Different MI methods were applied for subjects missing due to

non-COVID-19 death or inability to walk, and for all other subjects with missing data. In summary, our sensitivity analyses yielded HL estimates of median differences of 11.6 m to 14.5 m, and many of the 95% CIs included 0.

We also performed a supplementary analysis using the MMRM method. Based on all 6MWT assessments (not treating censored assessments as missing), the least square (LS) mean difference between patisiran and placebo was 13.2 m (95% CI -3.5, 29.9) (Table 5).

Table 5. Sensitivity/Supplementary Analyses of Change From Baseline at Month 12 in 6MWT

	Death/Inability to Walk **# Imputed: Patisiran N=5, Placebo N=9**	**All Other** **# Imputed: Patisiran N=10, Placebo N=8**	**HL Estimate of Median Difference** **(Patisiran – Placebo) (95% CI)**
Primary	Single imputation worst 10th percentile	MI assume MAR	14.7 (0.7, 28.7)
Sensitivity use the same HL estimation method as the primary analysis	**Death/Inability to Walk** **# Imputed: Patisiran N=5, Placebo N=9**	**All Other** **# Imputed: Patisiran N=9, Placebo N=5**	**HL Estimate of Median Difference** **(Patisiran – Placebo) (95% CI)**
	MI worst 10th percentile	MI assume MAR	13.7 (0.0, 27.5)
	MI worst 10th percentile	Control-based MI	13.3 (-0.5, 27.1)
	MI Month 12 zero	MI assume MAR	14.5 (0.4, 28.6)
	MI Month 12 zero	Control-based MI	14.1 (0.0, 28.2)
	MI assume MAR	MI assume MAR	12.5 (-1.1, 26.1)
	MI assume MAR	Control-based MI	12.0 (-1.6, 25.5)
	Control-based MI	MI assume MAR	12.0 (-1.6, 25.5)
	Control-based MI	Control-based MI	11.6 (-2.0, 25.2)
Supplementary use MMRM method	**Patisiran (N=167)** **LS Mean (SE)**	**Placebo (N=164)** **LS Mean (SE)**	**LS Mean Difference** **(Patisiran – Placebo) (95% CI)**
	-12.9 (6.0)	-26.1 (6.0)	13.2 (-3.5, 29.9)

Source: Statistical Reviewer

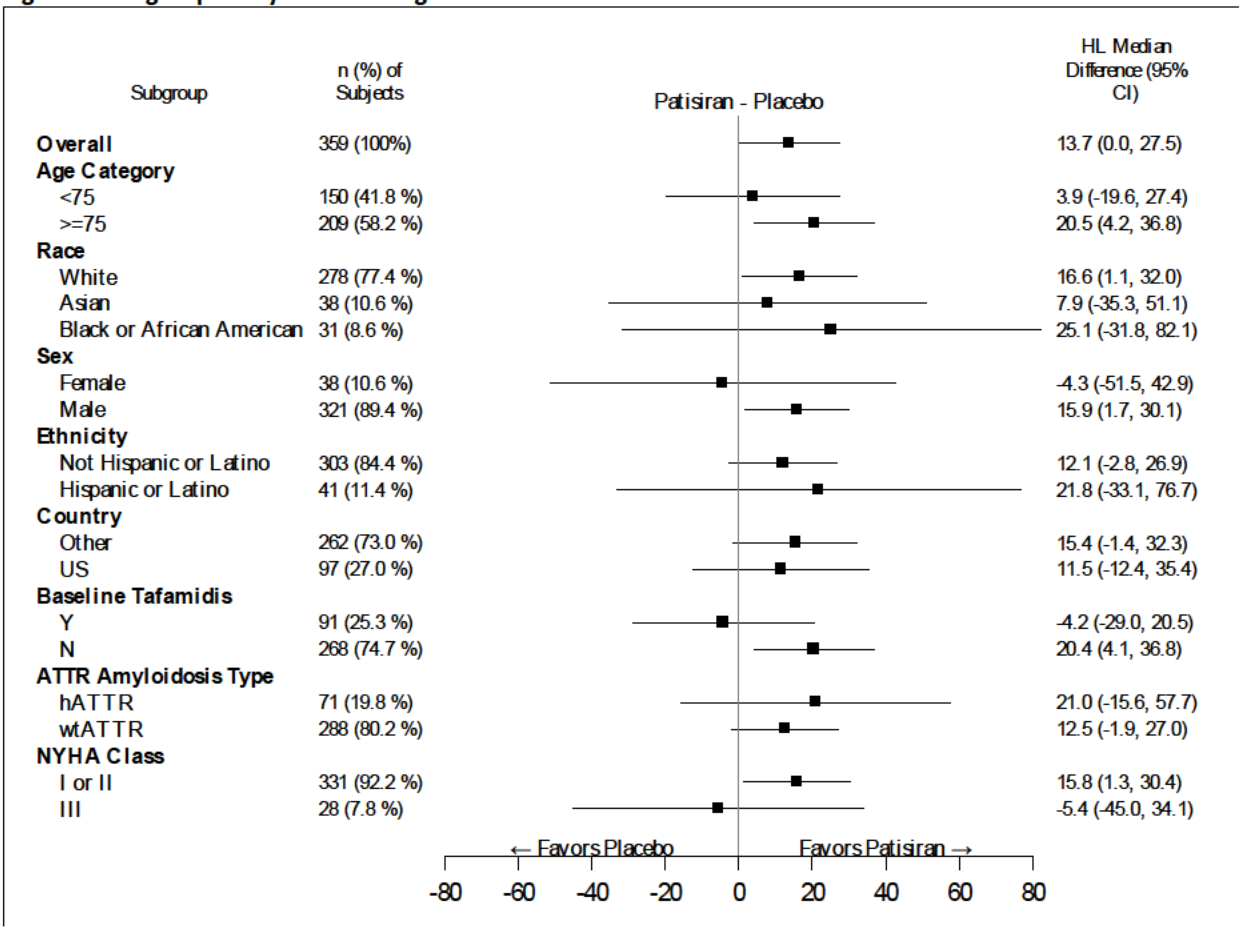
HL estimate and 95% CI were performed on the 100 multiply imputed datasets. The HL estimate (95% CI) stratified by baseline tafamidis use is presented.

The MMRM model included baseline 6MWT, treatment, visit, baseline tafamidis use, type of ATTR amyloidosis, age group, treatment-by-visit interaction, treatment-by-baseline tafamidis interaction, visit-by-baseline tafamidis interaction, and treatment-by-visit-by-baseline tafamidis interaction as covariates. The LS mean coefficients were computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age group).

Abbreviations: 6MWT, 6-meter walk test; ATTR, transthyretin-mediated amyloidosis; CI, confidence interval; HL, Hodges-Lehmann; LS, least square; MAR, missing at random; MI, multiple imputation; MMRM, mixed effects model repeated measure; SE, standard error

Subgroup analyses were performed based on the sensitivity analysis method that included all 6MWT assessments, with MI 10th worst percentile of missing data due to non-COVID-19 death or inability to walk, and MI assuming MAR for all other missing (Figure 3). Numerically, some subgroups (such as female, NYHA class III, and subjects on tafamidis at baseline) had point estimates for the treatment difference in 6MWT that slightly favored placebo but with wide CIs. However, caution should be exercised when interpreting these findings because the subgroups were small.

Figure 3. Subgroup Analyses for Change From Baseline at Month 12 in 6MWT



Source: Statistical Reviewer

Missing Month 12 values due to non-COVID-19 death or inability to walk due to progression of ATTR amyloidosis were multiply imputed as the worst 10th percentile change observed among all subjects in the double-blind period, capped by the worst possible change for the subject. Missing Month 12 data due to other reasons were multiply imputed (assuming data were missing at random) to create 100 complete datasets. HL estimates and 95% CIs were performed on the 100 multiply imputed datasets. All available assessments were included.

Abbreviations: ATTR, transthyretin-mediated amyloidosis; CI, confidence interval; ATTRv, hereditary ATTR; NYHA, New York Heart Association; wtATTR, wild-type ATTR

Secondary Endpoints

The primary and secondary endpoints were tested in a prespecified hierarchical order for multiplicity control. The study was powered to assess the primary endpoint (6MWT) and the first secondary endpoint (KCCQ-OSS), but not the other secondary endpoints.

KCCQ-OSS

The first secondary endpoint was the change from baseline at Month 12 in KCCQ-OSS. At Month 12, there were 9 (5.0%) patisiran-treated subjects and 11 (6.2%) placebo-treated subjects who had missing KCCQ-OSS, all due to reasons not related to COVID-19 ; 2 (1.1%) patisiran-treated subjects and 3 (1.7%) placebo-treated subjects had assessments censored (treated as missing) because they were on or after the onset of a COVID-19 SAE. The primary analysis was based on the MMRM method. An MMRM analysis including all available assessments, including censored assessments, was conducted as a sensitivity analysis.

Baseline KCCQ-OSS values were similar between the treatment groups (mean of about 70 points). On the primary analysis, patisiran demonstrated a statistically significantly greater change from baseline in KCCQ-OSS at Month 12 compared to placebo; the LS mean difference was 3.7 points (95% CI 0.2, 7.2) (Table 6).

Table 6. Primary Analysis of Mean Change From Baseline at Month 12 in KCCQ-OSS, MMRM Model

Statistic	Patisiran (N=181)	Placebo (N=178)
Baseline (points)		
n	181	178
Mean (SE)	69.8 (1.6)	70.3 (1.6)
Median (Q1, Q3)	71.4 (53.9, 88.5)	72.4 (56.5, 88.8)
Change from baseline at Month 12 estimated from MMRM model (treated assessments obtained on or after the onset of COVID-19 SAEs as missing)		
LS mean (SE)	0.3 (1.3)	-3.4 (1.3)
LS mean difference (95% CI)	3.7 (0.2, 7.2)	
p-Value	0.04	

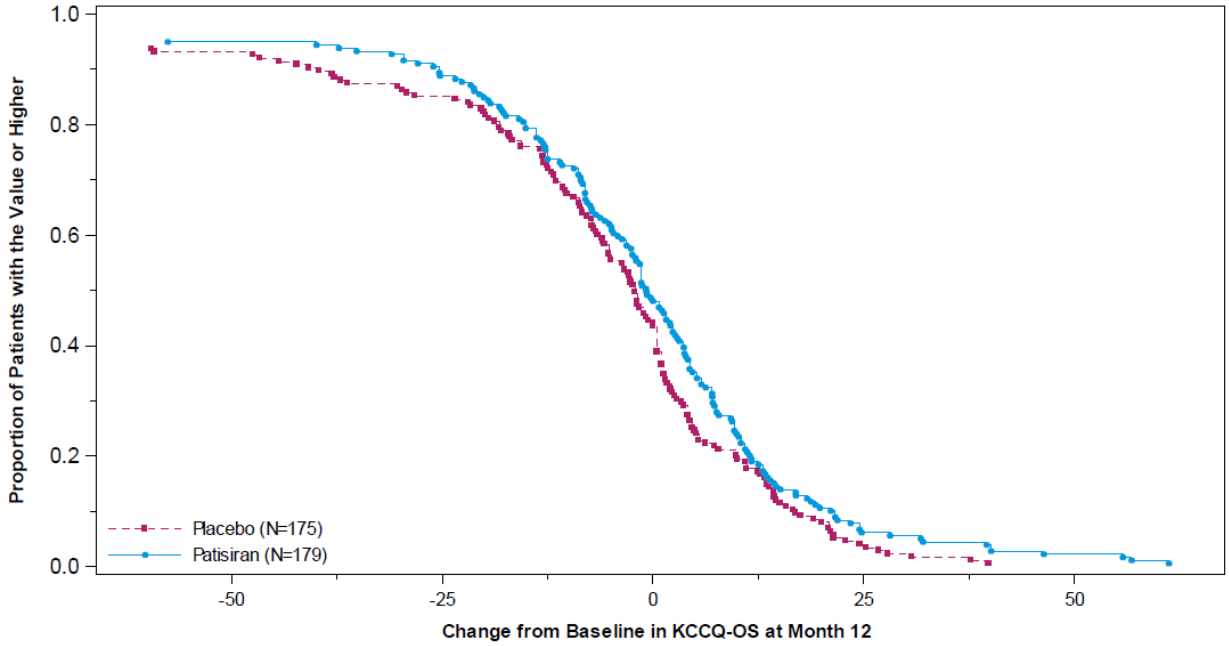
Source: Statistical Reviewer

The MMRM model included baseline KCCQ-OSS, treatment, visit, baseline tafamidis use, type of ATTR amyloidosis, age group, treatment-by-visit interaction, treatment-by-baseline tafamidis interaction, visit-by-baseline tafamidis interaction, and treatment-by-visit-by-baseline tafamidis interaction as covariates. The LS mean coefficients were computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age group).

Abbreviations: ATTR, transthyretin-mediated amyloidosis; CI, confidence interval; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS, least square; MMRM, mixed effects model repeated measures; Q, quartile; SAE, serious adverse event; SE, standard error

As mentioned in Section 1.3, a LS mean difference of 3.7 points on the 0 to 100 transformed score scale was considered small, which is evidenced by the minimal separation observed between the treatment arms in the eCDF curves (Figure 4), where a positive change (>0) to the right represents an improvement in the KCCQ-OSS.

Figure 4. Empirical Cumulative Distribution Function Plot of Change From Baseline at Month 12 in KCCQ-OSS, 0-100 Scoring



Source: Applicant's figure in Clinical Study Report ALN-TTR02-011, Figure 14.2.2.8
Abbreviation: KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score

We conducted a sensitivity analysis for the mean change from baseline at Month 12 in KCCQ-OSS, using the MMRM model but including all available assessments (not treating one patisiran-treated and three placebo-treated subjects who underwent assessments on or after the onset of a COVID-19 SAE as missing). The results were consistent with those of the primary analysis.

We also performed a sensitivity analysis with all available KCCQ-OSS (not treating assessments obtained on or after the onset of COVID-19 SAEs as missing) using control-based MI to impute missing data, and conducted an analysis of covariance. On this sensitivity analysis, the LS mean difference in KCCQ-OSS between patisiran and placebo was 2.8 (95% CI -2.5, 8.1) at Month 12 (Table 7).

Table 7. Sensitivity Analyses of Mean Change From Baseline at Month 12 in KCCQ-OSS

Statistic	Patisiran N=181	Placebo N=178
Baseline		
n	181	178
Mean (SE)	69.8 (1.6)	70.3 (1.6)
Median (Q1, Q3)	71.4 (53.9, 88.5)	72.4 (56.5, 88.8)
Change from baseline at Month 12 estimated from MMRM model (included all available assessments)		
LS mean (SE)	0.4 (1.3)	-3.4 (1.3)
LS mean difference (95% CI)	3.8 (0.3, 7.3)	
Nominal p-value	0.03	

Statistic	Patisiran N=181	Placebo N=178
Change from baseline at Month 12 from ANCOVA Model, with control-based MI of missing data		
LS mean (SE)	0.5 (1.9)	-2.3 (2.0)
LS mean difference (95% CI)	2.8 (-2.5, 8.1)	
Nominal p-value	0.30	

Source: Statistical Reviewer

Assessments collected after a serious COVID-19 adverse event were not treated as missing.

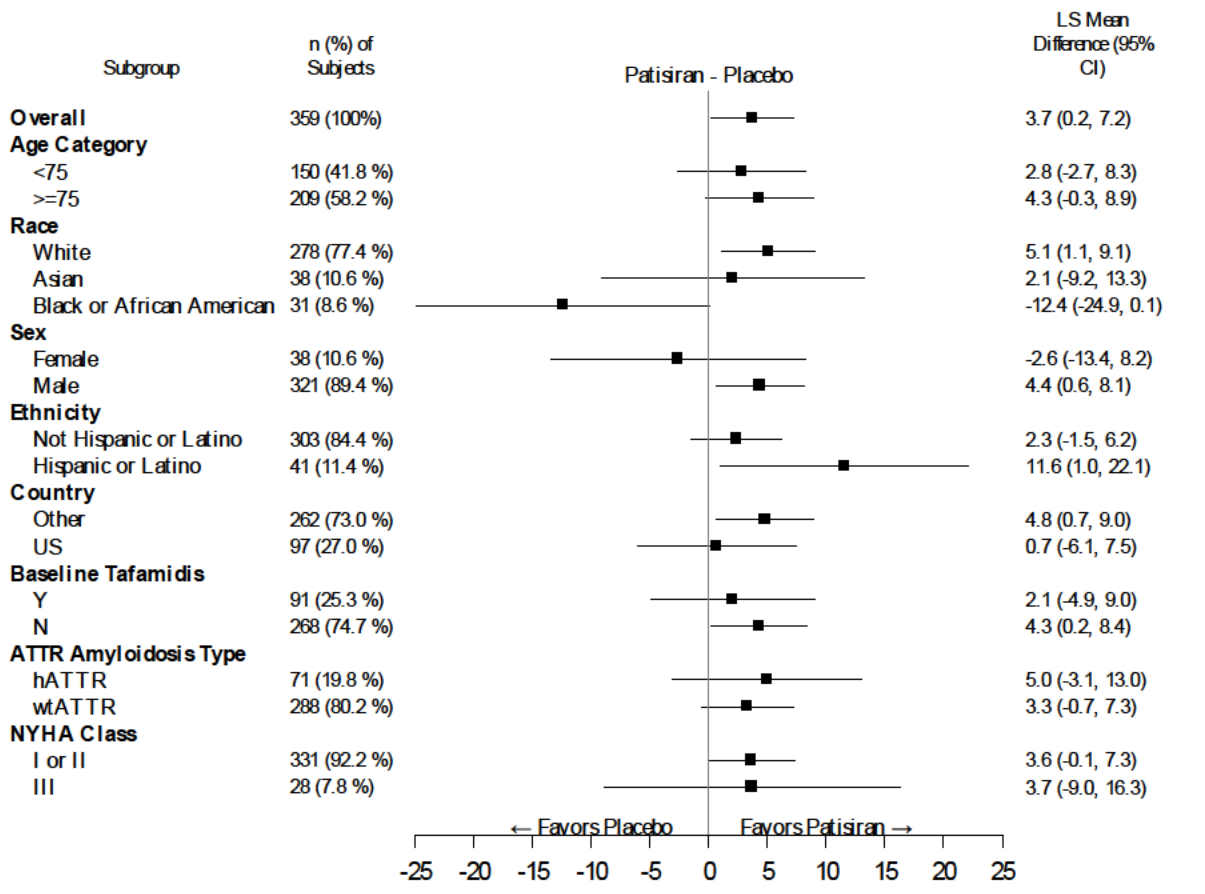
The MMRM model included baseline KCCQ-OSS, treatment, visit, baseline tafamidis use, type of ATTR amyloidosis, age group, treatment-by-visit interaction, treatment-by-baseline tafamidis interaction, visit-by-baseline tafamidis interaction, and the treatment-by-visit-by-baseline tafamidis interaction as covariates. The LS mean coefficients are computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age group).

In the ANCOVA model, missing values were multiple imputed with control-based method. The ANCOVA model included baseline KCCQ-OSS, treatment, baseline tafamidis use, type of ARRT amyloidosis, age at randomization, and treatment by baseline tafamidis interaction as covariates. The LS mean coefficients are computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age group).

Abbreviations: ANCOVA, analysis of covariance; ATTR, transthyretin-mediated amyloidosis; CI, confidence interval; COVID-19, coronavirus disease 2019; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS, least square; MI, multiple imputation; MMRM, mixed effects model repeated measures; Q, quartile; SE, standard error

Subgroup analyses for the endpoint of KCCQ-OSS were performed based on the prespecified analysis, which treated assessments obtained on or after the onset of COVID-19 SAEs as missing and used the MMRM model (Figure 5). Several of the subgroups were small, and the 95% CIs were wide for the subgroup treatment effects.

Figure 5. Subgroup Analyses for Change From Baseline at Month 12 in KCCQ-OSS



Source: Statistical Reviewer

The analyses were conducted by the MMRM method, in which the outcome variable was change from baseline in KCCQ-OSS. The model for each subgroup included baseline KCCQ-OSS, treatment arm, visit, subgroup, treatment-by-visit interaction, treatment-by-subgroup interaction, visit-by-subgroup interaction, and treatment-by-visit-by-subgroup interaction as covariates. Subgroup analysis by baseline tafamidis use also included age group and ATTR amyloidosis type as covariates. Other subgroup analyses also included baseline tafamidis use as a covariate. The LS mean differences and 95% CIs were estimated from the MMRM model. The LS mean coefficients were computed using the observed proportions of the categorical covariates (baseline tafamidis use, ATTR amyloidosis type, and age group). Assessments collected after a COVID-19 SAE were treated as missing.

Abbreviations: ATTR, transthyretin-mediated amyloidosis; CI, confidence interval; COVID-19, coronavirus disease 2019; ATTRv, hereditary ATTR; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS, least square; MMRM, mixed effects model repeated measures; NYHA, New York Heart Association; SAE, serious adverse event; SE, standard error; wtATTR, wild-type ATTR

Other Secondary Endpoints

None of the other secondary endpoints was statistically significant. The results are listed in Table 8.

Table 8. Results for Other Secondary Endpoints

Endpoint	Stratified Win Ratio (95% CI)	p-Value
[a] Composite of all-cause mortality, frequency of CV events, and change from baseline in 6MWT over the DB period	1.27 (0.99, 1.61)	0.057
	Hazard Ratio (95% CI)	**Nominal p-Value**
[b] Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the DB period in subjects not on Tafamidis at baseline	1.00 (0.62, 1.60)	0.99
[b] Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits over the DB period in all subjects	0.88 (0.58, 1.34)	0.56

Source: Statistical Reviewer based on the Applicant's prespecified analysis.

[a] Each subject pair is compared in a stepwise fashion (mortality, CV events, 6MWT). Heart transplantation and/or left ventricular assist device placement were handled in the same manner as death. Deaths and CV events due to COVID-19 were excluded from the analysis. A win ratio >1 represents a favorable outcome for patisiran.

[b] Hazard ratios, 95% CIs, and p-values were derived using the Andersen-Gill model, including treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates. A hazard ratio <1 represents a favorable outcome for patisiran. Heart transplantation and left ventricular assist device placement were handled in the same manner as death. Deaths, hospitalizations, and urgent HF visits due to COVID-19 were excluded from the analysis.

Abbreviations: 6MWT, 6-meter walk test; ATTR, transthyretin-mediated amyloidosis; CI, confidence interval; COVID-19, coronavirus disease 2019; CV, cardiovascular; DB, double-blind; HF, heart failure; NYHA, New York Heart Association

Overall, 43 (23.8%) subjects in the patisiran arm and 46 (25.8%) in the placebo arm had at least one event of all-cause hospitalization or urgent HF visit (Table 9). The total number of all-cause hospitalizations was 65 in each treatment arm (excluded 1 event in the patisiran arm and 3 in the placebo arm due to COVID-19); the total number of urgent HF visits was 4 in each treatment arm. For all-cause hospitalizations and urgent HF visits, the relative rate ratio (patisiran/placebo) from the Poisson regression model was 0.96 (95% CI 0.69, 1.35), and the estimated difference in incidence rate (patisiran-placebo) was -1.0 (95% CI -13.6, 11.6) per 100 patient-years.

Overall, 6 (3.3%) subjects in the patisiran arm (3.2 per 100 patient-years) and 10 (5.6%) subjects in the placebo arm (5.5 per 100 patient-years) died prior to Day 417 (Table 10). These comprised one patisiran-treated subject who died due to COVID-19, two placebo subjects who were treated as death due to cardiac transplant, and two placebo subjects (one non-CV death and one undetermined death) and one patisiran subject (CV death) whose deaths occurred after Month 12 and prior to Day 417. The hazard ratio for death from the Cox proportional hazard model was 0.52 (95% CI 0.19, 1.45), and the estimated difference in incidence rate (patisiran-placebo) was -2.3 (95% CI -6.5, 2.0) per 100 patient-years. These analyses are limited by very low event rates.

Table 9. All-Cause Hospitalizations and Urgent Heart Failure Visits Over the Double-Blind Period

Statistic	All Subjects		Baseline Tafamidis		No Baseline Tafamidis	
	Patisiran N=181	Placebo N=178	Patisiran N=46	Placebo N=45	Patisiran N=135	Placebo N=133
Number of subjects with at least 1 event, n (%)	43 (23.8)	46 (25.8)	8 (17.4)	13 (28.9)	35 (25.9)	33 (24.8)
All-cause hospitalizations	42 (23.2)	44 (24.7)	8 (17.4)	11 (24.4)	34 (25.2)	33 (24.8)
Urgent HF visits	4 (2.2)	3 (1.7)	0	2 (4.4)	4 (3.0)	1 (0.8)
Total number of events, N	69	69	15	21	54	48
All-cause hospitalization	65	65	15	18	50	47
Urgent HF visits	4	4	0	3	4	1
Incidence rate of all-cause hospitalizations and urgent HF visits per 100 patient-years	37.3	38.4	31.4	45.9	39.4	35.8
Relative rate ratio of all-cause hospitalizations and urgent HF visits (patisiran÷placebo) (95% CI)	0.96 (0.69, 1.35)		0.64 (0.33, 1.27)		1.08 (0.73, 1.60)	
Difference in incidence rate of all-cause hospitalizations and urgent HF visits (patisiran−placebo) (95% CI) per 100 patient-years	-1.0 (-13.6, 11.6)		-14.5 (-39.8, 10.8)		3.6 (-11.0, 18.2)	

Source: Statistical Reviewer

Relative rate ratios were derived using a Poisson regression model. For the all-subjects analysis, the Poisson regression model included treatment arm, baseline tafamidis use, treatment-by-baseline tafamidis interaction, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates; the logarithm of the follow-up time was an offset variable. For the analyses by baseline tafamidis use, the Poisson regression model included treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates; the logarithm of the follow-up time was an offset variable.

Incidence rate per 100 patient-years was calculated as: (total number of events ÷ total patient-years of follow-up) × 100.

Differences in incidence rates were based on the Poisson regression model with treatment as a covariate and the logarithm of the follow-up time as an offset variable.

Abbreviations: ATTR, transthyretin-mediated amyloidosis; CI, confidence interval; HF, heart failure; HYHA, New York Heart Association

Table 10. Summary of Death up to Day 417

Statistic	All Subjects		Baseline Tafamidis		No Baseline Tafamidis	
	Patisiran N=181	Placebo N=178	Patisiran N=46	Placebo N=45	Patisiran N=135	Placebo N=133
Total deaths, n (%)	6 (3.3)	10 (5.6)	1 (2.2)	3 (6.7)	5 (3.7)	7 (5.3)
CV death	3 (1.7)	3 (1.7)	1 (2.2)	0	2 (1.5)	3 (2.3)
Death due to COVID-19	1 (0.6)	0	0	0	1 (0.7)	0
Heart transplant or LVAD placement	0	2 (1.1)	0	2 (4.4)	0	0
Non-CV death	1 (0.6)	3 (1.7)	0	1 (2.2)	1 (0.7)	2 (1.5)
Undetermined death	1 (0.6)	2 (1.1)	0	0	1 (0.7)	2 (1.5)
Incidence rate per per 100 PY	3.2	5.5	2.1	6.5	3.6	5.1
Hazard ratio (patisiran/placebo) (95% CI)	0.52 (0.19, 1.45)		0.30 (0.03, 2.86)		0.64 (0.20, 2.02)	
Difference in incidence rate (patisiran−placebo) (95% CI) per 100 PY	-2.3 (-6.5, 2.0)		-4.4 (-12.8, 4.0)		-1.6 (-6.5, 3.4)	

Source: Statistical Reviewer

The hazard ratio and 95% CI were estimated using the Cox proportional hazards model with treatment group as a covariate.

Incidence rate per 100 patient-years was calculated as: (total number of events ÷ total patient-years of follow-up) × 100.

Differences in incidence rates were based on the Poisson regression model with treatment as a covariate and the logarithm of the follow-up time as an offset variable.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CV, cardiovascular; LVAD, left ventricular assist device; PY, patient-years

3.2 Safety Issues

There are no significant safety concerns with patisiran.

3.2.1 Sources of Data for Safety

The safety evaluation focused on Study APOLLO-B (Section 3.1.1). The safety population comprised 359 subjects (Table 1). The primary safety analysis focused on the 12-month double-blind period.

3.2.2 Safety Summary

Safety results from APOLLO-B were largely consistent with the current United States Prescribing Information for the ATTRv polyneuropathy population and expected risks for the subject population. Overall, the rates of treatment-emergent adverse events, SAEs, fatal adverse events, and events leading to discontinuation of study drug were balanced between the patisiran and placebo groups (Table 11).

Table 11. Treatment-Emergent Adverse Events, APOLLO-B Double-Blind Period

Event Category	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
SAE	61 (33.7)	63 (35.4)	-1.7 (-11.5, 8.1)
SAEs with fatal outcome	4 (2.2)	4 (2.2)	-0.0 (-3.1, 3.0)
Life-threatening SAEs	7 (3.9)	6 (3.4)	0.5 (-3.4, 4.4)
AE leading to permanent discontinuation of study drug	5 (2.8)	5 (2.8)	-0.0 (-3.5, 3.4)
AE leading to dose modification of study drug	20 (11.0)	23 (12.9)	-1.9 (-8.6, 4.8)
AE leading to interruption of study drug	20 (11.0)	23 (12.9)	-1.9 (-8.6, 4.8)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
Any AE	165 (91.2)	168 (94.4)	-3.2 (-8.6, 2.1)
Severe and worse	47 (26.0)	53 (29.8)	-3.8 (-13.1, 5.5)
Moderate	70 (38.7)	65 (36.5)	2.2 (-7.9, 12.2)
Mild	48 (26.5)	50 (28.1)	-1.6 (-10.8, 7.6)

Source: adae.xpt; software, R

Treatment-emergent adverse events were defined as occurring after the treatment start day and before the treatment end day +28.

Duration was a mean of 366 days (standard deviation 57.6 days, median 378 days).

Severity was assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

Adverse events that could impact a subject's quality of life that were included in the benefit-risk framework (Section 4) include:

- Infusion-related reactions.
- Muscle spasms and pain.
- Arthralgia.

3.2.2.1 Infusion-Related Reactions

Infusion-related reactions were evaluated as a single preferred term of "infusion-related reaction." These were more frequent in patisiran-treated subjects (Table 12). There were no SAEs. Most adverse events were mild, but events of moderate severity were more frequent in patisiran- than in placebo-treated subjects. One patisiran-treated subject discontinued at Day 106 after a persistent adverse event of moderate severity with the preferred term infusion-related reaction.

Table 12. Infusion-Related Reaction AEs, Safety Population, APOLLO-B Double-Blind Period

Adverse Event Category	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
Any preferred term in group	22 (12.2)	16 (9.0)	3.2 (-3.2, 9.5)
Infusion-related reaction	22 (12.2)	16 (9.0)	3.2 (-3.2, 9.5)
Maximum severity			
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	0	0	0 (0, 0)
Moderate	7 (3.9)	1 (0.6)	3.3 (0.3, 6.3) *
Mild	15 (8.3)	15 (8.4)	-0.1 (-5.9, 5.6)
Serious	0	0	0 (0, 0)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	1 (0.6)	0	0.6 (-0.5, 1.6)

Source: adae.xpt; software, R

Treatment-emergent adverse events were defined as occurring after the treatment start day and before the treatment end day +28.

Duration was a mean of 366 days (standard deviation 57.6 days, median 378 days).

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

3.2.2.2 Muscle Spasms and Pain

Muscle spasms and related preferred terms (listed in Table 13)were significantly more frequent in patisiran-treated subjects. All events in the patisiran-treated subjects were nonserious and most were mild. There were no serious events or events leading to discontinuation. There was one severe adverse event with the preferred term of muscle spasms in a patisiran-treated subject who also experienced severe fatigue, muscular weakness of the legs, and back pain (Table 13).

Table 13. Muscle Spasms and Pain AEs, Safety Population, APOLLO-B Double-Blind Period

Adverse Event Category	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
Any preferred term in group	24 (13.3)	12 (6.7)	6.5 (0.4, 12.7)
Muscle spasms	12 (6.6)	4 (2.2)	4.4 (0.2, 8.6)
Myalgia	6 (3.3)	3 (1.7)	1.6 (-1.6, 4.9)
Musculoskeletal discomfort	2 (1.1)	1 (0.6)	0.5 (-1.3, 2.4)
Musculoskeletal pain	4 (2.2)	3 (1.7)	0.5 (-2.3, 3.4)
Musculoskeletal chest pain	0	2 (1.1)	-1.1 (-2.7, 0.4)
Maximum severity			
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	1 (0.6)	0	0.6 (-0.5, 1.6)
Moderate	5 (2.8)	2 (1.1)	1.6 (-1.2, 4.5)
Mild	18 (9.9)	10 (5.6)	4.3 (-1.2, 9.8)
Serious	0	0	0 (0, 0)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)

Source: adae.xpt; software, R

Treatment-emergent adverse events were defined as occurring after the treatment start day and before the treatment end day +28.

Duration was a mean of 366 days (standard deviation 57.6 days, median 378 days).

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

3.2.2.3 Arthralgia

Arthralgia and related preferred terms (listed in Table 14)were observed more frequently in patisiran-treated subjects. All such events were nonserious and most were mild. There were no SAEs or events leading to discontinuation. There was one SAE of arthralgia in the placebo-treated subjects (Table 14).

Table 14. Arthralgia AEs, Safety Population, Study APOLLO-B

Adverse Event Category	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
Any preferred term in group	20 (11.0)	13 (7.3)	3.7 (-2.2, 9.7)
Arthralgia	14 (7.7)	8 (4.5)	3.2 (-1.7, 8.2)
Pain in extremity	10 (5.5)	5 (2.8)	2.7 (-1.4, 6.8)
Limb discomfort	1 (0.6)	0	0.6 (-0.5, 1.6)
Maximum severity			
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	0	0	0 (0, 0)
Moderate	7 (3.9)	3 (1.7)	2.2 (-1.2, 5.6)
Mild	13 (7.2)	10 (5.6)	1.6 (-3.5, 6.6)
Serious	0	1 (0.6)	-0.6 (-1.7, 0.5)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)

Source: adae.xpt; software, R

Treatment-emergent adverse events were defined as occurring after the treatment start day and before the treatment end day +28.

Duration was a mean of 366 days (standard deviation 57.6 days, median 378 days).

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Additional safety analyses are presented in Section 6.1.

3.3 Risk Mitigation

There are no significant safety concerns with patisiran for ATTR amyloidosis with cardiomyopathy. Risks can be managed by the product label.

4 Benefit-Risk Framework

Disclaimer: This predecisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Transthyretin amyloidosis (ATTR) is an underrecognized and progressively disabling condition affecting most organ systems. • Cardiomyopathy is a common manifestation of ATTR (ATTR-CM) caused by deposition of misfolded toxic amyloid fibrils in the myocardial extracellular space and is associated with a worse prognosis • Patients typically present with decompensated heart failure (HF) symptoms, elevated cardiac biomarkers out of proportion to symptoms, arrhythmias, or conduction abnormalities. • Rates of cardiovascular hospitalization and death are both high in patients with symptomatic ATTR-CM; median survival is 2 to 5 years.	ATTR-CM is a rare, progressively disabling, and fatal condition.
Current Treatment Options	• Tafamidis is the only FDA-approved treatment for ATTR-CM. • Tafamidis is a once-daily, oral medication that demonstrated highly favorable benefits on all-cause mortality, cardiovascular hospitalizations, functional capacity, and quality-of-life indices with no safety concerns identified in the pivotal trial supporting its approval. • Patisiran, vutrisiran, and inotersen are small interfering RNA and antisense oligonucleotide agents approved for treatment of the polyneuropathy of ATTRv amyloidosis. • Tafamidis works by stabilizing TTR protein and inhibiting its misfolding; patisiran, vutrisiran, and inotersen suppress the production of transthyretin (TTR) protein in the liver. Other investigational agents under development target other steps in the disease pathway, such as disrupting the amyloid fibril deposits. • Patients with ATTR may benefit from a liver or heart transplant, although this requires life-long management and not all patients are eligible.	Approval of tafamidis markedly improved the treatment of patients with ATTR-CM (wild-type and variant), and it is now the standard of care. Additional treatment options would be beneficial for patients but should be considered in the context of background tafamidis use. In particular, there is a need for therapies that target other steps in the disease pathway, to address the root cause of amyloidosis, and to reverse the organ dysfunction caused by accumulation of toxic misfolded amyloid fibrils.

	Evidence and Uncertainties	Comments to the Advisory Committee
Benefits	• The pivotal trial (Study 011, APOLLO-B) demonstrated a smaller decrease from baseline in the 6-minute walk test (6MWT) in patisiran- compared to placebo-treated subjects. However, the magnitude of the difference was small (approximately 14 m) and its clinical meaningfulness is uncertain in patients who at baseline had a median 6MWT of 358-368 meters. • Results for the KCCQ-OSS were also statistically significant but the small effect size (approximately 3.7 points on a 0-100 transformed score range) raises the question of clinical meaningfulness in patients who at baseline had a mean score of 70 points. • Among subjects on background tafamidis (approximately 25% of each treatment arm), there was no evidence of treatment effect on 6MWT or KCCQ-OSS. • Results for cardiovascular events and survival were highly uncertain, precluding conclusions about effects on these outcomes.	While the results from the APOLLO-B study statistically favor patisiran over placebo, the magnitude of the treatment effect on function and quality of life is small and may not be clinically meaningful. Any benefit observed is in the context of slowing the rate of decline, not halting or reversing the progression of the disease. Furthermore, treatment with patisiran did not appear to confer any benefit when used in subjects on tafamidis.
Risks and Risk Management	• No significant risks were seen in the pivotal trial and very few subjects discontinued treatment due to adverse events. • Infusion-related reaction was observed more frequently in patisiran than placebo-treated subjects (12% versus 9%). Events were mostly mild, but moderate severity was seen more often with patisiran than placebo. No serious events were observed. One patisiran subject discontinued at Day 106 after a persistent moderate infusion-related reaction. • Muscle pain or spasms and joint pain were observed more frequently in patistiran- than in placebo-treated subjects (13.3% versus 6.7% for muscle pain and spasms; 11% and 7.3% for joint pain). There was one severe muscle spasm event in the patisiran group in a subject who had several confounding factors. All other events were nonserious and most were mild.	Patisiran has no significant safety concerns and was tolerated by almost all subjects. However, some subjects experienced symptomatic adverse events that could represent a quality-of-life concern in a long-term therapy such as patistran.

Summary of Benefit-Risk

For a drug to be approved for marketing in the United States, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. A benefit-risk assessment for patisiran for ATTR cardiomyopathy requires careful consideration of the

evidence and remaining uncertainties about its key benefits (as demonstrated in the development program) and potential risks. This assessment should consider the unmet need for patients with this progressive disease.

The pivotal trial for patisiran for ATTR-cardiomyopathy demonstrated statistically significant benefits of small magnitude. There was no evidence of treatment effect in subjects also taking tafamidis on the 6MWT or KCCQ-OSS endpoints. Statistical uncertainty precludes conclusions about the effect of patisiran on cardiovascular events or survival.

While there were no concerning risks identified, a positive benefit-risk profile cannot be concluded if there is no meaningful benefit of the therapy to patients in how they feel, function, or survive. In the context of the small effect sizes seen for patisiran over placebo, the relatively minor risks of infusion-related reactions, muscle pain and spasm, and joint pain, become tradeoffs that require consideration.

Table 15. Benefit-Risk Effects Table

Outcome	Measure Definition	Patisiran vs. Placebo (95% CI)	Uncertainties/Strength of Evidence
Benefit Assessment			
Function	Primary endpoint: change from baseline at Month 12 in 6MWT; HL estimate of median difference with prespecified analysis; meters • Overall population • Subjects on background tafamidis • Subjects not on background tafamidis	 • 15 (1, 29) • -3 (-28, 22) • 21 (5, 38)	Clinical meanginfulness of the effect size is uncertain. Baseline 6MWT averaged 363 m and declined in both groups over the 12-month period.
Health status (symptom frequency, symptom burden, quality of life, physical limitations, and social limitations)	Secondary endpoint: change from baseline to Month 12 in KCCQ-OSS; LS mean difference with prespecified analysis; points: • Overall population • Subjects on background tafamidis • Subjects not on background tafamidis	 • 4 (0, 7) • 2 (-5, 9) • 4 (0, 8)	Clinical meaningfulness of the effect size (3.7 points) is uncertain given the 100-point scale of the KCCQ-OSS. Baseline KCCQ-OSS averaged 70 points..

Outcome	Measure Definition	Patisiran vs. Placebo (95% CI)	Uncertainties/Strength of Evidence
Benefit Assessment			
Cardiovascular events	Frequency of cardiovascular events (CV hospitalization and urgent heart failure visit events) over the 12-month double-blind period: • Relative rate ratio (from Poisson regression) • EAIR difference per 100 person-years	 • 0.96 (0.62, 1.49) • -0.2 (-10.4, 9.9)	Results are not statistically significant but study was not powered for this outcome.
Survival	All cause mortality over the 12-month double-blind period including heart transplantation and/or heart VAD replacement • Hazard ratio • EAIR difference per 100 person-years	 • 0.36 (0.11, 1.14) • -3.4 (-7.5, 0.7)	Results are not statistically significant but study was not powered for this outcome.
Risk Assessment			
Infusion-related reactions	Risk difference (in percent) for systemic infusion related reactions during the double-blind period (12 months)	3.2 (-3.2, 9.5)	This may be bothersome to patients but rarely led to discontinuation of drug in the trial.
Muscle pain and spasms and joint pain	Exposure-adjusted incidence rate difference (in percent per 100 person-years) during the double-blind period (12 months) for: • Muscle pain and spasms • Arthralgia	 • 7.3 (0.3, 14.3) • 3.4 (-1.9, 8.7)	These may have an impact on patient mobility and comfort.

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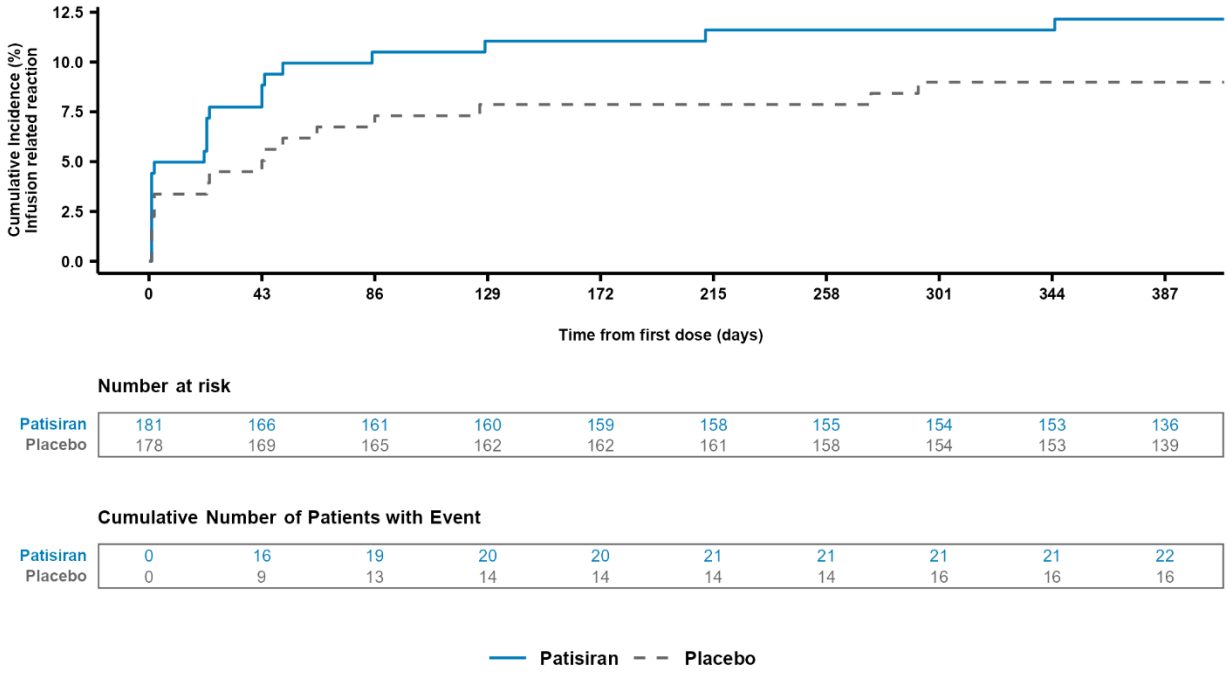
6 Appendix

6.1 Safety Analysis

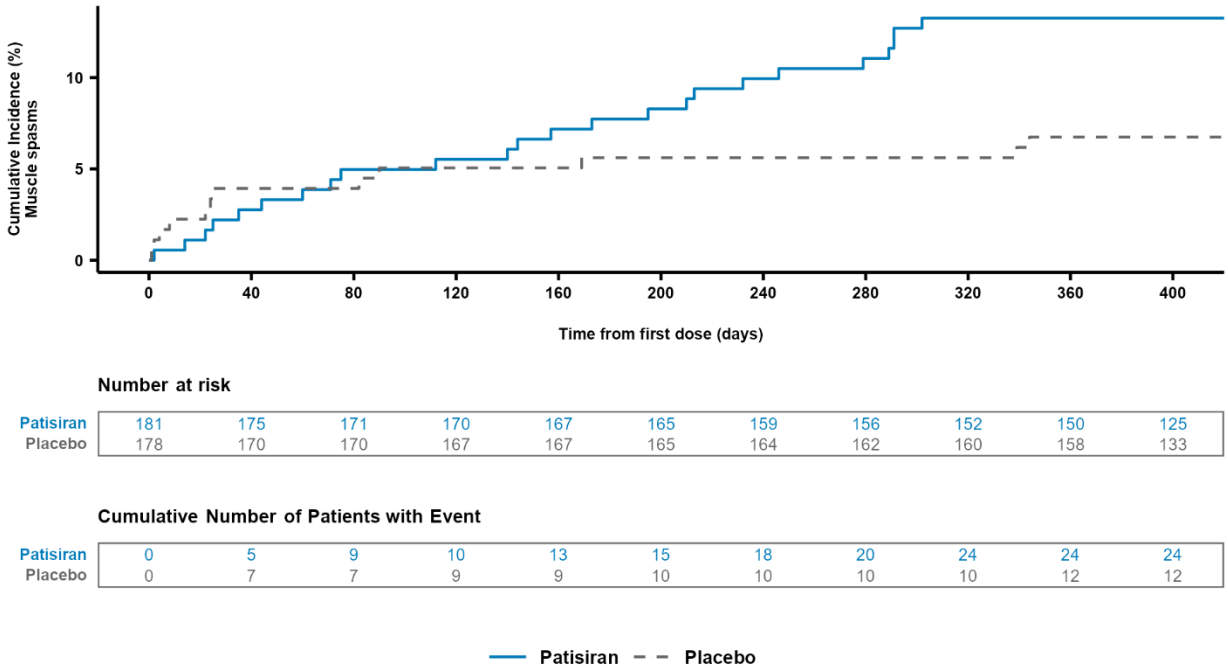
6.1.1 Time-To-Event Plots for Safety Issues

Figure 6. Cumulative Incidence of Infusion-Related Reactions, Safety Population, Study APOLLO-B



Source: adae.xpt; software, R

Figure 7. Cumulative Incidence of Muscle Spasms and Related Terms, Safety Population, Study APOLLO-B



Number at risk

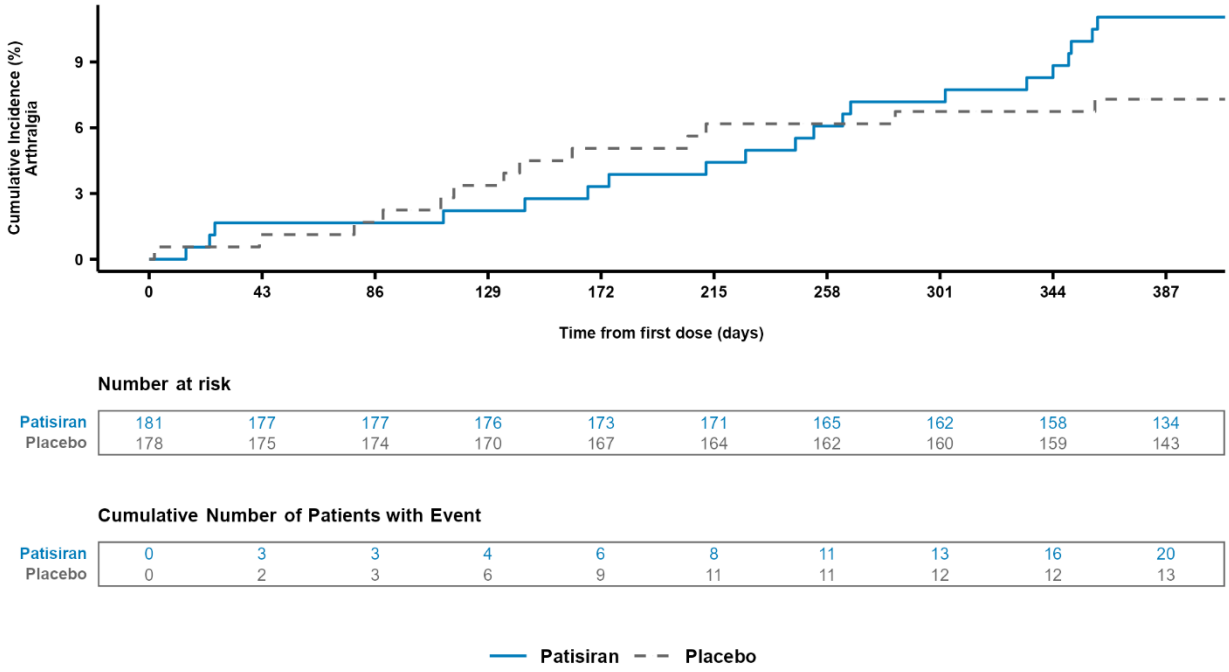
Patisiran	181	175	171	170	167	165	159	156	152	150	125
Placebo	178	170	170	167	167	165	164	162	160	158	133

Cumulative Number of Patients with Event

Patisiran	0	5	9	10	13	15	18	20	24	24	24
Placebo	0	7	7	9	9	10	10	10	10	12	12

Source: adae.xpt; software, R
Terms included: muscle spasms, myalgia, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal chest pain.

Figure 8. Cumulative Incidence of Arthralgia and Related Terms, Safety Population, Study APOLLO-B



Number at risk

Patisiran	181	177	177	176	173	171	165	162	158	134
Placebo	178	175	174	170	167	164	162	160	159	143

Cumulative Number of Patients with Event

Patisiran	0	3	3	4	6	8	11	13	16	20
Placebo	0	2	3	6	9	11	11	12	12	13

Source: adae.xpt; software, R
Terms included: arthralgia, pain in extremity, limb discomfort.

6.1.2 Adverse Events

The most common AEs by preferred term are discussed above as safety issues. Other common preferred terms had risk differences close to or below zero, meaning that their incidences were equivalent between the groups or higher in the placebo group (Table 16).

Table 16. AEs by Preferred Term Occurring in ≥5% of Any Arm, Safety Population, Study APOLLO-B

Preferred Term	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
Any AE	165 (91.2)	168 (94.4)	-3.2 (-8.6, 2.1)
Muscle spasms	12 (6.6)	4 (2.2)	4.4 (0.2, 8.6)
Arthralgia	14 (7.7)	8 (4.5)	3.2 (-1.7, 8.2)
Infusion related reaction	22 (12.2)	16 (9.0)	3.2 (-3.2, 9.5)
Pain in extremity	10 (5.5)	5 (2.8)	2.7 (-1.4, 6.8)
Diarrhea	15 (8.3)	14 (7.9)	0.4 (-5.2, 6.1)
Constipation	20 (11.0)	19 (10.7)	0.4 (-6.1, 6.8)
Back pain	12 (6.6)	12 (6.7)	-0.1 (-5.3, 5.1)
Nausea	8 (4.4)	9 (5.1)	-0.6 (-5.0, 3.8)
Insomnia	10 (5.5)	11 (6.2)	-0.7 (-5.5, 4.2)
Gout	11 (6.1)	12 (6.7)	-0.7 (-5.7, 4.4)
Nasopharyngitis	10 (5.5)	12 (6.7)	-1.2 (-6.2, 3.7)
Fatigue	12 (6.6)	15 (8.4)	-1.8 (-7.3, 3.7)
Headache	6 (3.3)	11 (6.2)	-2.9 (-7.3, 1.5)
Syncope	8 (4.4)	13 (7.3)	-2.9 (-7.7, 2.0)
Fall	10 (5.5)	15 (8.4)	-2.9 (-8.2, 2.4)
Orthostatic hypotension	3 (1.7)	9 (5.1)	-3.4 (-7.1, 0.3)
Dizziness	9 (5.0)	15 (8.4)	-3.5 (-8.6, 1.7)
Atrial fibrillation	16 (8.8)	26 (14.6)	-5.8 (-12.4, 0.9)
COVID-19	14 (7.7)	25 (14.0)	-6.3 (-12.7, 0.1)
Cardiac failure	54 (29.8)	68 (38.2)	-8.4 (-18.1, 1.4)

Source: adae.xpt; software, R

Treatment-emergent adverse events were defined as occurring after the treatment start day and before the treatment end day +28.

Duration was a mean of 366 days (standard deviation 57.6 days, median 378 days).

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event

The overall incidence of SAEs was similar between the groups (Table 17).

Table 17. Subjects With Serious Adverse Events by System Organ Class and Preferred Term Occurring in ≥1.5% of Any Arm, Safety Population, Study APOLLO-B

System Organ Class Preferred Term	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
Any SAE	61 (33.7)	63 (35.4)	-1.7 (-11.5, 8.1)
Gastrointestinal disorders (SOC)	8 (4.4)	4 (2.2)	2.2 (-1.5, 5.9)
Cardiac disorders (SOC)	32 (17.7)	28 (15.7)	1.9 (-5.8, 9.7)
Cardiac failure	15 (8.3)	13 (7.3)	1.0 (-4.6, 6.5)
Atrial fibrillation	5 (2.8)	4 (2.2)	0.5 (-2.7, 3.7)
Atrioventricular block complete	2 (1.1)	4 (2.2)	-1.1 (-3.8, 1.5)
Coronary artery disease	0	3 (1.7)	-1.7 (-3.6, 0.2)
Respiratory, thoracic and mediastinal disorders (SOC)	4 (2.2)	2 (1.1)	1.1 (-1.6, 3.7)

System Organ Class Preferred Term	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
Renal and urinary disorders (SOC)	3 (1.7)	2 (1.1)	0.5 (-1.9, 3.0)
Injury, poisoning and procedural complications (SOC)	7 (3.9)	6 (3.4)	0.5 (-3.4, 4.4)
Musculoskeletal and connective tissue disorders (SOC)	4 (2.2)	4 (2.2)	-0.0 (-3.1, 3.0)
Osteoarthritis	1 (0.6)	3 (1.7)	-1.1 (-3.3, 1.0)
Nervous system disorders (SOC)	7 (3.9)	7 (3.9)	-0.1 (-4.1, 3.9)
Ischemic stroke	3 (1.7)	0	1.7 (-0.2, 3.5)
Syncope	2 (1.1)	4 (2.2)	-1.1 (-3.8, 1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	2 (1.1)	3 (1.7)	-0.6 (-3.0, 1.8)
Immune system disorders (SOC)	1 (0.6)	5 (2.8)	-2.3 (-4.9, 0.4)
Amyloidosis	1 (0.6)	4 (2.2)	-1.7 (-4.1, 0.7)
General disorders and administration site conditions (SOC)	1 (0.6)	7 (3.9)	-3.4 (-6.4, -0.3)
Chest pain	0	3 (1.7)	-1.7 (-3.6, 0.2)
Infections and infestations (SOC)	8 (4.4)	15 (8.4)	-4.0 (-9.1, 1.1)
COVID-19	2 (1.1)	3 (1.7)	-0.6 (-3.0, 1.8)
Pneumonia	1 (0.6)	3 (1.7)	-1.1 (-3.3, 1.0)

Source: adae.xpt; software, R

Treatment-emergent adverse events defined as occurring after treatment start day and before the treatment end day +28.

Shown are SOCs with incidences of SAEs of at least 1.5% in either arm and preferred terms that meet the same criteria.

Serious adverse event defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration was a mean of 366 days (standard deviation 57.6 days, median 378 days).

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

The overall incidence of AEs leading to discontinuation was identical between the groups (Table 18).

Table 18. Subjects With AEs Leading to Treatment Discontinuation by Preferred Term, Safety Population, Study APOLLO-B

Preferred Term	Patisiran N=181 n (%)	Placebo N=178 n (%)	Risk Difference (%) (95% CI)
Any AE leading to discontinuation	5 (2.8)	5 (2.8)	0.0 (-3.5, 3.4)
Asthenia	1 (0.6)	0	0.6 (-0.5, 1.6)
Atrial thrombosis	1 (0.6)	0	0.6 (-0.5, 1.6)
Infusion related reaction	1 (0.6)	0	0.6 (-0.5, 1.6)
Pancreatitis	1 (0.6)	0	0.6 (-0.5, 1.6)
Sciatica	1 (0.6)	0	0.6 (-0.5, 1.6)
Weight decreased	1 (0.6)	0	0.6 (-0.5, 1.6)
Pancreatic carcinoma metastatic	0	1 (0.6)	-0.6 (-1.7, 0.5)
Cardiac failure	1 (0.6)	2 (1.1)	-0.6 (-2.5, 1.3)
Amyloidosis	0	2 (1.1)	-1.1 (-2.7, 0.4)

Source: adae.xpt; software, R

Treatment-emergent adverse events were defined as occurring after the treatment start day and before the treatment end day +28.

Duration was a mean of 366 days (standard deviation 57.6 days, median 378 days).

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class