CADTH

CADTH COMMON DRUG REVIEW

# Clinical Review Report

**Patisiran (Onpattro)**

**(Alnylam Netherlands B.V.)**

**Indication:** Treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis.


| | |
|---|---|
| Service Line: | CADTH Common Drug Review |
| Version: | Final (With Redactions) |
| Publication Date: | August 2019 |
| Report Length: | 122 Pages |

CADTH



**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

## Table of Contents

**Tables**

## Figures

# Abbreviations

| | |
|---|---|
| Σ5 NCS | sum of five attributes of nerve conduction studies |
| 10MWT | 10 metre walk test |
| ANCOVA | analysis of covariance |
| ATTR | transthyretin-mediated |
| CI | confidence interval |
| CMAP | compound muscle action potential |
| COMPASS 31 | Composite Autonomic Symptom Score 31 |
| CORD | Canadian Organization for Rare Disorders |
| EQ-5D-5L | EuroQol 5-Dimensions 5-Levels |
| FAP | familial amyloidotic polyneuropathy |
| hATTR | hereditary transthyretin-mediated |
| ITC | indirect treatment comparison |
| LS | least squares |
| LV | left ventricular |
| LVEF | left ventricular ejection fraction |
| MAIC | matching-adjusted indirect comparison |
| mBMI | modified body mass index |
| MCID | minimal clinically important difference |
| mITT | modified intention-to-treat |
| mNIS+7 | modified Neurologic Impairment Score +7 |
| mNIS+7ionis | modified Neurologic Impairment Score +7 outcome measure used in the phase III randomized controlled trial for inotersen |
| NIS | Neurologic Impairment Score |
| NIS+7 | Neurologic Impairment Score +7 |
| NIS-LL | Neuropathy Impairment Score–Lower Limbs |
| NIS-R | Neurologic Impairment Score–Reflexes |
| NIS-W | Neurologic Impairment Score–Weakness |
| Norfolk QoL-DN | Norfolk Quality of Life-Diabetic Neuropathy |
| NT-proBNP | N-terminal prohormone brain-type natriuretic peptide |
| PND | polyneuropathy disability |
| QST | quantitative sensory testing |
| RCT | randomized controlled trial |
| RNAi | ribonucleic acid interference |
| R-ODS | Rasch-built Overall Disability Scale |
| SD | standard deviation |
| SE | standard error |
| SEM | standard error of the mean |
| siRNA | small interfering ribonucleic acid |
| SNAP | sensory nerve action potential |
| Thr60Ala | threonine to alanine substitution at position 60 |
| TTR | transthyretin |
| V122I | valine to isoleucine substitution at position 122 |
| V30M | valine to methionine substitution at position 30 |
| VAS | visual analogue scale |

| | |
|---|---|
| **Drug** | Patisiran (Onpattro) |
| **Indication** | Treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated (hATTR) amyloidosis |
| **Reimbursement Request** | As per indication |
| **Dosage Form(s)** | 2 mg/mL; 5 mL solution in a single-use 10 mL vial |
| **NOC Date** | June 8, 2019 |
| **Manufacturer** | Alnylam Netherlands B.V. |

# Executive Summary

## Introduction

Hereditary transthyretin-mediated (hATTR) amyloidosis is a rare, progressive, often fatal condition caused by an autosomal dominant mutation in the transthyretin (TTR) gene. TTR is a plasma transport protein for thyroxine and vitamin A that is produced predominantly in the liver.[1] In patients with TTR gene mutations, the protein is destabilized, causing it to disassociate, misfold, and aggregate into amyloid fibrils that are deposited in various tissues in the body. Amyloid accumulation often causes a peripheral neuropathy with the involvement of motor, sensory, and autonomic fibres that leads to progressive muscle weakness and disability, pain, and wasting, and may lead to gastrointestinal dysfunction and other autonomic symptoms such as orthostatic hypotension. Cardiac amyloid deposits lead to cardiac hypertrophy, arrhythmias, and heart failure.[1] Neurologic impairment may be rapidly progressive, particularly in the first five years after symptom onset.[2] Neuropathic pain and weakness are reported by patients as the most difficult symptoms to cope with; for many patients, these symptoms are incapacitating or have a serious impact on their lives. Heart failure and sudden cardiac death are common causes of death among those with hATTR amyloidosis.[3] hATTR amyloidosis is known to be endemic in Portugal, Sweden, and specific regions of Japan, but has been reported in 36 countries worldwide and may be under-diagnosed.[4] Globally, it is estimated there are 10,186 persons with hATTR amyloidosis and polyneuropathy (range: 5,526 to 38,468).[4] The prevalence in Canada is not known, but extrapolation from other regions estimates that the number of patients with hATTR amyloidosis and polyneuropathy ranges from 12 (low) to 53 (mid) to 270 (high).[4]

Patisiran is a double-stranded, small interfering ribonucleic acid that, through a process called ribonucleic acid interference (RNAi), causes the catalytic degradation of TTR messenger ribonucleic acid in the liver, which reduces serum TTR protein and subsequent amyloid deposits in tissue.[5] The drug is formulated as lipid nanoparticles to deliver the small interfering ribonucleic acid to hepatocytes, the primary source of transthyretin. Patisiran is approved by Health Canada for the treatment of polyneuropathy in adult patients with hATTR amyloidosis.[5] The product is available as a 2 mg/mL lipid complex solution for IV administration (5 mL solution in a 10 mL single-use vial) that must be diluted and infused over 80 minutes. The recommended dosage is 0.3 mg/kg every three weeks, with a maximum dose of 30 mg for patients who weigh 100 kg or greater.[5] All patients should receive premedication at least 60 minutes prior to each dose to prevent infusion-related reactions. The premedications include IV corticosteroid, acetaminophen, IV histamine-1 receptor blocker, and IV histamine-2 receptor blocker.[5]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of patisiran 2 mg/mL IV solution for the treatment of hATTR amyloidosis with polyneuropathy in adults.

## Results and Interpretation

### Included Studies

One double-blind, parallel-design, placebo-controlled, phase III randomized controlled trial (RCT) met the inclusion criteria for the systematic review (the APOLLO study). In this trial, adults diagnosed with familial amyloidotic polyneuropathy (FAP) with documented TTR mutation were enrolled and randomized (2:1) to patisiran 0.3 mg/kg IV or placebo IV every three weeks for 18 months (N = 225). The objective was to determine the superiority of patisiran versus placebo on the change from baseline to 18 months on neurological impairment as measured by the modified Neurologic Impairment Score +7 (mNIS+7). Other secondary outcomes included health-related quality of life, motor strength, disability, gait speed, nutritional status, and autonomic symptoms, which were part of the statistical testing hierarchy.

In the APOLLO study, the mean age of patients was 59.6 years and 62.2 years in the patisiran and placebo groups, respectively, and most patients (74%) were male. For 72% of patients, the onset of hATTR amyloidosis symptoms occurred when they were 50 years or older and, on average, patients had been diagnosed with hATTR amyloidosis 2.5 years prior to enrolment. Approximately half of patients were classified as FAP stage I (46%) and stage II (53%), and 53% had previously been treated with tafamidis or diflunisal. Overall, 49% of patients had New York Heart Association functional class I heart failure and 50% had class II, with a similar distribution between treatment groups.

The available evidence consisted of a single placebo-controlled RCT that lasted 18 months. Limitations included the differential losses to follow up, with 7% versus 29% of patients withdrawing from the trial, and 7% versus 38% of patients stopping treatment early in the patisiran and placebo groups, respectively. The APOLLO study was not designed to evaluate mortality, cardiac morbidity, or hospitalizations, which are important outcomes to patients. Although the trial tested several outcomes measuring different aspects that may be affected by hATTR amyloidosis, for most of these instruments, the minimum differences that an individual patient would identify as important were unknown. There was limited data on subgroups of interest to this review and, as patients with liver transplant were excluded from the study, there is no data on the efficacy of patisiran in this population.

### Efficacy

Although identified as key efficacy outcomes of interest in this review, the APOLLO study was not designed to assess mortality, cardiovascular morbidity, or hospitalizations as efficacy end points. Data pertaining to each of these outcomes were not systematically captured but were extracted from safety evaluations (post hoc), and no formal hypotheses were stated or tested. Seven patients in the patisiran group (5%) and six patients in the placebo group (8%) died during the APOLLO study. All seven deaths in the patisiran group and three deaths in the placebo group were adjudicated as a cardiovascular event.

The impacts of neuropathy on functional status and health-related quality of life were measured using the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire, which was a key secondary outcome. The 35-item questionnaire includes

five domains — physical functioning/large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy — and the total score ranges from −4 to 136, with lower scores indicating better health-related quality of life.[6] In patients with hATTR amyloidosis, the Norfolk QoL-DN showed moderate to high correlation with objective measures of neurologic function, discriminant validity, and acceptable test-retest reliability.[6] No minimal clinically important difference (MCID) was found in the literature. For the change from baseline to 18 months, least squares (LS) mean difference of −21.1 points (95% confidence interval [CI], −27.2 to −15.0) was found for patisiran versus placebo ($P$ < 0.0001) (see Table 1). Another health-related quality of life instrument, the EuroQol 5-Dimensions questionnaire, showed results that were consistent with the Norfolk QoL-DN findings, although ED-5D was outside the statistical testing hierarchy and should be interpreted as inconclusive.

The primary outcome in APOLLO was the change from baseline in the mNIS+7 score, which is a 304-point composite measure used to assess neurological impairment.[7] The components of the mNIS+7 are (1) Neurologic Impairment Score–Weakness, known as NIS-W (192 points) and Neurologic Impairment Score–Reflexes (20 points), which are based on physical examination of the lower limbs, upper limbs, and cranial nerves; (2) electrophysiological measures of small- and large-nerve fibre function to determine the sum of five attributes of nerve conduction studies (10 points); (3) sensory testing of touch pressure by body surface area and heat pain by body surface area to determine the quantitative sensory testing score (80 points); and (4) postural blood pressure to assess autonomic function two points).[7] A higher score on the mNIS+7 indicates worse neurological function. The LS mean change from baseline to 18 months was 28.0 points (standard error 2.6) and −6.0 points (standard error 1.7) in the placebo and patisiran groups, respectively, with LS mean difference of −34.0 points (95% CI, −39.9 points to −28.1 points) that was statistically significant in favour of patisiran ($P$ < 0.0001) (see Table 1). The direction and magnitude of the treatment effects for the change from baseline in mNIS+7 were similar in the sensitivity analyses and the subgroup analyses based on the FAP stage, as observed in the base-case analysis. The results of the NIS-W subscale were also statistically significant with a LS mean difference of −17.9 points (95% CI, −22.3 points to −13.4 points; $P$ < 0.0001). No MCID was found in the literature for the mNIS+7 or NIS-W.

All other secondary outcomes within the statistical testing hierarchy showed statistically significant differences between patisiran and placebo. Disability was measured using the patient-reported Rasch-built Overall Disability Scale (R-ODS), a 24-item instrument that captures activity and social participation limitations in patients (score range of zero [worst limitations] to 48 [no limitations]). Statistically significant differences in change from baseline at month 18 were detected in favour of patisiran versus placebo (LS mean difference of 9.0 points (95% CI, 7.0 points to 10.9 points; $P$ < 0.0001; MCID unknown) (see Table 1). Gait speed was measured using the 10 metre walk test. The difference between treatments for change from baseline at month 18 was statistically significant, with a LS mean difference of 0.31 m/s (95% CI, 0.23 m/s to 0.39 m/s; $P$ < 0.0001) that exceeded the MCID of 0.05 m/s that has been reported in the literature. Modified body mass index (mBMI) was calculated to evaluate nutritional status (kg/m$^2$ multiplied by albumin in g/L). The LS mean difference in the change from baseline at month 18 was 116 (95% CI, 82 to 149; $P$ < 0.0001). Autonomic symptom severity and frequency was measured using the Composite Autonomic Symptom Score 31 questionnaire (scored from zero to 100, with a decrease in scores indicating improvement in symptoms). The difference between groups in change from baseline to 18 months was statistically significant in favour of patisiran (LS mean difference of −7.5; 95% CI, −11.9 to −3.2; $P$ = 0.0008). No MCID was identified in the literature.

The primary and key secondary outcomes showed a consistent pattern of treatment effects, with mean scores in the patisiran group remaining stable over 18 months and scores in the placebo group suggesting a decline in the patients' disease status. Based on the natural history of the disease, progression in neuropathic impairment would be expected in patients who remain untreated.[8] While all outcomes included in the statistical hierarchy were statistically significant, the clinical relevance of the differences observed was difficult to evaluate. The only outcome with an estimated MCID was the 10 metre walk test (0.05 m/s), and the difference between groups exceeded this threshold (0.31 m/s). The clinical experts consulted for this review stated that the mNIS+7 outcome measure is not used in clinical practice, although some components may be part of routine neurological examinations. The FDA considered the mNIS+7 to be an acceptable outcome measure in clinical trials, though it noted that some components of the mNIS+7 are biomarkers, with no direct clinical benefit, and differences in motor and sensory function detected by the physician might not be perceptible to the patient or result in improved function in daily activities.[8] However, the results of the Norfolk QoL-DN and R-ODS suggest that differences were perceived by patients.

Cardiac biomarker and echocardiogram data were reported in the APOLLO study; however, these data had a number of limitations. First, it is unclear if these measures represent direct clinical benefit in patients with hATTR amyloidosis. These outcomes were outside the statistical testing hierarchy and should be interpreted with consideration of the risk of type I error. In addition, the proportion of patients with a history of cardiac disorders appears to differ between groups at baseline, which may bias the cardiac outcome data. There was a planned analysis of a cardiac subgroup but randomization was not stratified for this group; consequently, the distribution of known and unknown confounders may not be balanced. And, indeed, a number of imbalances were observed between treatment groups in the baseline characteristics. Moreover, it is unclear if the criteria used to define this subgroup (left ventricular wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension) was clinically relevant, or if other diagnostic criteria should have been used to identify those with cardiomyopathy. Considering these limitations, no conclusions could be drawn with regard to the cardiac biomarker and echocardiogram data reported in APOLLO.

No direct evidence comparing patisiran with other drugs for hATTR amyloidosis was identified. The APOLLO study was 18 months in duration; thus, the efficacy of patisiran in the longer term is uncertain. A potential source of bias in the APOLLO study was the differential losses to follow-up (placebo 29%, patisiran 7%). The primary analysis assumed that patients were missing at random, which may not be true as the available data suggests that patients who withdrew had worse outcomes than those who remained in the trial. Sensitivity analyses were conducted to test the impact of missing data, including one that assumed patients were missing not at random. Although the results of these analyses were similar to the primary analysis, these analyses cannot fully account for the impact of missing data. Even so, the potential bias due to the missing data would likely bias toward the null rather than overestimate the treatment effects of patisiran.

The manufacturer submitted an indirect comparison that compared patisiran with inotersen, based on data from two phase III trials (APOLLO and NEURO-TTR). In this analysis, individual patient data from APOLLO was used to calculate the mNIS+7$_{ionis}$, a composite that used different sensory and autonomic testing than the mNIS+7 in APOLLO, but the same Neurologic Impairment Score–Weakness, Neurologic Impairment Score–Reflexes, and nerve conduction studies. Two indirect comparisons were calculated, one using the Bucher method and a second using matching-adjusted indirect comparison methods. Both

analyses suggested that patisiran was statistically superior to inotersen for the change from baseline in mNIS+7$_{ionis}$ and the Norfolk QoI-DN scores. Although the differences between treatments were statistically significant, the clinical significance of the differences is unclear, given the lack of MCID for these outcome measures. A second indirect comparison comparing patisiran with tafamidis was identified in the literature, but due to differences in the patient populations and outcome measures, the results carry a high level of uncertainty and no strong conclusions could be drawn from this analysis.

### Harms

In the APOLLO study, most patients (97%) experienced an adverse event, with diarrhea, peripheral edema, and infusion-related reactions reported most frequently among those who received patisiran. The percentage of patients who reported a serious adverse event was similar for the patisiran (37%) and placebo (40%) groups, but the percentage of patients who stopped treatment due to adverse events was lower in the patisiran group than in the placebo group (5% versus 14%). Infusion-related reactions were reported more frequently in the patisiran group than in the placebo group (19% versus 9%); however, only one patient treated with patisiran stopped treatment due to these events and no events met the criteria for a serious adverse event. The most common infusion-related reactions in the patisiran group were back pain, abdominal pain, headache, arthralgia, and dyspnea. Flushing was the most common infusion-related reaction in the placebo. Some of these adverse events were associated with premedications administered prior to the infusions and, as a result, the premedication regimen was modified. The manufacturer stated that there was no increase in infusion-related reactions with the reduced dose premedication regimen.

No data were reported on comparative safety in the manufacturer-provided indirect comparison between patisiran and inotersen, and no other comparative safety data for patisiran versus tafamidis or diflunisal were identified in the literature.

No new safety signals were detected in the open-label extension studies; however, these data were limited by the small sample size, select patient population, and lack of control group or blinding. Moreover, the APOLLO study had limited power to detect infrequent adverse events, or those with a longer lag time. Considering that patisiran is part of a new drug class and controlled data were limited to a single RCT that was 18 months in duration, additional data are required to determine the safety of the drug in the longer term.

## Clinical Expert Input[1]

There is a substantial need for more effective treatments for hATTR amyloidosis than the treatment options that are currently available in Canada. The two main treatment options for hATTR amyloidosis patients are diflunisal, a non-steroidal anti-inflammatory drug that is not specifically approved by Health Canada for treating hATTR amyloidosis, and liver transplant. Neither of these treatment options reverse the course of disease and, in many patients, the disease will continue to progress. Patients may not respond to these treatments or may experience intolerable adverse effects. Further, there may be barriers to access.

Due to the limitations associated with the currently available treatments, it is highly likely that there will be a strong desire within the clinical and patient communities to use RNAi

[1] This information is based on information provided by a clinical expert panel consulted by CDR reviewers for the purpose of this review.

treatments that are being developed to treat hATTR amyloidosis as first-line therapy, prior to diflunisal or liver transplant. The clinical experts believe that the upcoming RNAi treatments should be used only in patients with a confirmed genetic diagnosis of hATTR amyloidosis who present with clear clinical symptoms and do not have any contraindications to the drugs. There was disagreement among the panellists as to whether the eligibility of patients for treatment with RNAi therapy should be based on the inclusion criteria of clinical trials of these treatments or whether it is appropriate to treat a broader population of hATTR amyloidosis patients for which there is very little (or no) clinical trial evidence.

Panellists discussed that there is no defined threshold for determining when a patient should be considered symptomatic and the situation may be confounded by coexisting conditions, such as occupational carpal tunnel syndrome or diabetic neuropathy. The panel agreed that it is difficult to establish an objective guideline of when to start treatment and that this is best left to the expert opinion of the treating physician. The trials recruited patients with earlier stages of polyneuropathy who were not confined to a wheelchair and those who had not undergone a liver transplant. Panellists discussed that patients with advanced polyneuropathy, who are confined to a wheelchair, may still have sensory and motor function in the hands and arms that may be preserved with treatment. More data are required to know if such patients, as well as those with a liver transplant who were continuing to progress, would benefit from treatment.

The treatments with an IV route of administration should be administered under the care of specialist(s), primarily neurologists and cardiologists, in centres that routinely administer infusions, such as hospitals, university centres, specialty clinics, and private centres. A clinically meaningful response to treatment could be considered an improvement in symptoms or stabilization of neurologic impairment as assessed clinically. Patients who exhibit a reduced rate of decline may also be responding to treatment, although judging the rate of decrease compared with the natural history of the disease could be challenging as no clear thresholds are available. There was no consensus among panellists of what measure is most suitable to assess response to treatment and the panel acknowledged that it will be difficult to establish criteria for treatment discontinuation. Continued disease progression may indicate that the patient is not responding to treatment, although disease progression itself is not an indicator of nonresponse. The decision to stop treatment should not be based on only one outcome, such as ambulation, because non-ambulatory individuals may still have function in the upper limbs that is important for maintaining acceptable quality of life (e.g., ability to feed oneself).

There are many unknowns associated with the RNAi treatments that are being developed for hATTR amyloidosis. Overall, the clinical experts believe that RNAi treatments offer many advantages over the current standard of care, although direct evidence of superiority is lacking. Given the limitations associated with currently available treatments for hATTR amyloidosis, most patients will likely request the new RNAi treatments; i.e., it is highly likely that RNAi treatments will become first-line therapy for hATTR amyloidosis and that there will be a strong desire within the clinical and patient community to treat hATTR amyloidosis patients with polyneuropathy with an RNAi-based therapy, including transitioning patients on current standard of care to an RNAi treatment.

## Conclusions

One double-blind, placebo-controlled, phase III RCT evaluated the safety and efficacy of patisiran in patients with hATTR amyloidosis and polyneuropathy FAP stage I and II. After 18 months of treatment, patients treated with patisiran showed statistically significant differences versus those treated with placebo in neurological impairment, measured using the mNIS+7 composite score, and health-related quality of life, based on the Norfolk QoL-DN questionnaire. Statistically significant differences were also demonstrated in favour of patisiran for disability (measured using the R-ODS), gait speed, unintended weight loss (measures by mBMI), and autonomic symptoms (measured by the Composite Autonomic Symptom Score 31 instrument).

Infusion-related reactions were reported more frequently in the patisiran group than the placebo group; however, these events rarely required the patient to stop treatment. Considering that patisiran is part of a new drug class and comparative data were limited to a single placebo-controlled RCT that was 18 months in duration, additional data are required to determine the safety and efficacy of patisiran in the longer term.

No direct evidence was available comparing patisiran with other treatments for hATTR amyloidosis, though an indirect comparison suggests patisiran may be statistically superior to inotersen for the change from baseline in mNIS+7$_{ionis}$ and the Norfolk Qol-DN. However, the clinical significance of the differences calculated is unclear, given the lack of MCID for these outcome measures. The indirect comparison provided no data on the comparative safety.

### Table 1: Summary of Key Efficacy Outcomes in the APOLLO Study (Modified Intention-to-Treat)

| | Baseline | | 18 Months | | | LS Mean Difference Patisiran vs. Placebo (95% CI) | *P* Value[a] |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | LS Mean Change From Baseline (SE) | | |
| **mNIS+7[b]** | | | | | | | |
| Placebo | 77 | 74.6 (37.0) | 51 | 101.1 (45.4) | 28.0 (2.6) | | |
| Patisiran | 148 | 80.9 (41.5) | 137 | 75.1 (43.2) | −6.0 (1.7) | −34.0 (−39.9 to −28.1) | < 0.0001 |
| **NIS-W[c]** | | | | | | | |
| Placebo | 77 | 29.0 (23.0) | 51 | 46.3 (31.8) | 17.9 (2.0) | | |
| Patisiran | 148 | 32.7 (25.2) | 137 | 33.7 (28.3) | 0.05 (1.3) | −17.9 (−22.3 to −13.4) | < 0.0001 |
| **Norfolk QoL-DN[d]** | | | | | | | |
| Placebo | 76 | 55.5 (24.3) | 48 | 71.7 (29.3) | 14.4 (2.7) | | |
| Patisiran | 148 | 59.6 (28.2) | 136 | 55.4 (30.6) | −6.7 (1.8) | −21.1 (−27.2 to −15.0) | < 0.0001 |
| **R-ODS[e]** | | | | | | | |
| Placebo | 76 | 29.8 (10.8) | 54 | 21.0 (13.4) | −8.9 (0.9) | | |
| Patisiran | 148 | 29.7 (11.5) | 138 | 29.5 (12.7) | 0.0 (0.6) | 9.0 (7.0 to 10.9) | < 0.0001 |
| **10MWT Gait Speed (m/s)[f]** | | | | | | | |
| Placebo | 77 | 0.79 (0.32) | 55 | 0.56 (0.40) | −0.24 (0.04) | | |

| | Baseline | | 18 Months | | | LS Mean Difference Patisiran vs. Placebo (95% CI) | *P* Value[a] |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | LS Mean Change From Baseline (SE) | | |
| Patisiran | 147 | 0.80 (0.4 ) | 138 | 0.85 (0.50) | 0.08 (0.02) | 0.31 (0.23 to 0.39) | < 0.0001 |
| **mBMI (kg/m$^2$ × Albumin g/L)** | | | | | | | |
| Placebo | 77 | 989.9 (214.2) | 52 | 892.7 (221.1) | −119.4 (14.5) | | |
| Patisiran | 148 | 969.7 (210.5) | 133 | 975.4 (228.6) | −3.7 (9.6) | 115.7 (82.4 to 149.0) | < 0.0001 |
| **COMPASS 31[g]** | | | | | | | |
| Placebo | 76 | 30.3 (16.4) | 53 | 33.1 (17.6) | 2.2 (1.9) | | |
| Patisiran | 146 | 30.6 (17.6) | 136 | 25.6 (17.1) | −5.3 (1.3) | −7.5 (−11.9 to −3.2) | 0.0008 |

10MWT = 10 metre walk test; CI = confidence interval; COMPASS 31 = Composite Autonomic Symptom Score 31; LS = least squares; mBMI = modified body mass index; MMRM = mixed-effects model for repeated measures; mNIS+7 = modified Neurologic Impairment Score +7; NIS = Neurologic Impairment Score; NIS-W = Neurologic Impairment Score–Weakness; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation; SE = standard error; V30M = valine to methionine substitution at position 30; vs. = versus.

[a] Analysis based on a MMRM that included baseline score, treatment, visit, treatment-by-visit interaction, genotype (V30M or non-V30M), age at onset (< 50 years or ≥ 50 years), region (North America, Western Europe, other), and prior tetramer stabilizer use (yes or no) for mNIS+7 and NIS-W. The same MMRM was used for all other outcomes with the addition of baseline NIS score (< 50 or ≥ 50) as a covariate. All outcomes in were included in the statistical testing hierarchy. The total number of patients randomized was 225 (placebo, 77, and patisiran, 148).

[b] The mNIS+7 composite outcome is scored from 0 (no impairment) to 304 (maximum impairment). mNIS+7 was the primary outcome in the APOLLO study.

[c] Maximum score of 192 points for the NIS-W subscale (a higher score indicates greater impairment). NIS-W is a component of the mNIS+7.

[d] The range of possible scores is −4 to 136 for the Norfolk Qol-DN, with a decrease in scores indicating an improvement in quality of life.

[e] The R-ODS is scored from zero to 48, with zero being the worst disability and 48 the best (no limitations).

[f] Patients who were unable to walk had gait speed imputed as zero.

[g] The COMPASS 31 is a measure of autonomic neuropathy symptoms and is scored from zero to 100. A decrease in scores indicates improvement in symptoms.

Source: Clinical Study Report for the APOLLO study.[7]

## Table 2: Summary of Harms in the APOLLO Study

| Adverse Event | APOLLO[a] | |
|---|---|---|
| | Placebo N = 77 | Patisiran N = 148 |
| Deaths, n (%) | 6 (8) | 7 (5) |
| Patients with ≥ 1 SAE, n (%) | 31 (40) | 54 (37) |
| Patients who stopped treatment due to adverse events, n (%) | 11 (14) | 7 (5) |
| Infusion-related reactions, n (%) | 7 (9) | 28 (19) |
| Cardiac arrhythmias (HLGT), n (%) | 22 (29) | 28 (19) |
| AV block complete, n (%) | 0 | 3 (2.0) |
| Night blindness, n (%) | 1 (1.3) | 0 |
| Anti-drug antibodies, n (%) | 1 (1.3) | 5 (3.4) |

AV = atrioventricular; HLGT = high-level group term; SAE = serious adverse event.

[a] Safety population (all randomized patients who received at least one dose of study drug).

Source: Clinical Study Report for the APOLLO study.[7]

# Introduction

## Disease Prevalence and Incidence

Hereditary transthyretin-mediated (hATTR) amyloidosis is a rare, progressive, often fatal condition caused by an autosomal dominant mutation in the transthyretin (TTR) gene. TTR is a plasma transport protein for thyroxine and vitamin A that is produced predominantly in the liver.[1] In its natural state TTR exists as a tetramer, but TTR gene mutations can destabilize the protein, causing it to disassociate, misfold, and aggregate into amyloid fibrils that are deposited in various tissues in the body. Amyloid accumulation causes a peripheral neuropathy involving motor, sensory, and autonomic fibres that leads to progressive muscle weakness and disability, pain, wasting, gastrointestinal dysfunction, and other autonomic symptoms, such as orthostatic hypotension.[1] Cardiac amyloid deposits lead to cardiac hypertrophy, arrhythmias, and heart failure.[1] The leptomeningeal form of TTR amyloidosis is associated with cerebral amyloid angiopathy and ocular amyloidosis.[1] Although patients may be classified as having predominantly neurological or cardiac disease manifestations, these distinctions may be artificial as neuropathy, cardiomyopathy, vitreous opacities, kidney disease, and meningeal involvement may be present to various degrees in each patient with hATTR amyloidosis.[9]

Neurologic impairment may be rapidly progressive, particularly in the first five years after symptom onset.[2] Symptoms of nerve damage (i.e., tingling, numbness, burning pain, carpal tunnel, and weakness) were rated by patients who provided input to this review as the most difficult. For many, these symptoms were incapacitating or had a serious impact on their lives. Other serious or incapacitating symptoms included diarrhea, sexual dysfunction, changes in sweating, dizziness upon standing, weight loss, and depression. Walking and activities of daily living become increasingly difficult, leaving patients completely dependent upon caregivers. Progressive heart failure and sudden cardiac death are common causes of death among those with hATTR amyloidosis.[3] Survival estimates reported in the literature vary, ranging from five to 15 years after diagnosis.[2,9]

hATTR amyloidosis is known to be endemic in Portugal, Sweden, and specific regions of Japan, but has been reported in 36 countries worldwide and may be under-diagnosed.[4] Globally, it is estimated that there are 10,186 persons with hATTR amyloidosis and polyneuropathy (range: 5,526 to 38,468).[4] Epidemiological studies of hATTR amyloidosis in Canada have not been conducted but when available prevalence estimates are extrapolated to the Canadian population, the number of persons with hATTR amyloidosis and polyneuropathy ranges from 12 (low) to 53 (mid) to 270 (high).[4]

More than 100 disease-causing TTR gene mutations have been reported, and the geographic distribution of hATTR mutations is variable.[1,4] Based on the Transthyretin Amyloid Outcome Survey, a global longitudinal registry of patients with amyloid transthyretin (ATTR) amyloidosis, the most commonly reported mutations among US patients were valine to isoleucine substitution at position 122 (V122I) (n/N = 91/201, 45%) and threonine to alanine substitution at position 60 (Thr60Ala) (n = 41, 20%), whereas the valine to methionine substitution at position 30 (or V30M) was most common mutation among patients from 16 other countries (n/N = 1,627/2,034, 80%).[10] The phenotype varies among and within various mutations, and the timing, development, and severity of the disease can vary greatly.[11] Thus, some carriers of the gene may live to an advanced age without symptoms, but their children may be clinically affected.[1] For example, in Portugal, penetrance is high, with 80% of V30M carriers showing disease symptoms by age 50.[1] This

is in contrast with endemic regions of northern Sweden, where penetrance of the V30M mutation is low (11% by the age of 50).[1]

## Standards of Therapy

Patients may receive supportive care to manage symptoms of the disease. Disease-modifying treatments include liver transplant and diflunisal. Liver transplant lowers the production of mutant TTR by approximately 95% and can slow or halt the progression of the disease; it is not curative.[1] However, nerve function may not improve and some patients do not perceive an improvement in their health-related quality of life.[1] Outcomes are generally most favourable if liver transplant, or heart and liver transplant, is performed in young patients with early stage disease.[1] Access is limited by the availability of donor organs, surgical morbidity is high, and transplant patients require lifelong immunosuppressant therapy. In the Transthyretin Amyloid Outcome Survey cohort, 3.3% of symptomatic patients in the US had liver transplant compared with 18.6% of the rest of world.[10] Twenty-year survival after liver transplant was 55.3%, based on data from 1,940 patients with the V30M and other mutations in the Familial Amyloidotic Polyneuropathy World Transplant Registry.[12] Among those with non-V30M mutations, median survival after liver transplant, or liver and heart transplant, was 7.1 years and 7.8 years, respectively, although survival varied for different mutations.[11] Multivariate analysis showed that modified body mass index (mBMI), early onset disease (< 50 years of age), disease duration prior to transplant, and V30M versus other mutations were significantly associated with survival following transplant.[12] Diflunisal is a nonsteroidal anti-inflammatory drug that has been used as a tetramer stabilizer to delay neurological progression in patients with hATTR amyloidosis and polyneuropathy (although Health Canada has not approved this use).[13] This drug has a number of adverse effects that limits its use, particularly for those with heart failure or renal impairment, which is common among those with hATTR amyloidosis (see Table 3). Moreover, the available evidence to support the use of diflunisal in hATTR amyloidosis is limited to a single randomized controlled trial (RCT) that had a number of methodological issues.[13] The experts who provided input for this review agreed that there is a significant unmet need given the limitations of these therapies for hATTR amyloidosis.

In October 2018, inotersen was approved in Canada for the treatment of stage I or stage II polyneuropathy in adults with hATTR amyloidosis (see Table 3).[14] Inotersen is an antisense oligonucleotide that selectively binds to TTR messenger ribonucleic acid (RNA) causing the degradation of TTR messenger RNA, and preventing the synthesis of mutant and wild-type TTR in the liver.[14] At the time this report was written, inotersen was under review by the CADTH Common Drug Review.

Tafamidis, another tetramer stabilizer, is approved in Europe for stage I symptomatic polyneuropathy in patients with hATTR amyloidosis.[15] A phase III trial of tafamidis in patients with hATTR amyloidosis and cardiomyopathy has recently been published,[16] and this drug was approved by the FDA for treatment of the cardiomyopathy of hATTR or wild-type TTR amyloidosis in adults, to reduce cardiovascular mortality and cardiovascular-related hospitalization.[17] Tafamidis has not been approved for use in Canada but has been accessible via Health Canada's Special Access Programme.

## Drug

Patisiran is a double-stranded, small interfering ribonucleic acid (siRNA) that, through a process called RNA interference (RNAi), causes the catalytic degradation of TTR messenger RNA in the liver, which reduces serum TTR protein and subsequent amyloid deposits in tissue.[5] The drug is formulated as lipid nanoparticles to deliver the siRNA to hepatocytes, the primary source of TTR.

Patisiran is approved by Health Canada for the treatment of polyneuropathy in adult patients with hATTR amyloidosis.[5] The product is available as a 2 mg/mL lipid complex solution for IV administration (5 mL solution in a 10 mL single-use vial) that must be diluted and infused over 80 minutes. The recommended dosage is 0.3 mg/kg IV every three weeks, with a maximum dose of 30 mg for patients who weigh 100 kg or greater.[5] All patients should receive premedication at least 60 minutes prior to each dose to prevent infusion-related reactions. The premedications include IV corticosteroid (dexamethasone 10 mg or equivalent), acetaminophen 500 mg orally, IV histamine-1 blocker (diphenhydramine 50 mg or equivalent) and IV histamine-2 blocker (ranitidine 50 mg or equivalent).[5]

### Table 3: Key Characteristics of Patisiran, Inotersen, Tafamidis, and Diflunisal

| | Patisiran | Inotersen | Tafamidis | Diflunisal |
|---|---|---|---|---|
| **Mechanism of action** | RNA interference (direct sequence-specific degradation of TTR mRNA in the liver) | RNA interference (antisense oligonucleotide that degrades TTR mRNA) | Stabilizer of TTR | Nonsteroidal anti-inflammatory drug (stabilizer of TTR) |
| **Indication** | Treatment of polyneuropathy in adults with hATTR amyloidosis[a] | Stage I or stage II polyneuropathy in adults with hATTR amyloidosis[a] | Treatment of TTR amyloidosis in adult patients with stage I symptomatic polyneuropathy to delay peripheral neurologic impairment[b]<br><br>Treatment of the cardiomyopathy of hATTR or wild-type TTR amyloidosis in adults to reduce CV mortality and hospitalization[c] | Not approved by Health Canada for hATTR amyloidosis |
| **Route of administration** | IV | SC | oral | oral |
| **Recommended dosage** | 0.3 mg/kg IV every 3 weeks, with a maximum dose of 30 mg for patients who weigh 100 kg or more | 284 mg SC every week via pre-filled syringe | 20 mg capsule once daily | 250 mg twice daily |
| **Serious side effects and safety issues** | Infusion-related reactions; reduced vitamin A levels<br><br>Contraindications: severe hypersensitivity to product | Thrombocytopenia; glomerulonephritis, reduced vitamin A levels<br><br>Contraindicated in patients with platelet count < 100 × $10^9$/L, urine protein to creatinine ratio | Urinary tract infections, vaginal infection, diarrhea, upper abdominal pain<br><br>Contraindications: hypersensitivity to product | Gastrointestinal ulceration and bleeding, altered renal function, renal decompensation, fluid retention, congestive heart failure |

| | Patisiran | Inotersen | Tafamidis | Diflunisal |
|---|---|---|---|---|
| | | ≥ 113 mg/mmol, estimated glomerular filtration rate < 45 mL/L/min/1.73 $m^2$, severe liver impairment, or hypersensitivity to the product | | Contraindications: hypersensitivity to product, active peptic ulcer |
| **Other** | Must be administered by a health care professional in a supervised setting. Premedications are required to minimize the risk of infusion-related reactions; vitamin A supplementation is recommended | Monitoring of platelet count is required (every 2 weeks) with dose adjustment or drug discontinuation for platelet levels < 100 × $10^9$/L; vitamin A supplementation is recommended | – | Drug not routinely stocked in Canadian pharmacies |

CV = cardiovascular; hATTR = hereditary transthyretin-mediated; mRNA = messenger ribonucleic acid; RNA = ribonucleic acid; SC = subcutaneous; TTR = transthyretin.

[a] Health Canada indication.

[b] European Medicines Agency indication.

[c] US FDA indication.

Source: Onpattro draft product monograph,[5] Tegsedi product monograph,[14] Tafamidis summary of product characteristics,[18] Diflunisal product monograph,[19] Berk et al. (2013),[13] Vyndaqel prescribing information.[17]

# Objectives and Methods

## Objectives

To perform a systematic review of the beneficial and harmful effects of patisiran 2 mg/mL IV solution for the treatment of hATTR amyloidosis with polyneuropathy in adults.

## Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review and Health Canada, as well as those meeting the selection criteria presented in Table 4.

### Table 4: Inclusion Criteria for the Systematic Review

| | |
|---|---|
| **Patient Population** | Adults with hATTR amyloidosis with polyneuropathy<br><br>Subgroups:<br>• polyneuropathy stage<br>• patients with cardiac manifestations<br>• patients who had previously undergone liver transplant |
| **Intervention** | Patisiran 0.3 mg/kg IV every 3 weeks |
| **Comparators** | • Inotersen<br>• Diflunisal[a]<br>• Tafamidis[b]<br>• Supportive care<br>• Placebo |
| **Outcomes** | **Efficacy Outcomes**<br>• Mortality (e.g., cardiovascular or all-cause)[c]<br>• Hospitalizations (e.g., cardiovascular or all-cause)<br>• Cardiovascular morbidity[c]<br>• Health-related quality of life[c]<br>• Neurological impairment (including autonomic nervous system)[c]<br>• Neurological symptoms (e.g., pain)[c]<br>• Disability[c]<br>• Functional status[c]<br>• Nutritional status<br>• Cardiac biomarkers or measures of cardiac structure and function (e.g., NT-proBNP, troponin I, LV wall thickness, LV longitudinal strain, LVEF)<br><br>**Harms Outcomes**<br>AEs, SAEs, WDAEs, infusion-related reactions, signs or symptoms of vitamin A deficiency (e.g., night blindness), atrioventricular block, anti-drug antibodies |
| **Study Design** | Published and unpublished phase III and phase IV RCTs |

AE = adverse events; hATTR = hereditary transthyretin-mediated; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

[a] Off-label use in Canada.

[b] Not approved for use in Canada but is available through Health Canada's Special Access Programme for patients with hATTR amyloidosis.

[c] These outcomes were identified as being of particular importance to patients in the input that CADTH received from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Onpattro (patisiran).

No methodological filters were applied to limit retrieval to study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on February 22, 2019. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on June 19, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature — literature that is not commercially published — was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies**,** health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings**,** drug class reviews, and databases. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

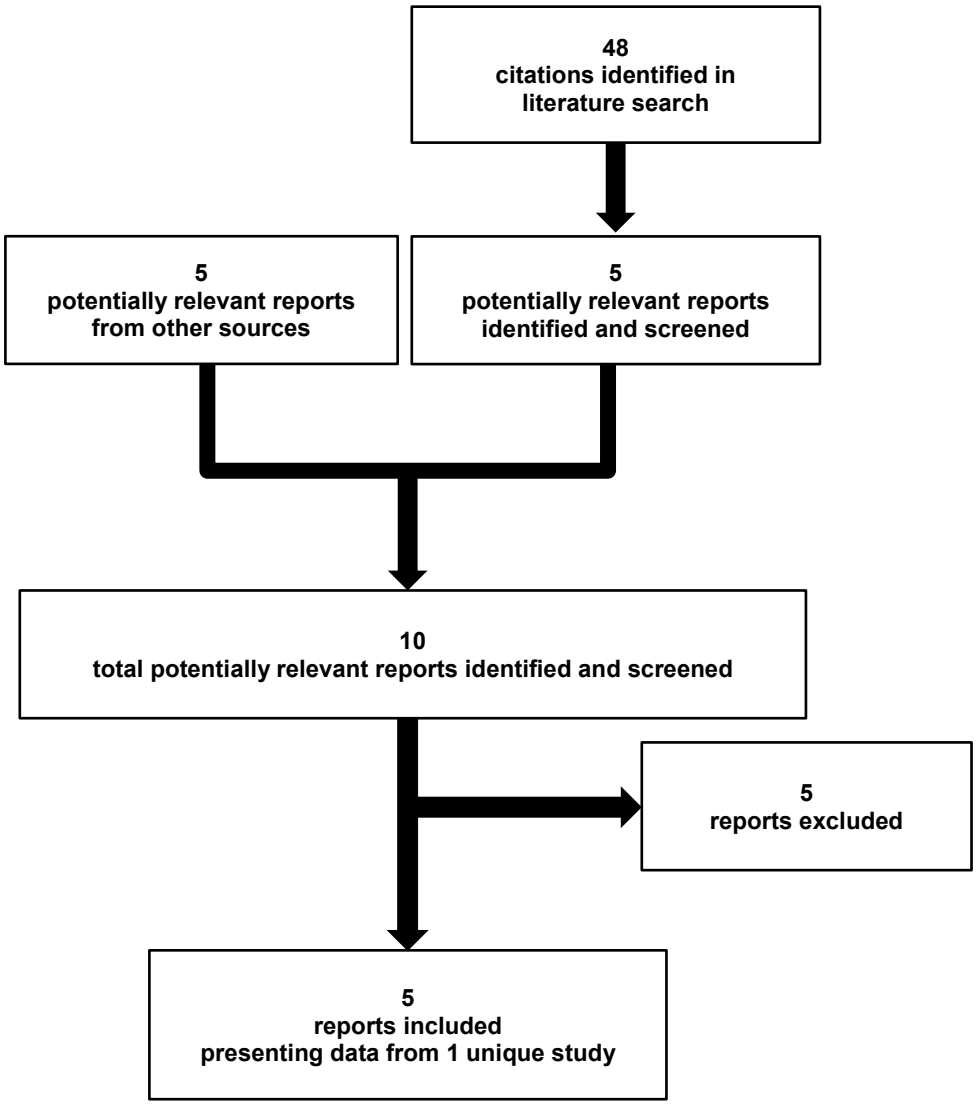
Two CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

# Results

## Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (see Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 3.

### Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



## Table 5: Details of Included Studies

| | | APOLLO |
|---|---|---|
| Designs and Populations | **Study design** | Double-blind, placebo-controlled, phase III RCT |
| | **Locations** | US, Canada, Mexico, Europe, Asia, Argentina, Brazil (44 centres, 19 countries) |
| | **Randomized (N)** | 225 |
| | **Inclusion criteria** | Adults (18 to 85 years of age) with diagnosis of FAP with documented TTR mutation, and:<br>• NIS score of 5 to 130 and a polyneuropathy disability score of ≤ 3b<br>• NCS sum of the sural SNAP, tibial CMAP, ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥ 2 points<br>• Karnofsky Performance Status of ≥ 60%[a]<br>• absolute neutrophil count ≥ 1,500 cells/mm³, and a platelet count ≥ 50,000 cells/mm³<br>• aspartate transaminase and alanine transaminase levels ≤ 2.5 × ULN, total bilirubin within normal limits, INR ≤ 2.0 (patients on anticoagulant therapy with an INR of ≤ 3.5 were allowed)<br>• serum creatinine ≤ 2 × ULN<br>• no active infection with hepatitis B or hepatitis C by serology |
| | **Exclusion criteria** | • Prior liver transplant<br>• New York Heart Association heart failure classification III or IV<br>• Other known causes of sensorimotor or autonomic neuropathy<br>• Had known primary amyloidosis or leptomeningeal amyloidosis<br>• Type I diabetes<br>• Type II diabetes mellitus for ≥ 5 years<br>• Vitamin B12 levels below the lower limit of normal<br>• Untreated hypothyroidism or hyperthyroidism<br>• Major surgery within the past 3 months or had a major surgery planned during the study period<br>• HIV infection<br>• Active infection requiring systemic antiviral or antimicrobial therapy that was not completed prior to the first dose of study drug administration<br>• Malignancy within 2 years<br>• Acute coronary syndrome within the past 3 months<br>• Uncontrolled cardiac arrhythmia or unstable angina<br>• History of alcohol abuse within the past 2 years or daily heavy alcohol consumption<br>• Anticipated survival was less than 2 years<br>• Currently using a prohibited medication |
| Drugs | **Intervention** | Patisiran 0.3 mg/kg IV every 3 weeks |
| | **Comparator(s)** | Placebo |
| Duration | **Phase** | |
| | Screening | 42 days |
| | Double-blind | 18 months |
| | Follow-up | 21 days[b] |
| Outcomes | **Primary end point** | Change from baseline in mNIS+7 score at 18 months |
| | **Other end points** | Change from baseline to 18 months in:<br>• Norfolk QoL-DN questionnaire<br>• Neurologic Impairment Score–Weakness score |

| | | APOLLO |
|---|---|---|
| | | • Rasch-built Overall Disability Scale<br>• timed 10 metre walk test<br>• modified body mass index<br>• Composite Autonomic Symptom Score<br>• EQ-5D-5L<br>• FAP stage and polyneuropathy disability score<br>• NT-proBNP, troponin I<br>• LVEF, LV wall thickness and longitudinal strain<br>• harms |
| NOTES | **Publications** | Adams et al. (2018)[20]<br>Solomon et al. (2019)[21] |

CMAP = compound muscle action potential; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FAP = familial amyloidotic polyneuropathy; INR = international normalized ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; mNIS+7 = modified Neurologic Impairment Score +7; NCS = nerve conduction study; NIS = Neurologic Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = N-terminal prohormone brian-type natriuretic peptide; RCT = randomized controlled trial; SNAP = sensory nerve action potential; TTR = transthyretin; ULN = upper limit of normal.

Note: Two additional reports were included: an FDA report and CADTH Common Drug Review submission.[8,22]

[a] Karnofsky Performance Status of 60% is defined as follows: Required occasional assistance but was able to care for most of their personal needs.

[b] Patients who did not enter the extension study had a final follow-up visit 56 days after the last dose was received.

Source: Clinical Study Report for the APOLLO study.[7]

## Included Studies

### Description of Studies

One double-blind, parallel-design, placebo-controlled, phase III RCT met the inclusion criteria for the systematic review (the APOLLO study). In this trial, adults diagnosed with familial amyloidotic polyneuropathy (FAP) with documented TTR mutation were enrolled and randomized (2:1) to patisiran or placebo every three weeks for 18 months (N = 225). Randomization was stratified by Neurologic Impairment Score (NIS) (five to 49 versus 50 to 130), early onset (< 50 years of age) with V30M mutation versus all other mutations, including late onset with V30M mutation, and previous use of tafamidis or diflunisal versus no prior tetramer stabilizer use. An interactive response or voice system was used to allocate patients to treatment groups. The study objective was to determine the superiority of patisiran versus placebo on the change from baseline to 18 months on the modified Neurologic Impairment Score +7 (mNIS+7).

Patients from 19 countries and 44 study centres were randomized and treated, including five patients from one study centre in Canada. Countries that randomized ≥ 10 patients were the US, France, Taiwan, Spain, Japan, Germany, Mexico, Portugal, and South Korea.

Patients who completed the 18-month study were eligible to enrol in the extension study, where all patients received patisiran 0.3 mg/kg IV every three weeks (Study ALN-TTR02-006). The phase II and phase III extension studies for patisiran (ALN-TTR02-003 and ALN-TTR-006, respectively) did not meet the criteria for the systematic review but have been included as supplementary data in Appendix 6.

## Populations

### *Inclusion and Exclusion Criteria*

Eligibility criteria for the APOLLO study included adults (18 to 85 years of age) with a diagnosis of FAP with documented transthyretin (TTR) mutation, who had a NIS of five to 130 and a polyneuropathy disability (PND) score of ≤ 3b (i.e., no impairment to walking with the help of two sticks or crutches). Patients were excluded if they had prior liver transplant, New York Heart Association heart failure classification III or classification IV (i.e., symptoms with less than ordinary physical activity or symptoms at rest), history of uncontrolled cardiac arrhythmias or unstable angina, or acute coronary syndrome within the past three months, type I diabetes, type II diabetes mellitus for ≥ five years, or other known causes of polyneuropathy. Other inclusion and exclusion criteria are listed in Table 5.

Patients who had participated in a clinical study with an antisense oligonucleotide must have had completed a three-month washout prior to start of the study drug administration. Any patients taking tafamidis, doxycycline, or tauroursodeoxycholic acid prior to enrolment must have had completed a 14-day washout, and those taking diflunisal must have had at least a three-day washout prior to randomization.

### *Baseline Characteristics*

In the APOLLO study, the mean age of patients was 59.6 years to 62.2 years, and 74% to 75% of patients were male in the patisiran and placebo groups, respectively (see Table 6). In most patients (72%), the onset of hATTR amyloidosis symptoms occurred when they were 50 years or older, and the mean duration from diagnosis of hATTR amyloidosis to study initiation ranged from 2.4 years to 2.6 years. Approximately half of patients were classified as FAP stage I (46%) and stage II (53%), and 53% had previously been treated with tafamidis or diflunisal. There were some differences in the race distribution between groups, with a higher percentage of white patients (76% versus 65%) and lower percentage of Asian patients (18% versus 33%) in the patisiran group than in the placebo group, respectively. The patisiran group also had a higher mean baseline mNIS+7 score (80.9 points) than the placebo group (74.6 points).

The V30M mutation was present in 52% and 38% of the placebo and patisiran groups, respectively (see Table 6). The most common non-V30M mutations were Ala97Ser, Thr60Ala, Glu89Gln, and Ser50Arg (present in > 5% of patients). [redacted] Overall, 49% of patients had New York Heart Association functional class I heart failure and 50% had class II (data were missing for three patients), with a similar distribution between treatment groups.

The manufacturer prospectively identified a cardiac subgroup with pre-existing cardiac amyloid involvement defined as baseline left ventricular (LV) wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension. In total, 36 placebo patients (47%) and 90 patisiran patients (61%) met the criteria for inclusion in this group. The mean age of patients in the

cardiac subpopulation was [redacted], 78% were male, 63% were white, and 60% were New York Heart Association class II (62% patisiran, 56% placebo). Of note: Randomization was not stratified for pre-existing cardiac involvement and [redacted] A summary of baseline characteristics for the cardiac subpopulation are listed in Table 20.

## Table 6: Summary of Baseline Characteristics

| Characteristic | APOLLO | |
|---|---|---|
| | Placebo N = 77 | Patisiran N = 148 |
| Mean age (SD), years | 62.2 (10.8) | 59.6 (12.0) |
| Male, n (%) | 58 (75) | 109 (74) |
| Race, n (%) | | |
| White | 50 (65) | 113 (76) |
| Asian | 25 (33) | 27 (18) |
| Other or missing | 2 (3) | 8 (5) |
| Years since diagnosis of hATTR amyloidosis, mean (SD) | 2.6 (3.2) | 2.4 (3.3) |
| Age at hATTR amyloidosis symptom onset, n (%) | | |
| < 50 years | 20 (26) | 42 (28) |
| ≥ 50 years | 57 (74) | 106 (72) |
| Mean mNIS+7 (SD) | 74.6 (37.0) | 80.9 (41.5) |
| Polyneuropathy disability score, n (%) | | |
| I | 20 (26) | 36 (24) |
| II | 23 (30) | 43 (29) |
| IIIA | 22 (29) | 41 (28) |
| IIIB | 11 (14) | 28 (19) |
| IV | 1 (1) | 0 |
| Familial amyloidotic polyneuropathy stage | | |
| 0 | 0 | 0 |
| I | 37 (48) | 67 (45) |
| II | 39 (51) | 81 (55) |
| III | 1 (1) | 0 |
| Genotype, n (%) | | |
| V30M | 40 (52) | 56 (38) |
| Non-V30M | 37 (48) | 92 (62) |
| New York Heart Association functional class,[a] n (%) | | |
| I | 40 (52) | 70 (47) |
| II | 36 (47) | 77 (52) |
| III or IV | 0 | 0 |
| Missing | 1 (1) | 1 (1) |
| Previous Tetramer stabilizer use, n (%) | | |

| Characteristic | APOLLO | |
|---|---|---|
| Tafamidis | 27 (35) | 47 (32) |
| Diflunisal | 14 (18) | 31 (21) |
| None | 36 (47) | 70 (47) |

hATTR = hereditary transthyretin-mediated; mNIS+7 = Modified Neurologic Impairment Score +7; SD = standard deviation; V30M = valine to methionine substitution at position 30.

[a] Class I: no symptoms; class II: symptoms with ordinary physical activity; class III: symptoms with less than ordinary physical activity; class IV: symptoms at rest.

Source: Clinical Study Report for the APOLLO study.[7]

## Interventions

The patients randomized to patisiran received 0.3 mg/kg every three weeks, diluted in 0.9% sodium chloride and infused IV over at least 70 minutes. Those who weighed ≥ 105 kg were dosed based on 104 kg body weight. Patients randomized to placebo received a normal saline IV infusion infused over at least 70 minutes. Patients and all site personnel were blinded to treatment allocation, except for the pharmacists who prepared the study drug infusions. Infusion bags containing patisiran had an opalescent colour; thus, all infusion bags (and IV lines) were covered with amber bags to prevent blinded persons from viewing the bags. Both the study drug and placebo bags had the same total volume for infusion. Blinded study personnel who performed assessments related to efficacy end points were separate from personnel who monitored the administration of the study drug and monitored the well-being of the patient during the study.

All patients received premedications to minimize the risk of an infusion reaction. Premedications included corticosteroids, acetaminophen, histamine-2 receptor blocker and histamine-1 receptor blocker (see Table 7). In the original protocol, patients received premedications the evening prior to the study drug infusion, as well as one hour prior to the infusion, based on the schedule used in the phase II trial. However, some patients experienced adverse events in the phase II extension study (e.g., flushing) that were thought to be related to the corticosteroid doses administered. A reduced premedication regimen was implemented in these patients with no increase in infusion-related reactions. Based on this information, the premedication schedule in the APOLLO study was amended during the trial so that patients received a reduced premedication regimen (see Table 7).

During the study, patients were prohibited from using tafamidis, diflunisal, doxycycline, tauroursodeoxycholic acid, and corticosteroids (other than those administered as premedications, used to manage an infusion reaction, or topical, inhaled, or intra-articular corticosteroids). Low doses (< 20 mg per day prednisone) or short courses (≤ five days) of corticosteroids were allowed for patients with chronic inflammatory disorders such as asthma or rheumatoid arthritis.

All patients received oral vitamin A supplements at the recommended daily allowance (no further details on dosages received were provided in the Clinical Study Report).

A clinical adjudication committee reviewed blinded patient data at nine months and determined if the patient showed signs of rapid disease progression. Rapid disease progression was defined as a ≥ 24-point increase in the mNIS+7 (based on the average of two measurements) and FAP stage progression relative to baseline. Any patients who met these criteria were allowed to discontinue the study drug, follow a modified visit schedule, and receive the local standard of care, including tetramer stabilizers. Blinding to the study drug was maintained throughout the follow-up period, including for those who stopped treatment early.

## Table 7: Premedication Schedule

| Timing | Initial Premedication Schedule | Modified Premedication Schedule |
|---|---|---|
| **Evening prior to study drug dose** | • Oral dexamethasone (8 mg) or equivalent<br>• Oral acetaminophen (500 mg) or equivalent<br>• Oral H2 blocker (e.g., ranitidine 150 mg, famotidine 20 mg, or equivalent)<br>• Oral H1 blocker, 10 mg cetirizine (hydroxyzine 25 mg, fexofenadine, or equivalent may be substituted if patient does not tolerate cetirizine) | None |
| **60 minutes prior to the infusion** | • IV dexamethasone (20 mg) or equivalent<br>• Oral acetaminophen (500 mg) or equivalent<br>• IV H2 blocker (e.g., ranitidine 150 mg, famotidine 20 mg, or equivalent)<br>• IV H1 blocker; diphenhydramine 50 mg (or other equivalent IV H1 blocker) or oral hydroxyzine 25 mg, fexofenadine 25 mg, or cetirizine 10 mg may be substituted for any patient who does not tolerate IV H1 blocker | • IV dexamethasone (10 mg) or equivalent<br>• Oral acetaminophen (500 mg) or equivalent<br>• IV H2 blocker (e.g., ranitidine 50 mg, famotidine 20 mg, or equivalent)<br>• IV H1 blocker; diphenhydramine 50 mg (or other equivalent IV H1 blocker) or oral hydroxyzine 25 mg, fexofenadine 25 mg, or cetirizine 10 mg may be substituted for any patient who does not tolerate IV H1 blocker |

H1 = histamine-1 receptor blocker; H2 = histamine-2 receptor blocker.

Source: Clinical Study Report for the APOLLO study.[7]

### Outcomes

In the APOLLO study, there were two types of study sites:

1. Patient care sites could screen, dose, and manage the well-being of patients and collect safety assessments, but could not perform efficacy assessments (16 sites).
2. Central assessment sites could perform efficacy assessments in addition to performing the same assessments as at a patient care site (screen, dose, and manage the well-being of patients) (30 sites).

All patients were sent to a central assessment site for efficacy assessments at the screening, baseline, nine-month, and 18-month visits. Assessors who performed efficacy assessments at a central sites were different from site personnel who monitored the administration of the study drug during the study and monitored the well-being of the patient during the study. The Clinical Study Report stated that this was instituted so that patient management and adverse event monitoring (e.g., infusion reactions) would not influence efficacy assessment evaluation. Efficacy outcomes were assessed at baseline, month 9, and month 18, except for mBMI, which was assessed at month 3, month 6, month 12, month 15, and month 18.

The primary outcome was the change from baseline to 18 months in the mNIS+7. The mNIS+7 assessment tool is a 304-point composite measure of neurologic impairment that includes the following measures and components:

- a physical exam of the lower limbs, upper limbs, and cranial nerves to assess motor strength and weakness, and determine the component score for Neurologic Impairment Score–Weakness, or NIS-W (192 points total) and Neurologic Impairment Score–Reflexes, or NIS-R (20 points)
- sensory testing to determine the quantitative sensory testing (QST) score, which includes assessing touch pressure by body surface area and heat pain by body surface

area (this is conducted using a Computer Aided Sensory Evaluator IV device, and is scored out of a total of 80 points)

- electrophysiologic measures of small- and large-nerve fibre function to determine the sum of five attributes of nerve conduction studies that include assessment of the ulnar compound muscle action potential (CMAP), ulnar sensory nerve action potential, sural sensory nerve action potential, tibial CMAP, and peroneal CMAP (total 10 points)
- the measurement of postural blood pressure was measured to assess autonomic function (2 points total).[7,22]

The instrument is scored from zero (no impairment) to 304 (maximum impairment). Baseline, nine-month, and 18-month mNIS+7 scores were the average of two measurements taken at least 24 hours apart, but no more than seven days apart. Tests were conducted by neurologists or electromyography technicians who were trained and certified by the Mayo Clinic, US. All data were assessed by blinded reviewers at the Mayo Clinic to determine if the evaluation met the quality and acceptability standards. Repeat tests could be requested if the quality was not acceptable.

The available information on the validity, reliability, and responsiveness of the efficacy outcomes are described in Appendix 5. No studies were identified that examined the validity, reliability, or minimal clinically important difference (MCID) of the mNIS+7 used in the APOLLO trial; however, a similar version of the mNIS+7 that was used in the inotersen RCT (i.e., mNIS+7$_{ionis}$; see Table 26) and its components did show statistically significant correlation with PND score and the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) score in patients with hATTR amyloidosis.[23] The experts consulted for this review stated that the mNIS+7, as defined by the APOLLO trial, is not used in clinical practice to monitor patients; however, some components, such as the NIS-W, may be part of routine neurological assessments.

Secondary outcomes included the following: Norfolk QoL-DN questionnaire, NIS-W, Rasch-built Overall Disability Scale (R-ODS), 10 metre walk test (10MWT), mBMI, and the Composite Autonomic Symptom Score 31 (COMPASS 31).

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that assesses the impacts of neuropathy on functional status. It includes five domains: physical functioning and large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy.[6] The domains are aggregated to provide a total score (range −4 to 136), with higher scores representing poorer health status.[22] In patients with hATTR amyloidosis, the Norfolk Qol-DN showed moderate to high correlation with objective measures of neurologic function (i.e., NIS and QST).[6] It showed discriminant validity for patients with and without hATTR amyloidosis, and for different stages of the disease.[6] Test–retest reliability was acceptable.[6] No MCID was found in the literature.

An assessment of the disability each patient experienced was measured using the R-ODS. The R-ODS is comprised of a 24-item linearly weighted scale that captures activity and social participation limitations in patients.[7] The questions are rated on a three-level scale, from 0 (unable to perform), 1 (able to perform but with difficulty), and 2 (able to perform without difficulty).[22] It is scored from 0 to 48 with 0 being the worst disability and 48 the best (no limitations).[22]

The 10MWT test is conducted to assess a patient's ability to ambulate without assistance from another person, although ambulatory aids such as canes and walkers are permitted.[7]

The test measures functional mobility and walking speed in meters per second over the short distance. No MCID was identified for the 10MWT in patients with hATTR amyloidosis; however, in patients who had survived a stroke or older adults with mobility difficulties, a change of 0.05 m/s was estimated as a MCID. In the APOLLO study, the 10MWT scores were the average of two measurements taken at least 24 hours apart, but no more than seven days apart.

The nutritional status of patients was evaluated using the mBMI, calculated as the product of body mass index (weight in kilograms divided by the square of height in metres) and serum albumin (g/L). The mBMI corrects for hypoalbuminemia and edema and may reflect nutritional status more accurately than body mass index in conditions such as hATTR amyloidosis that are affected by wasting.

COMPASS 31 is a patient-reported measure to assess changes in autonomic symptoms. It consists of 31 questions that evaluate six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor.[7] Questions include either yes or no answers (scored as 1/0), present/not present (scored as 0/1), frequency of symptoms as "rarely or never," "occasionally or sometimes," "frequently or a lot of the time," and "almost always or constantly" (scored as 0, 1, 2, and 3, respectively), severity of symptoms as "mild," "moderate," and "severe" (scored as 1, 2, and 3, respectively), and the time course of symptoms (scored as 0 to 3, with 0 representing improvement, 1 representing no change, 2 representing some worsening, and 3 representing much worsening).[24] The scoring for changes in bodily function depended on the individual question.[24] Scores range from 0 to 100, with higher scores representing more severe symptoms.[25]

Exploratory outcomes in the APOLLO study included the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L), a generic quality of life instrument. The instrument is comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on five levels: level 1 is "no problems," level 2 is "slight problems," level 3 is "moderate problems," level 4 is "severe problems," and level 5 is "extreme problems" or "unable to perform."[26] The corresponding scoring of EQ-5D-5L health states is based on a scoring algorithm that is derived from preference data obtained from interviews using choice-based techniques (e.g., time trade-off) and discrete choice experiment tasks.[26] For the EQ-5D-5L index score, a Canadian-specific MCID of 0.037 points has been reported in the literature.[26] No MCID in hATTR amyloidosis was identified. Another component of the EQ-5D-5L is a visual analogue scale (VAS), which asks respondents to rate their health on a visual scale from zero (worst health imaginable) to 100 (best health imaginable).[26] Both the index score and VAS score were reported in the APOLLO study.

In APOLLO, ambulation and changes in disease stage were evaluated through physician assessment of PND score and FAP stage (see Table 8). Cardiac structure and function was assessed through echocardiogram and measurement of biomarkers of cardiac function, including serum levels of N-terminal prohormone brain-type natriuretic peptide, or NT-proBNP (chemiluminescence assay, normal range less than 144.63 pmol/L) and troponin I (chemiluminescence assay, normal range less than 0.10 mcg/L). These biomarkers are indicators of cardiac stress and injury, and the NT-proBNP has been correlated with mortality in patients with ATTR. Echocardiograms were analyzed centrally and the quantification of cardiac biomarkers was performed at a central laboratory. All of these outcomes were considered exploratory in the APOLLO study and were outside the statistical testing hierarchy.

## Table 8: Hereditary Transthyretin-Mediated Amyloidosis Ambulation and Disease Staging Descriptions

| PND Scores | | FAP Stages | |
|---|---|---|---|
| 0 | No symptoms | 0 | No symptoms |
| I | Sensory disturbances but preserved walking capability | I | Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs |
| II | Impaired walking capacity but ability to walk without a stick or crutches | II | Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk |
| IIIA | Walking with the help of one stick or crutch | III | Wheelchair bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs |
| IIIB | Walking with the help of two sticks or crutches | | |
| IV | Confined to a wheelchair or bedridden | | |

FAP = familial amyloidotic polyneuropathy; PND = polyneuropathy disability.

Source: Clinical Study Report for the APOLLO study.[7]

An adverse event was any untoward medical occurrence in a patient or clinical investigational patient who was administered a pharmaceutical product, whether or not considered drug-related.

A serious adverse event was any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was an important medical event that may have jeopardized the patient or may have required intervention to prevent one of the other outcomes listed.

### Statistical Analysis

The primary outcome in the APOLLO study was the change from baseline to 18 months in the mNIS+7 score, which was analyzed using a mixed-effects model for repeated measures (MMRM). Statistical models for the mNIS+7 and NIS-W subscore included covariates for baseline score and fixed effects variables for the treatment, visit, treatment-by-visit interaction, genotype (V30M or non-V30M), age at onset (< 50 or ≥ 50 years), region (North America, Western Europe, other), and prior tetramer stabilizer use (yes or no). Missing data were not imputed and assumed to be missing at random. For any patient who started an alternative treatment for hATTR amyloidosis (i.e., liver transplant, or tafamidis or diflunisal for more than 14 days) during the study period, their efficacy assessments after starting therapy were treated as missing. This would apply to any patients who met the criteria for rapid disease progression and started other therapies (see the Interventions section for more information). Details of the statistical analysis are summarized in Table 9.

Sample size calculations assumed the mNIS+7 score would show a mean increase of 24 points (standard deviation [SD] 16) over 18 months in the placebo group, based on natural history data from six patients with hATTR amyloidosis.[27] A sample of 200 patients would provide 90% power to detect an 8.95-point mean difference between treatment groups in the mNIS+7 (two-sided alpha 0.05), assuming 25% of patients discontinued early. The manufacturer did not provide justification for the 8.95 treatment effect expected in the trial.

A statistical hierarchy was used to control the overall type I error for the secondary outcomes. The change from baseline to 18 months outcome data were tested in the following order:

- Norfolk QoL-DN questionnaire total score
- NIS-W score
- R-ODS
- 10MWT
- mBMI
- COMPASS 31.

If the preceding outcome was significant at a two-sided 0.05 significance level, the next outcome was tested. If statistical significance was not achieved, then subsequent outcomes were tested and nominal *P* values were reported but statistical significance was not inferred. A MMRM model was used for the secondary outcomes, including the same covariates as the model used for the primary outcome with the addition of baseline NIS score (< 50 or ≥ 50) (see Table 9).

Other outcomes in the APOLLO study that were of interest to this review included the EQ-5D-5L index score and VAS, the FAP stage and PND score, cardiac biomarkers (NT-proBNP, troponin I) as well as left ventricular ejection fraction (LVEF), and LV wall thickness and longitudinal strain as measured by echocardiogram. There was no control for multiplicity for these outcomes. The EQ-5D data were analyzed using a MMRM model that included baseline score, treatment, visit, treatment-by-visit interaction, genotype, age at onset, region, and prior tetramer stabilizer use (see Table 9). Other exploratory outcomes in the APOLLO study were reported descriptively or analyzed using a MMRM model that included baseline value, treatment, visit, and treatment-by-visit covariates. After examining the NT-proBNP data, changes were made to the planned analysis because the data were highly skewed and violated the normality assumption of the MMRM model. To normalize the data, NT-proBNP values were natural log-transformed and then analyzed using a MMRM model that included log-transformed baseline NT-proBNP value, treatment, visit, and treatment-by-visit interaction terms as covariates. The adjusted geometric mean fold change from baseline and 95% confidence interval (CI) were reported, as well as the ratio of adjusted mean fold change (patisiran/placebo) and 95% CI. These values were calculated by back-transforming the least squares (LS) mean and 95% CI values.

Four different sensitivity analyses were conducted for the primary outcome (mNIS+7) using different methods to impute missing data: (1) multiple imputation / analysis of covariance (ANCOVA); (2) pattern-mixture model; (3) MMRM, including all observed data (i.e., data post-alternative treatment); and (4) MMRM based on revised mNIS+7 total score (see Table 9). In the multiple imputation / ANCOVA method, missing data were multiply imputed separately for each treatment group using a regression procedure. One hundred imputed data sets were generated using a regression procedure that included the following covariates: baseline score; genotype; age at ATTR onset; prior tetramer stabilizer use; region; Karnofsky Performance Status; FAP stage (stage I versus stage II or stage III); cardiac subgroup; gender; and, if available, the nine-month efficacy results. Each imputed data set was analyzed using an ANCOVA model (covariates baseline score, treatment, genotype, age at onset, region, and prior tetramer stabilizer use), and all the LS mean and standard error (SE) estimates were combined to produce the inferential results (SAS v.9.3 PROC MI and MIANALYZE).

The sensitivity analysis that used the pattern-mixture model was based on multiple imputation with mixed missing data mechanisms. The following methods were used to impute missing data.

1. **Patients who have missing data and are alive before month 18**
    a. Placebo patients who have missing data (either month 9 or month 18): The missing data are considered missing at random (MAR) and will be imputed using multiple imputation estimated from placebo patients. The imputation is done regardless of whether a patient was on treatment or discontinued treatment before the scheduled efficacy assessment.
    b. Patisiran patients who have missing data (either month 9 or month 18) while on treatment: Patients are expected to continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, missing data during the on-treatment period (within 60 days of their last dose) are considered MAR and will be imputed using multiple imputation estimated from all non-missing data collected on treatment from the patisiran group.
    c. Patisiran patients who have missing data (either month 9 or month 18) after stopping their study treatment: Patients will no longer benefit from treatment in the future and will have a trajectory similar to placebo patients. Therefore, missing data after treatment discontinuation (more than 60 days after the last dose of the study drug) will be imputed using the data from placebo patients.
2. **Patients who die before month 18 and have missing data:** Assuming that deaths observed in the study will likely be related to worsening of disease, the missing data at month 18 will be imputed by taking random samples from the worst 10% mNIS+7 change scores in the entire population. The imputation will be done for patients from both the patisiran and placebo groups.

In the pattern-mixture model, missing values were imputed 100 times and each data set was analyzed using an ANCOVA model. The resulting 100 estimates were combined using Rubin's formula and 95% CI, constructed with a similar procedure as the multiple imputation / ANCOVA sensitivity analysis.

The third sensitivity analysis included mNIS+7 assessments performed after the initiation of alternative treatments for hATTR amyloidosis, using the MMRM model (i.e., all observed data). The final sensitivity analysis used alternative measures to impute missing data for components of the mNIS+7. In the primary analysis of the mNIS+7 total score, a "within treatment group" imputation algorithm was used for the imputation of missing component data. This meant that, at each visit, if a patient had a missing component for mNIS+7, the value was imputed using data from other patients receiving that treatment and who had non-missing data for that component at that visit. In a sensitivity analysis, any such missing values were imputed as the mean value for the component at the visit from all patients (combining placebo and patisiran groups). The analysis of this revised mNIS+7 derived scores was conducted using the MMRM model.

Two sensitivity analyses were planned for the Norfolk QoL-DN outcome: multiple imputation for the missing data (ANCOVA) model, and the MMRM model, including data post-alternative treatment.

Numerous pre-specified subgroup analyses were conducted for the mNIS+7 and Norfolk QoL-DN scores, using MMRM models with the baseline mNIS+7 score as a continuous covariate and genotype (V30M versus non-V30M) as a factor. Of these, the subgroup by FAP stage (stage I versus stage II or stage III) was of interest to this review. Analysis of the echocardiogram and cardiac biomarker data were pre-planned for the cardiac subgroup. Cardiac subgroup analyses for the mNIS+7 and the Norfolk QoL-DN were conducted as a post-hoc analysis.

## Table 9: Description of Statistical Analysis Methods

| Outcome | Primary Analysis | Sensitivity Analysis |
|---|---|---|
| **mNIS+7** | MMRM (mITT)<br>• Covariates: Baseline score, treatment, visit, treatment-by-visit interaction, genotype (V30M or non-V30M), age at onset (<50 or ≥ 50 years), region (North America, Western Europe, other), prior tetramer stabilizer use (yes or no)<br>• For any patient who had a liver transplant or used tafamidis or diflunisal for more than 14 days, any assessments after starting these alternative therapies were treated as missing and excluded from the analysis. | • Multiple imputation for missing data, ANCOVA model<br>• Pattern-mixture model<br>• MMRM, including data post-alternative treatment<br>• MMRM revised mNIS+7 Total Score |
| **Norfolk QoL-DN total score** | MMRM (mITT)<br>• Covariates: Baseline score, treatment, visit, treatment-by-visit interaction, genotype, age at onset, region, prior tetramer stabilizer use, baseline NIS (< 50 or ≥ 50)<br>• Data after starting alternative treatments were treated as missing. | • Multiple imputation for missing data, ANCOVA model<br>• MMRM, including data post-alternative treatment |
| **NIS-W subscore** | MMRM (mITT)<br>• Covariates: Baseline score, treatment, visit, treatment-by-visit interaction, genotype, age at onset, region, prior tetramer stabilizer use<br>• Data after starting alternative treatments were treated as missing. | – |
| **R-ODS**<br>**10MWT[a]**<br>**mBMI[b]**<br>**COMPASS 31** | MMRM (mITT)<br>• Covariates: Baseline score, treatment, visit, treatment-by-visit interaction, genotype, age at onset, region, prior tetramer stabilizer use, baseline NIS (< 50 or ≥ 50)<br>• Data after starting alternative treatments were included in analysis. | – |
| **EQ-5D-5L index score[c]**<br>**EQ-5D VAS[c]** | MMRM (mITT)<br>• Covariates: Baseline score, treatment, visit, treatment-by-visit interaction, genotype, age at onset, region, prior tetramer stabilizer use<br>• Data after starting alternative treatments were included in analysis. | – |
| **PND score[c]**<br>**FAP stage[c]** | • Descriptive analysis (mITT) | – |
| **Cardiac outcomes[c,d]** | • Descriptive analysis for mITT population | – |

| Outcome | Primary Analysis | Sensitivity Analysis |
|---|---|---|
| **LV thickness**<br>**LV longitudinal strain**<br>**LVEF**<br>**NT-proBNP**<br>**Troponin I** | MMRM for cardiac subpopulation<br>• Covariates: Baseline score, treatment, visit, treatment-by-visit interaction | |

10MWT = 10 metre walk test; ANCOVA = analysis of covariance; COMPASS 31 = Composite Autonomic Symptom Score 31; EQ-5D = EuroQol 5-Dimensions; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FAP = familial amyloidotic polyneuropathy; LV = left ventricular; LVEF = left ventricular ejection fraction; mBMI = modified body mass index; mITT = modified intention-to-treat; MMRM = mixed-effects model for repeated measures; mNIS+7 = modified Neurologic Impairment Score +7; NIS = Neurologic Impairment Score; NIS-W = Neurologic Impairment Score–Weakness; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Scale; VAS = visual analogue scale.

[a] For patients unable to perform the test, the walk speed was recorded as zero.

[b] Measured at month 3, month 6, month 12, month 15, and month 18.

[c] Exploratory outcomes in the APOLLO study.

[d] According to the statistical analysis plan for the APOLLO study, between-group differences in LV thickness, LV mass, LV longitudinal strain, LVEF, NT-proBNP, and troponin I were to be analyzed for the cardiac subgroup. Other analyses of cardiac parameters were conducted post hoc.

### *Analysis Populations*

The modified intention-to-treat population (mITT) consisted of all patients who were randomized and who received at least one dose of study drug, analyzed according to the treatment to which they were randomized. All efficacy outcomes were analyzed based on the mITT population.

The safety population included all patients who received at least one dose of study drug analyzed according to the treatment received.

The cardiac subpopulation included patients with pre-existing cardiac amyloid involvement, defined as baseline LV wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension.

## Patient Disposition

A total of 323 patients were screened for inclusion in the APOLLO study and 225 patients (70%) were randomized and treated (see Table 10). The reasons for excluding patients at screening were not reported. After randomization, 22 of 77 patients (29%) in the placebo group discontinued the study and 29 patients (38%) discontinued treatment, compared with 10 of 148 patients (7%) who withdrew and 11 patients (7%) who discontinued treatment in the patisiran group (Table 10). Withdrawals by patient, adverse events, death, or progressive disease were the most common reasons for stopping treatment in the placebo group. As reported in the Clinical Study Report, the reasons for withdrawal of consent in the majority of placebo patients were they “felt worsening of disease” or “felt disease progression.”[7] In the patisiran group, death and adverse events were the most commonly reported reasons for stopping treatment.

A total of seven patients met the criteria for rapid disease progression (six patients [8%] were from the placebo group, one patient (1%) was from the patisiran group). “Rapid disease progression” was defined as a ≥ 24-point increase from baseline in mNIS+7 and a ≥ one-level increase from baseline in the FAP stage at month 9, as determined by the clinical adjudication committee.

## Table 10: Patient Disposition

| | APOLLO | |
|---|---|---|
| | **Placebo** | **Patisiran** |
| **Screened, N** | 323 | |
| **Randomized, N (%)** | 225 (70) | |
| | 77 | 148 |
| **Discontinued Study, N (%)** | 22 (29) | 10 (7) |
| Adverse event | 6 (8) | 2 (1) |
| Death | 4 (5) | 6 (4) |
| Physician decision | 1 (1) | 0 |
| Protocol deviation | 0 | 1 (1) |
| Withdrawal by patient | 11 (14) | 1 (1) |
| **Discontinued Treatment, N (%)** | 29 (38) | 11 (7) |
| Adverse event | 7 (9) | 3 (2) |
| Death | 4 (5) | 5 (3) |
| Progressive disease[a] | 4 (5) | 1 (1) |
| Physician decision | 2 (3) | 0 |
| Protocol deviation | 0 | 1 (1) |
| Withdrawal by patient | 12 (16) | 1 (1) |
| **mITT, N** | 77 (100) | 148 (100) |
| **Safety, N** | 77 (100) | 148 (100) |

mITT = modified intention-to-treat.

[a] Patients with rapid disease progression who decided to stop treatment due to progressive disease.

Source: Clinical Study Report for the APOLLO study.[7]

## Exposure to Study Treatments

The median duration of study drug exposure was 18.6 months in both the patisiran group and the placebo group; however, the mean duration was longer for patisiran compared with placebo (17.7 months versus 15.0 months). The percentage of patients who received at least 25 of the planned 27 doses of study drug was 89% in the patisiran group and 60% in the placebo group. Figure 2 shows the time to treatment discontinuation in the two groups.

As noted previously, the premedication regimen changed during the study period. [redacted]

Eight patients stopped the study drug and were initiated on tetramer stabilizers during the study period. These included four placebo patients and one patisiran patient who had rapid disease progression, and three other placebo patients who did not meet the criteria for rapid disease progression. All patients completed the study and had their 18-month mNIS+7 assessments.

## Figure 2: Kaplan–Meier Plot of Time to Early Treatment Discontinuation (Modified Intention-to-Treat)

**Figure 2 contained confidential information and was removed at the request of the manufacturer.**

Source: Clinical Study Report for the APOLLO study.[7]

## Critical Appraisal

### Internal Validity

The APOLLO study randomized patients using accepted methods (interactive response or interactive voice response system), and used several methods to maintain blinding during the trial. This included covering the infusion bags and lines with amber-coloured bags, ensuring the active and placebo infusion bags had the same total volume, and using different personnel to conduct efficacy assessments and to administer the drug. It is possible that unblinding may have occurred due to infusion-related reactions, which were reported more frequently among patients in the patisiran group than in the placebo group (19% versus 9%). Given the subjective nature of many of the outcome measures, maintaining blinding was important during this trial; however, the FDA did not raise any concerns with regard to blinding.[8]

Generally, the baseline characteristics of patients appear to be similar between groups, although there were differences in the distribution of race and V30M genotype, and mean mNIS+7 score was higher (suggesting greater impairment) in the patisiran group than in the placebo group. Randomization was stratified by NIS score (five to 49 versus 50 to 130), early onset disease with V30M mutation versus others, and previous use of tetramer stabilizers — but not by cardiac disease. Thus, some differences were observed between groups in the proportion of patients with a history of cardiac disease, or who met the study's criteria for pre-existing cardiac amyloid involvement (placebo 47%; patisiran 61%). These baseline differences make it difficult to interpret the cardiac data presented, but the clinical experts consulted for this review agreed that any of the differences observed were unlikely to bias the key efficacy outcomes related to polyneuropathy.

The statistical analysis methods and the hierarchical testing procedure used to control for familywise type I error appear to be acceptable. The efficacy analyses were not based on the intention-to-treat population, but rather on an mITT population that had differential losses to the follow-up period. A greater percentage of patients in the placebo group than in the patisiran group was excluded from the MMRM analysis of the primary outcome (13% versus 5%), [redacted] More patients in the placebo group discontinued due to adverse events, progressive disease, or withdrawal of consent (the majority of which were related to disease progression). This suggests that patients who withdrew had worse clinical status than those who remained, which would violate the missing at random assumption. Four sensitivity analyses were conducted to test the impact of missing data, including one that assumed patients were missing not at random (pattern-mixture model); although the results of these analyses were similar to the primary analysis, these analyses cannot fully account for the impact of missing data. Even so, the differential missing data in the placebo group versus the patisiran group would likely bias toward the null rather than overestimate the treatment effects of patisiran.

The APOLLO study examined neurologic impairment as the primary outcome based on the mNIS+7 composite outcome. This outcome measure includes components of the NIS (NIS-

W and NIS-R), plus electrophysiologic measures of nerve fibre function and a measure of autonomic function. Although the mNIS+7 was designed to measure the aspects of neurologic impairment most affected by hATTR amyloidosis, the MCID is uncertain and the clinical relevance of some of the components is unclear. The Peripheral Nerve Society proposed that a mean difference between groups of two points for the NIS is meaningful in patients with diabetic polyneuropathy.[28] However, this value is based on the smallest degree of change that a physician can detect, rather than on any distribution or anchor-based statistical technique. Moreover, this was based on the NIS, which does not include the QST, nerve conduction studies, or autonomic components of the mNIS+7; thus, it is unclear if the two-point difference can be applied to the mNIS+7. The FDA stated that nerve conduction studies are biomarkers and do not represent direct clinical benefit.[8] Moreover, differences detected by the physician in motor and sensory function upon neurological examination might not be perceptible to the patient or result in improved function in daily activities.[8] The clinical experts consulted for this review stated that muscle strength and neuropathic pain are the main causes of disability that can be attributed to neuropathy and have the greatest impact on patients' daily lives. They also noted that changes in sensation may be important to patients, although they noted that the QST methods used in the APOLLO study are not used in clinical practice. These two components, the NIS-W (192 points) and the QST (80 points), contribute 89% of the points to the mNIS+7 score (total of 304 points), and may be the most clinically relevant to patients; however, the clinical significance of a change in scores is undefined. The FDA concluded that the mNIS+7 was an acceptable end point for this clinical trial but should be considered in the context of the results of the secondary outcomes, particularly health-related quality of life.[8]

Numerous other outcomes were evaluated within the statistical testing hierarchy, including health-related quality of life (using a disease-specific instrument [Norfolk QoI-DN]), disability (R-ODS), gait speed (10MWT), nutritional status (mBMI), and autonomic symptoms (COMPASS 31). These outcomes provide information on different aspects of patients' lives that may be affected by hATTR amyloidosis and that are important to patients; however, since there is no known MCID for the outcomes (except for the 10MWT), the clinical relevance of the treatment effects observed are difficult to interpret. While the change in the FAP stage and the PND stage were reported in the APOLLO study, these classifications are based predominately on motor function and ambulation; as well, the stages are broad and may be overlapping, and may not be sensitive to change in the short term. Moreover, these outcomes were outside the statistical testing procedure and thus should be interpreted as inconclusive. Health-related quality of life was also examined using the EQ-5D; however, this outcome was outside the statistical hierarchy and should be interpreted as inconclusive.

The APOLLO study was not designed or powered to test for differences in hospitalizations, cardiac morbidity, and mortality, which are important to patients. Data on hospitalizations and cardiac events were reported; however, these events were not systematically captured and instead were extracted post hoc from adverse event reports. Although certain cardiac biomarkers were measured as exploratory outcomes, it is unclear if these measures represent direct clinical benefit. Moreover, these were outside the statistical testing hierarchy, which precludes drawing conclusions from these data. In addition, the proportion of patients with a history of cardiac disorders appears to differ between groups at baseline, which may bias the cardiac outcome data. There was a planned analysis of a cardiac subgroup; however, randomization was not stratified for this group and the distribution of known and unknown confounders may not be balanced. And, indeed, a number of imbalances were observed between treatment groups in the baseline characteristics. Also,

it is unclear if the criteria used to define this group (LV wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension) was clinically relevant, or if other diagnostic criteria should have been used to identify those with cardiomyopathy.

The available evidence was limited to a single placebo-controlled RCT with treatment duration of 18 months. There was limited data on subgroups of interest to this review, and as patients with liver transplant were excluded from the study, there is no data on the efficacy of patisiran in this population. The trial had low power to detect infrequent adverse events, or those with a longer lag time. Treatment efficacy beyond 18 months is uncertain.

### External Validity

The APOLLO trial was conducted in 19 countries and included five patients from Canada. Thirty per cent of patients screened were excluded from the trial and the reasons for exclusion were not reported; consequently, it is unclear how the exclusions may impact the generalizability. Considering that little is known about the genotypic and phenotypic characteristics of patients with hATTR amyloidosis in Canada, it is difficult to assess the external validity of the findings. The patients enrolled were, on average, 60 years old, predominantly male and white, with a disease onset after 50 years of age. They were classified as stage I or stage II FAP, which excluded any patients who were wheelchair bound with severe sensory, motor, and autonomic involvement. Also excluded were those who had undergone a liver transplant, who had type I diabetes, had had type II diabetes for more than five years, or who had experienced New York Heart Association class III or class IV heart failure; thus, the generalizability to these patients is unknown.

The clinical experts consulted for this review stated that the mNIS+7 outcome measure as defined in the APOLLO study is not used in clinical practice, although some components, such as the NIS-W and NIS-R subscales, may be part of the neurological exams performed by clinicians.

Comparative data for patisiran versus other emerging treatments for hATTR amyloidosis (e.g., inotersen or tafamidis) are lacking.

## Efficacy

Only those efficacy outcomes identified in the review protocol (see Table 4) are reported here. See Appendix 4 for additional efficacy data.

The APOLLO study was not designed to evaluate the effects of patisiran on mortality, hospitalization, or cardiovascular morbidity; however, data on these outcomes were collected as part of the safety analysis and have been summarized in this section of the report.

### Mortality

Six patients in the placebo group (8%) and seven patients in the patisiran group (5%) died during the APOLLO study. Three of these deaths (one in the patisiran group and two in the placebo group) occurred in patients who were off treatment > 28 days after the last dose of study drug.

All 13 deaths were adjudicated by an independent committee, which classified all seven deaths in the patisiran group and three deaths in the placebo group as a cardiovascular event. In the patisiran group, the reason for death was sudden death in four patients, heart

failure in two patients and one presumed cardiovascular death. In the placebo group, two deaths were due to strokes and one was due to heart failure. Two deaths were classified as non-cardiovascular events (Staphylococcal sepsis and colorectal cancer metastatic) and there was insufficient information to classify the cause of death in one patient (acute kidney failure, urinary tract infection, and bacteremia).

[redacted]

One additional death was reported in a patient randomized to placebo who had withdrawn from the study and died after the end of study visit. This patient had withdrawn on day 566 due to deterioration of health status and worsening cardiac failure. The patient died on day 598 and the cause of death is unknown.

### Hospitalizations

Safety data from the APOLLO study were searched for serious adverse events or serious cardiac adverse events that resulted in hospitalizations or death (post hoc).

During the study period, [redacted]

[redacted]

### Cardiovascular Morbidity

Safety data were searched for cardiac events reported during the APOLLO study (post hoc).

In the overall study population, a higher proportion of patients in the placebo group reported a cardiac arrhythmia than in the patisiran group (29% versus 19%), based on the high-level group term query. Similar trends were noted for the cardiac subgroup that consisted of 36 placebo patients (47%) and 90 patisiran patients (61%). In the cardiac subgroup, 31% of the placebo group and 19% of the patisiran group had a treatment-emergent cardiac arrhythmia adverse event.

The proportion of patients who reported [redacted]

### Health-Related Quality of Life

The Norfolk QoL-DN questionnaire was used to assess the impacts of neuropathy on functional status, and was a key secondary outcome. At baseline, the mean score was 55.5 and 59.6 points in the placebo and patisiran groups, respectively (see Table 11). Over 18 months, the LS mean score in the placebo group increased 14.4 points and decreased 6.7 points in the patisiran group, for a LS mean difference of −21.1 points (95% CI, −27.2 points to −15.0 points in favour of patisiran; $P < 0.0001$). The change in Norfolk QoL-DN scores

over time are presented in Figure 6 in Ap. The direction and magnitude of the treatment effects were similar in the sensitivity analyses (see Table 21) and the subgroup analyses (see Figure 7) compared with the primary analysis. For the subgroup of patients with FAP stage I, the LS mean difference was −18.3 (95% CI, –26.6 to −10.0) and for those with FAP stage II or stage III, the difference observed was −24.6 (95% CI, −33.6 to −14.7; treatment-by-subgroup interaction term *P* value not reported).

For the Norfolk QoL-DN outcome, 206 of 225 patients contributed to the MMRM analysis (19 patients, or 8.4%, were missing from this analysis). [redacted]

The EQ-5D index score and VAS were reported as exploratory outcomes in the APOLLO study (see Table 11). Baseline values were similar in both treatment groups and, after 18 months, the placebo group showed a decrease in scores (LS mean −0.17 for the index and −7.1 for the VAS), while the LS mean change from baseline was positive for the patisiran group (0.03 for the index and 2.4 for the VAS). LS mean differences of 0.20 (95% CI, 0.15 to 0.25) were reported for the index score and 9.5 points (95% CI, 4.3 points to 14.8 points) for the VAS. A MCID of 0.037 points has been reported in the literature for the EQ-5D-5L index in a general Canadian population.

## Table 11: Quality-of-Life Results in APOLLO Study (Modified Intention-to-Treat)

| | Baseline | | 18 Months | | | LS Mean Difference Patisiran vs. Placebo (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | LS Mean Change From Baseline (SE) | | |
| **Norfolk QoL-DN[a,b]** | | | | | | | |
| Placebo | 76 | 55.5 (24.3) | 48 | 71.7 (29.3) | 14.4 (2.7) | | |
| Patisiran | 148 | 59.6 (28.2) | 136 | 55.4 (30.6) | −6.7 (1.8) | −21.1 (−27.2, −15.0) | < 0.0001 |
| **EQ-5D Index Score[c]** | | | | | | | |
| Placebo | 76 | 0.65 (0.17) | 55 | 0.47 (0.24) | −0.17 (0.02) | | |
| Patisiran | 148 | 0.62 (0.18) | 138 | 0.64 (0.22) | 0.03 (0.02) | 0.20 (0.15, 0.25) | NR |
| **EQ-5D VAS[c]** | | | | | | | |
| Placebo | 76 | 54.6 (18.0) | 55 | 47.8 (20.7) | −7.1 (2.3) | | |
| Patisiran | 148 | 55.7 (20.0) | 138 | 57.0 (21.6) | 2.4 (1.6) | 9.5 (4.3, 14.8) | NR |

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions; LS = least squares; mITT = modified intention-to-treat; NIS = Neurologic Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NR = not reported; SD = standard deviation; SE = standard error; V30M = valine to methionine substitution at position 30; VAS = visual analogue scale; vs. = versus.

[a] The range of possible scores is −4 to 136, with a decrease in scores indicating an improvement in quality of life.

[b] Analysis was based on a mixed-effects model for repeated measures that included baseline score, treatment, visit, treatment-by-visit interaction, genotype (V30M or non-V30M), age at onset (< 50 or ≥ 50 years), region (North America, Western Europe, other), prior tetramer stabilizer use (yes or no) and baseline NIS score (< 50 or ≥ 50) as covariates. Norfolk QoL-DN was included in the statistical testing hierarchy.

[c] EQ-5D was not included in the statistical testing hierarchy. Analyzed based on mixed-effects model for repeated measures that included baseline score, treatment, visit, treatment-by-visit interaction, genotype, age at onset, region, prior tetramer stabilizer use as covariates.

Source: Clinical Study Report for the APOLLO study.[7]

## Neurologic Impairment

At baseline, the mean scores for the mNIS+7 composite outcome were 74.6 in the placebo group and 80.9 in the patisiran group (see Table 12). The LS mean change from baseline to 18 months was 28.0 points and −6.0 points in the placebo and patisiran groups, respectively, with LS mean difference of −34.0 points (95% CI, −39.9 to −28.1) that was statistically significant in favour of patisiran ($P < 0.0001$). The direction and magnitude of treatment effects observed in the sensitivity analyses (Table 22) and the subgroup analyses were generally similar to those observed for the primary analysis (Figure 9). [redacted] The change in mNIS+7 scores over time are presented in Figure 10. These data show mNIS+7 scores in the patisiran group remaining stable over time, with the placebo group showing an increase in scores at both nine months and 18 months.

The NIS-W, a sub-component of the mNIS+7, also showed a statistically significant difference for patisiran versus placebo. The baseline NIS-W scores were 29.0 and 32.7 points in the placebo and patisiran groups, respectively, and the LS mean change from baseline was 17.9 and 0.05 points, respectively. The LS mean difference favoured patisiran over placebo (−17.9; 95% CI, −22.3 to −13.4 points), and was statistically significant ($P < 0.0001$). Figure 3 shows the change from baseline data for all components of the mNIS+7. No MCID was identified in the literature for the mNIS+7 or its components.

Of note, data from 87% of placebo patients and 95% of patisiran patients were included in the MMRM analysis of the primary outcome; [redacted] (see Table 23). Early outcome data for patients that left the trial before 18 months are displayed in Figure 11.

### Table 12: Neurological Impairment Results in APOLLO Study (Modified Intention-to-Treat)

| | Baseline | | 18 Months | | | LS Mean Difference Patisiran vs. Placebo (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | LS Mean Change From Baseline (SE) | | |
| **mNIS+7[a,b]** | | | | | | | |
| Placebo | 77 | 74.6 (37.0) | 51 | 101.1 (45.4) | 28.0 (2.6) | | |
| Patisiran | 148 | 80.9 (41.5) | 137 | 75.1 (43.2) | −6.0 (1.7) | −34.0 (−39.9, −28.1) | < 0.0001 |
| **NIS-W[b,c]** | | | | | | | |
| Placebo | 77 | 29.0 (23.0) | 51 | 46.3 (31.8) | 17.9 (2.0) | | |
| Patisiran | 148 | 32.7 (25.2) | 137 | 33.7 (28.3) | 0.05 (1.3) | −17.9 (−22.3, −13.4) | < 0.0001 |

CI = confidence interval; LS = least squares; mNIS+7 = modified Neurologic Impairment Score +7; NIS-W = Neurologic Impairment Score–Weakness; SD = standard deviation; SE = standard error; V30M = valine to methionine substitution at position 30; vs. = versus.

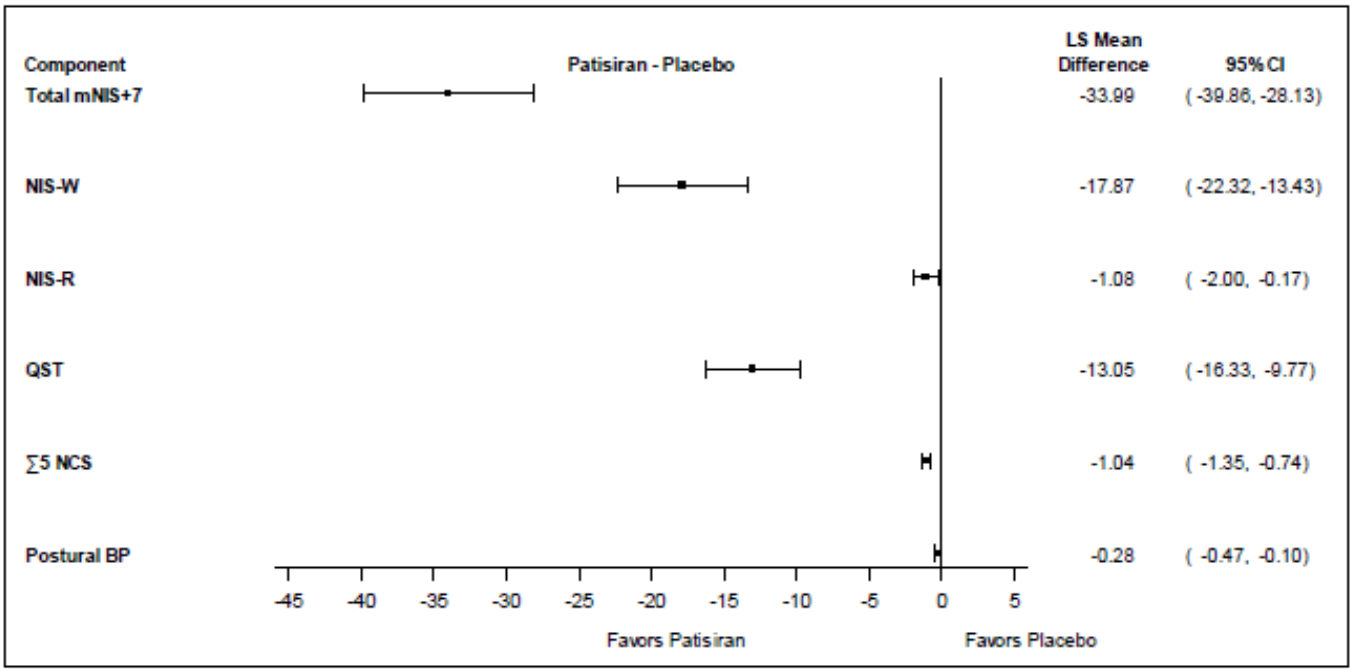
[a] The instrument is scored from 0 (no impairment) to 304 (maximum impairment).

[b] Analysis was based on a mixed-effects model for repeated measures that included baseline score, treatment, visit, treatment-by-visit interaction, genotype (V30M or non-V30M), age at onset (< 50 or ≥ 50 years), region (North America, Western Europe, other), and prior tetramer stabilizer use (yes or no). Outcome was included in the statistical testing hierarchy.

[c] Maximum score of 192 points.

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 3: mNIS+7 Component Change from Baseline to Month 18 in APOLLO Study (Mixed-Effects Model for Repeated Measures, Modified Intention-to-Treat)




BP = blood pressure; CI = confidence interval; LS = least squares; mNIS+7 = modified Neurologic Impairment Score +7; Σ5 NCS = sum of five attributes of nerve conduction studies; NIS-W = Neurologic Impairment Score–Weakness; NIS-R = Neurologic Impairment Score–Reflexes; QST = quantitative sensory testing.

Source: Clinical Study Report for the APOLLO study.[7]

The cumulative distribution in the change in mNIS+7 scores is presented in Figure 12. This graph shows that approximately half of patients in the patisiran group had stable or lower mNIS+7 scores at 18 months whereas most placebo patients showed an increase in scores, suggesting a deterioration in neurologic function.

### Disability and Functional Status

In the APOLLO study, the baseline R-ODS scores were 29.8 points and 29.7 points in the placebo and patisiran groups, respectively (see Table 13). At the end of the trial, the LS mean change score was zero in the patisiran group and −8.9 points in the placebo group. Statistically significant differences were detected in favour of patisiran versus placebo (LS mean difference of 9.0 points; 95% CI, 7.0 points to 10.9 points). No MCID for this outcome measure was identified in the literature.

Gait speed was measured using the 10MWT. At baseline, the placebo and patisiran groups reported a mean speed of 0.79 and 0.80 m/s, respectively (see Table 13). Over 18 months, the LS mean gait speed decreased −0.24 m/s in the placebo group and increased 0.08 m/s in the patisiran group. The difference between treatments was statistically significant (LS mean difference of 0.31 m/s; 95% CI, 0.23 m/s to 0.39 m/s) and exceeded the MCID of 0.05 m/s that has been reported in the literature for stroke survivors and older adults with mobility disabilities.

For the R-ODS outcome, 208 of 225 patients contributed to the MMRM analysis (17 patients, or 8%, were missing). Another 16 patients (7%) were missing or censored at

month 18 (i.e., contributed baseline and month 9 data but not month 18 data). For the 10MWT, 209 of 225 patients contributed to the MMRM analysis (16 patients, or 7%, were missing) and another 16 patients (7%) were missing or censored at month 18. Missing data were more common in the placebo group than in the patisiran group.

## Table 13: Other Efficacy Results in APOLLO Study (Modified Intention-to-Treat)

| | Baseline | | 18 Months | | | LS Mean Difference Patisiran vs. Placebo (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | LS Mean Change From Baseline (SE) | | |
| **R-ODS[a,b]** | | | | | | | |
| Placebo | 76 | 29.8 (10.8) | 54 | 21.0 (13.4) | −8.9 (0.9) | | |
| Patisiran | 148 | 29.7 (11.5) | 138 | 29.5 (12.7) | 0.0 (0.6) | 9.0 (7.0, 10.9) | < 0.0001 |
| **10MWT Gait Speed (m/s)[a,c]** | | | | | | | |
| Placebo | 77 | 0.79 (0.32) | 55 | 0.56 (0.40) | −0.24 (0.04) | | |
| Patisiran | 147 | 0.80 (0.4 ) | 138 | 0.85 (0.50) | 0.08 (0.02) | 0.31 (0.23, 0.39) | < 0.0001 |
| **mBMI (kg/m$^2$ × Albumin g/L)[a]** | | | | | | | |
| Placebo | 77 | 989.9 (214.2) | 52 | 892.7 (221.1) | −119.4 (14.5) | | |
| Patisiran | 148 | 969.7 (210.5) | 133 | 975.4 (228.6) | −3.7 (9.6) | 115.7 (82.4, 149.0) | < 0.0001 |
| **COMPASS 31[a,d]** | | | | | | | |
| Placebo | 76 | 30.3 (16.4) | 53 | 33.1 (17.6) | 2.2 (1.9) | | |
| Patisiran | 146 | 30.6 (17.6) | 136 | 25.6 (17.1) | −5.3 (1.3) | −7.5 (−11.9, −3.2) | 0.0008 |

10MWT = 10 metre walk test; CI = confidence interval; COMPASS 31 = Composite Autonomic Symptom Score 31; LS = least squares; mBMI = modified body mass index; NIS = Neurologic Impairment Score; R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation; SE = standard error; V30M = valine to methionine substitution at position 30.

[a] Analysis was based on a mixed-effects model for repeated measures that included baseline score, treatment, visit, treatment-by-visit interaction, genotype (V30M or non-V30M), age at onset (< 50 or ≥ 50 years), region (North America, Western Europe, other), prior tetramer stabilizer use (yes or no) and baseline NIS score (< 50 or ≥ 50) as covariates. All outcomes were included in the statistical testing hierarchy.

[b] The R-ODS is scored from 0 to 48, with 0 being the worst disability and 48 the best (no limitations).

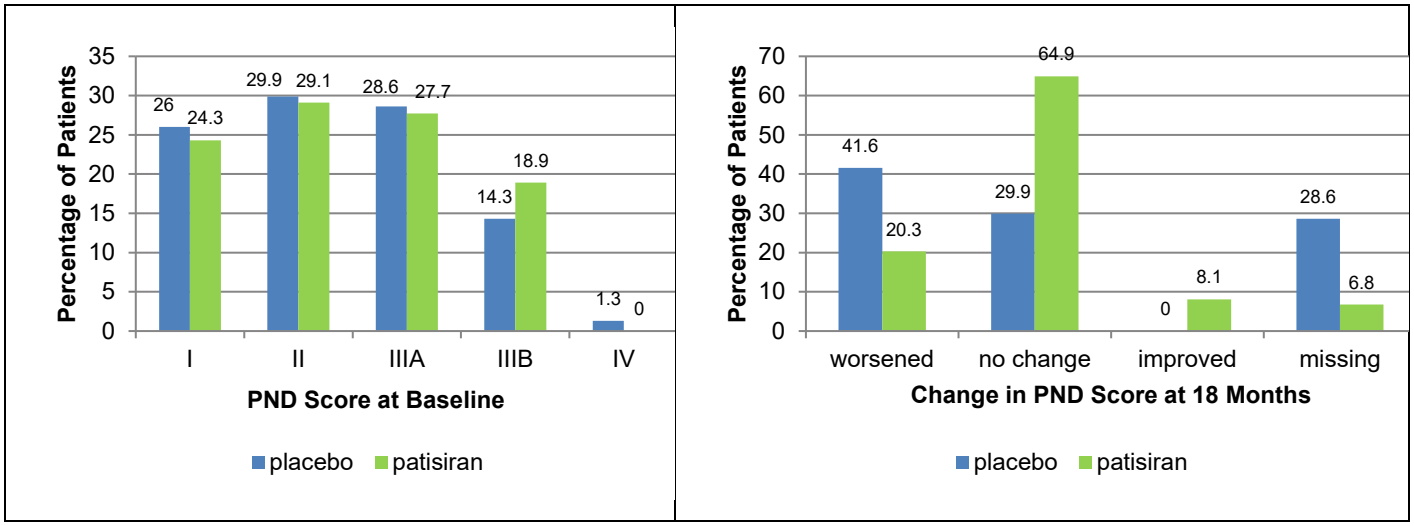
[c] Patients who were unable to walk had gait speed imputed as zero.

[d] The COMPASS 31 is a measure of autonomic neuropathy symptoms and is scored from 0 to 100. A decrease in scores indicates improvement in symptoms.

Source: Clinical Study Report for the APOLLO study.[7]

The PND score and FAP stage at baseline as well as the change from baseline at the end of the trial are shown in Figure 4 and Figure 5. In general, a lower percentage of patients in the patisiran group worsened and a higher percentage showed no change in PND score and FAP stage compared with the placebo group. These outcomes were reported descriptively and were not part of the statistical testing hierarchy.

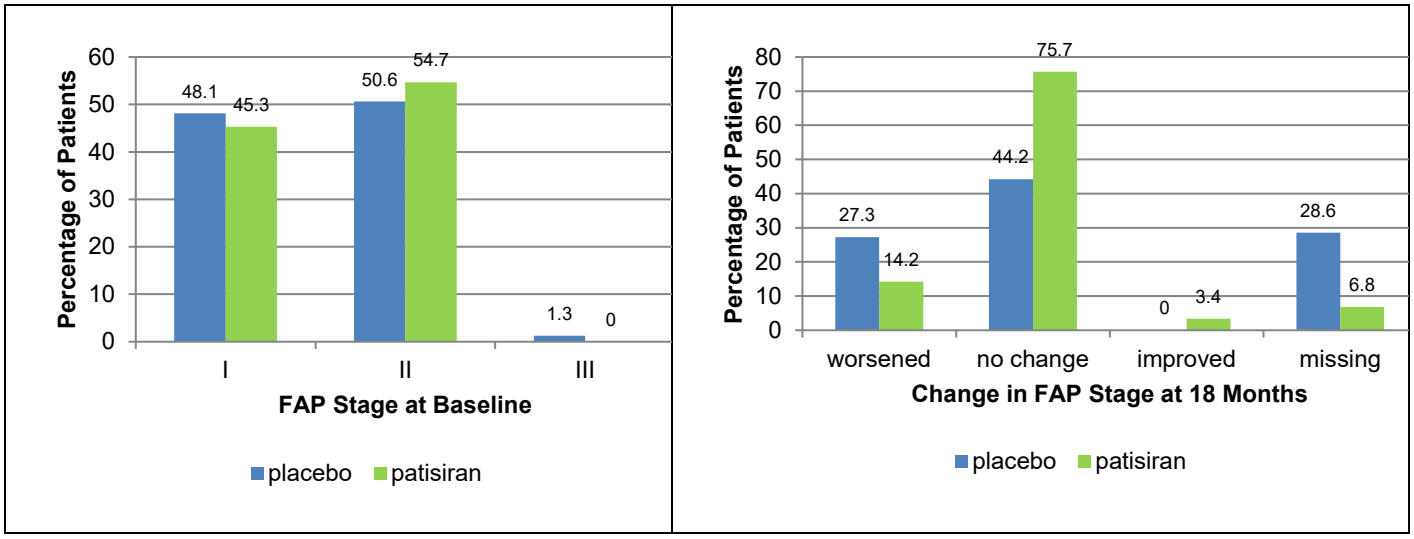
## Figure 4: Summary of Polyneuropathy Disability Score in APOLLO Study




PND = polyneuropathy disability.

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 5: Summary of Familial Amyloidotic Polyneuropathy Stage in APOLLO Study




FAP = familial amyloidotic polyneuropathy.

Source: Clinical Study Report for the APOLLO study.[7]

### Nutritional Status

Nutritional status was measured based on mBMI, which is kg/m$^2$ multiplied by albumin in g/L. The mean baseline mBMI values were 990 and 970 in the placebo and patisiran groups, respectively (see Table 13). The LS mean change from baseline to 18 months was −119 in the placebo group and −4 in the patisiran group, with a LS mean difference of 116 (95% CI, 82 to 149; $P < 0.0001$).

[redacted]

### Symptoms

Autonomic symptom severity and frequency were measured using the COMPASS 31 questionnaire (see Table 13). At baseline, the mean scores were 30.3 and 30.6 in the placebo and patisiran groups, with LS mean change from baseline of 2.2 and −5.3 points, respectively. The difference between groups was statistically significant in favour of patisiran (LS mean difference of −7.5; 95% CI, −11.9 to −3.2).

### Cardiovascular Biomarkers and Echocardiogram Results

A number of exploratory cardiovascular outcomes was reported in the APOLLO study, including cardiac biomarkers (NT-proBNP normal range less than 144.63 pmol/L), troponin I (normal range less than 0.10 mcg/L), and echocardiogram measures (LVEF, LV wall thickness, and longitudinal strain). Results were reported descriptively for the mITT population, with pre-planned statistical testing for these outcomes for the cardiac subpopulation only. All cardiac outcomes were outside the statistical testing hierarchy.

The troponin I data could not be interpreted due to limitations with assay sensitivity, which reported the majority of troponin I values (90%) as < 0.1 mcg/L. The manufacturer stated that the treatment effects of patisiran on troponin I could not be determined due to the lack of precision in these data. See Table 24 for the troponin I data.

Descriptive data for the NT-proBNP are reported in Table 14. These data were found to be highly skewed, which necessitated a change in the analysis plan (i.e., log transformation). In the mITT population, the geometric mean value at baseline was 62.8 pmol/L for both groups. At 18 months, the geometric mean was 99.8 pmol/L in the placebo group and 49.3 pmol/L in the patisiran group. A similar pattern was observed for the cardiac subpopulation, which included patients with pre-existing cardiac amyloid involvement (defined as baseline LV wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension). The adjusted geometric mean fold change in the NT-proBNP was 0.89 for the patisiran group and 1.97 for the placebo group, and the ratio of adjusted geometric mean fold change for patisiran versus placebo was 0.45 (95% CI, 0.34 to 0.59).

## Table 14: N-Terminal Prohormone Brain-Type Natriuretic Peptide Results in APOLLO Study

| | mITT Population | | | | Cardiac Subpopulation | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome / Treatment Group | Baseline | | 18 Months | | Baseline | | 18 Months | |
| | N | Geometric Mean (SE) | N | Geometric Mean (SE) | N | Geometric Mean (SE) | N | Geometric Mean (SE) |
| **NT-proBNP (pmol/L)[a,b,c]** | | | | | | | | |
| Placebo | 75 | 62.8 (10.2) | 53 | 99.8 (19.7) | 34 | 84.1 (17.9) | 24 | 132.1 (37.9) |
| Patisiran | 144 | 62.8 (7.0) | 137 | 49.3 (6.0) | 88 | 86.0 (12.2) | 80 | 64.3 (10.1) |

mITT = modified intention-to-treat; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; SE = standard error.

[a] Data for NT-proBNP were highly skewed, so data were analyzed as log-transformed change from baseline. The mixed-effects model for repeated measures included log-transformed baseline value, treatment, visit, and treatment-by-visit covariates. Geometric means were obtained by exponentially back-transforming the arithmetic mean of log-transformed NT-proBNP.

[b] Data converted by the CADTH Common Drug Review based on the following conversion factor: 1 pmol/L = 8.457 pg/mL.[29]

[c] Normal range less than 144.63 pmol/L.

Source: Clinical Study Report for the APOLLO study.[7]

Echocardiogram results from the APOLLO study are reported in Table 15. At baseline, the LVEF was 62.7% and 61.7% in the placebo and patisiran groups in the mITT population,

respectively. The mean change at 18 months was −1.3% for placebo and 0.6% for patisiran; no between-group comparisons were analyzed. Descriptive data for average peak longitudinal strain showed a mean change from baseline of 0.9% and 0.3%, and a mean change in LV wall thickness of −0.01 cm and −0.08 cm for placebo and patisiran groups, respectively. Of note, 18-month echocardiogram data were missing for up to 38% of the placebo group and 16% of the patisiran group.

Echocardiogram results for the cardiac subgroup suggested some differences between groups (see Table 15); however, randomization was not stratified for pre-existing cardiac amyloid involvement. Thus, it is unclear if these groups were balanced at baseline.

## Table 15: Echocardiogram Results in APOLLO Study

| Outcome / Treatment Group | mITT Population | | | | Cardiac Subpopulation | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | Change From Baseline to 18 Months | | Baseline | | Change From Baseline to 18 Months | | LS Mean Change From Baseline Patisiran vs. Placebo (95% CI)[a] |
| | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | |
| **Average Peak Longitudinal Strain (%)** | | | | | | | | | |
| Placebo | 72 | −16.3 (3.7) | 48 | 0.9 (2.7) | 36 | −15.7 (3.5) | 25 | 1.4 (0.5) | |
| Patisiran | 138 | −15.9 (3.7) | 124 | 0.3 (2.6) | 86 | −15.1 (3.4) | 75 | 0.04 (0.3) | −1.4 (−2.5, −0.3) |
| **LV Wall Thickness (cm)** | | | | | | | | | |
| Placebo | 74 | 1.57 (0.30) | 51 | −0.01 (0.17) | 36 | 1.64 (0.21) | 25 | −0.02 (0.03) | |
| Patisiran | 144 | 1.58 (0.32) | 132 | −0.08 (0.19) | 90 | 1.68 (0.26) | 79 | −0.11 (0.02) | −0.09 (−0.17, −0.02) |
| **LVEF (%)** | | | | | | | | | |
| Placebo | 74 | 62.7 (9.8) | 50 | −1.3 (7.8) | 36 | 62.2 (8.6) | 24 | 0.5 (1.4) | |
| Patisiran | 142 | 61.7 (10.0) | 128 | 0.6 (7.8) | 88 | 60.0 (9.9) | 77 | 1.0 (0.8) | 0.4 (−2.7, 3.6) |

CI = confidence interval; LS = least squares; LV = left ventricular; LVEF = left ventricular ejection fraction; mITT = modified intention-to-treat; SD = standard deviation.

[a] The mixed-effects model for repeated measures included covariates for baseline value, treatment, visit, and treatment-by-visit interaction.

Source: Clinical Study Report for the APOLLO study.[7]

## Harms

Only those harms identified in the review protocol are reported here (see the Objectives section). See Table 16, Table 17, and Table 18 for detailed harms data.

### Adverse Events

Most patients (97%) experienced one or more adverse events during the APOLLO study (see Table 16). The most frequently reported adverse events in the patisiran group were diarrhea (37%), peripheral edema (30%), infusion-related reactions (19%), and falls (17%). In the placebo group, the most common adverse events were diarrhea (38%), falls (29%), peripheral edema (22%), nausea (21%), urinary tract infections (18%), and constipation (17%).

## Table 16: Most Common Adverse Events

| Adverse Event | APOLLO | |
|---|---|---|
| | Placebo (N = 77) | Patisiran (N = 148) |
| **Patients With ≥ 1 Adverse Event, N (%)** | 75 (97) | 143 (97) |
| Most common adverse events,[a] N (%) | | |
| Diarrhea | 29 (38) | 55 (37) |
| Peripheral edema | 17 (22) | 44 (30) |
| Infusion-related reaction | 7 (9) | 28 (19) |
| Fall | 22 (29) | 25 (17) |
| Constipation | 13 (17) | 22 (15) |
| Nausea | 16 (21) | 22 (15) |
| Dizziness | 11 (14) | 19 (13) |
| Urinary tract infection | 14 (18) | 19 (13) |
| Fatigue | 8 (10) | 18 (12) |
| Headache | 9 (12) | 16 (11) |
| Cough | 9 (12) | 15 (10) |
| Insomnia | 7 (9) | 15 (10) |
| Nasopharyngitis | 6 (8) | 15 (10) |
| Vomiting | 8 (10) | 15 (10) |
| Asthenia | 9 (12) | 14 (10) |
| Pain in extremity | 8 (10) | 10 (7) |
| Muscular weakness | 11 (14) | 5 (3) |
| Anemia | 8 (10) | 3 (2) |
| Syncope | 8 (10) | 3 (2) |

[a] Frequency > 10%.

Source: Clinical Study Report for the APOLLO study.[7]

### Serious Adverse Events

Serious adverse events were reported by 40% of placebo patients and 37% of patisiran patients. Table 17 lists serious adverse events reported in two or more patients per treatment group. Diarrhea was the most frequently reported serious adverse event in the patisiran group (5%), and in the placebo group, acute kidney injury (5%) and urinary tract infections (5%) were reported most frequently.

### Treatment Withdrawals due to Adverse Events

The percentage of patients who stopped treatment due to adverse events was higher in the placebo group (14%) than in the patisiran group (5%). The only events that were reported in two or more patients per group were cardiac failure and acute kidney injury (see Table 17). One patient in the patisiran group stopped treatment due to an infusion-related adverse event.

### Deaths

During the APOLLO study, six patients (8%) died in the placebo group and seven patients (5%) died in the patisiran group. Please refer to the Efficacy section for a description of the deaths.

## Table 17: Serious Adverse Events, Deaths, and Treatment Withdrawals

| Adverse Event | APOLLO | |
|---|---|---|
| | Placebo (N = 77) | Patisiran (N = 148) |
| **Patients With ≥ 1 SAE, N (%)** | 31 (40) | 54 (37) |
| Most common SAEs,[a] N (%) | | |
| Diarrhea | 1 (1) | 8 (5) |
| Vomiting | 3 (4) | 1 (1) |
| Constipation | 2 (3) | 0 |
| Atrioventricular block complete | 0 | 3 (2) |
| Cardiac failure | 2 (3) | 3 (2) |
| Cardiac failure congestive | 2 (3) | 3 (2) |
| Acute kidney injury | 4 (5) | 1 (1) |
| Urinary tract infection | 4 (5) | 0 |
| Pneumonia | 3 (4) | 3 (2) |
| Pneumonia aspiration | 2 (3) | 0 |
| Orthostatic hypotension | 1 (1) | 3 (2) |
| Dehydration | 3 (4) | 1 (1) |
| Hyponatremia | 2 (3) | 0 |
| Hereditary neuropathic amyloidosis | 2 (3) | 0 |
| **Patients Who Stopped Treatment Due to Adverse Events, N (%)** | 11 (14) | 7 (5) |
| Cardiac failure | 1 (1) | 2 (1) |
| Acute kidney injury | 2 (3) | 0 |
| Other events reported in 1 patient | Iron deficiency anemia, general physical health deterioration, amyloidosis, bacteremia, Staphylococcal sepsis, urinary tract infection, colon cancer, colorectal cancer, ischemic stroke, posterior reversible encephalopathy syndrome, peripheral arterial occlusive disease, neuropathy peripheral | Infusion-related reaction, cardiac arrest, pulseless electrical activity, sudden cardiac death, acute pulmonary edema, dry mouth, dysphagia, muscular weakness, dysgeusia, hyperesthesia, hypoesthesia, skin atrophy |
| **Deaths, N (%)** | **6 (8)** | **7 (5)** |

SAE = serious adverse event.

[a] Frequency > 2%.

Source: Clinical Study Report for the APOLLO study.[7]

## Notable Harms

Infusion-related reactions were reported by 28 patients (19%; 145 events) in the patisiran group and seven patients (9%; 79 events) in the placebo group (see Table 18). Eight patients (5%) in the patisiran group experienced infusion interruptions due to infusion-related reactions (17 events). [redacted] The most common infusion-related reactions in the patisiran group included back pain (6%), flushing (4%), nausea (3%), abdominal pain (3%), headache (3%), arthralgia (2%), and dyspnea (2%). Flushing was the most common infusion reaction reported in the placebo group (8%). In the patisiran group, the median number of events per person was 2.5 events (range: one to 24) and 79% of patients had their first reaction within the first two doses of the study drug. The median number of events per person in the placebo group was 11 (range: one to 15). No anaphylaxis reactions were reported.[8]

One patient in the placebo group was reported to have night blindness; no events were reported in the patisiran group. A higher proportion of patients in the placebo group reported a treatment-emergent cardiac arrhythmia (29%) compared with the patisiran group (19%); however, three patients in the patisiran group versus none in the placebo group were reported to have complete atrioventricular block (see Table 18). Treatment-emergent anti-drug antibodies were reported in 3.4% and 1.3% of the patisiran and placebo groups, respectively.

### Table 18: Notable Harms

| Adverse Event | APOLLO | |
|---|---|---|
| n (%) | Placebo (N = 77) | Patisiran (N = 148) |
| Infusion-related reaction | 7 (9) | 28 (19) |
| Most Common Infusion Reactions[a] | | |
| Nausea | 0 | 5 (3.4) |
| Abdominal pain | 0 | 5 (3.4) |
| Arthralgia | 0 | 3 (2.0) |
| Back pain | 0 | 9 (6.1) |
| Headache | 1 (1.3) | 4 (2.7) |
| Dyspnea | 0 | 3 (2.0) |
| Flushing | 6 (7.8) | 6 (4.1) |
| Night blindness | 1 (1.3) | 0 |
| Cardiac arrhythmias (HLGT) | 22 (29) | 28 (19) |
| AV block complete | 0 | 3 (2.0) |
| AV block second degree | 0 | 1 (0.7) |
| AV block first degree | 4 (5.2) | 0 |
| AV block | 0 | 1 (0.7) |
| Anti-drug antibodies | 1/77 (1.3) | 5/145 (3.4) |

AV = atrioventricular; HLGT = high-level group term.

[a] Frequency > 2%.

Source: Clinical Study Report for the APOLLO study.[7]

# Clinical Expert Input

The following is a summary of input provided by a panel of four clinical experts who are specialists in treating patients with neurological conditions, including hATTR amyloidosis.

## Unmet Needs with Current Therapies

There is a substantial need for treatments for hATTR amyloidosis that are more effective than the treatment options currently available in Canada. The two main treatment options for hATTR amyloidosis patients are diflunisal, a nonsteroidal anti-inflammatory drug that is not specifically approved by Health Canada for treating hATTR amyloidosis, and liver transplant. Neither of these treatment options reverse the course of disease and, in many patients, the disease will continue to progress. Diflunisal can cause several adverse effects, such as renal dysfunction, low platelet counts, and worsening of congestive heart disease, while liver transplant is associated with substantial morbidity and possible mortality, even among younger and healthier patients. In addition to the potential for serious adverse effects, there are barriers to accessing current treatments for hATTR amyloidosis. Diflunisal is difficult to obtain as it is not routinely stocked in pharmacies. Liver transplant is only considered for a small percentage of patients with earlier stages of hATTR amyloidosis, and access is limited by the availability of donor organs and long wait times.

## Place in Therapy

Due to the limitations associated with the currently available treatments, it is highly likely that there will be a strong desire within the clinical and patient communities to use RNAi treatments that are being developed to treat hATTR amyloidosis as first-line therapy, prior to diflunisal treatment or liver transplant.

The clinical experts believe that the upcoming RNAi treatments should be used only in patients with a confirmed genetic diagnosis of hATTR amyloidosis, who present with clear clinical symptoms, and who do not have any contraindications to the drugs. There was disagreement among the panellists as to whether the eligibility of patients for treatment with RNAi therapy should be based on the inclusion criteria of clinical trials of these treatments or whether it is appropriate to treat a broader population of hATTR amyloidosis patients for which there is very little (or no) clinical trial evidence.

## Considerations for Appropriate Use in Clinical Practice

### *Identification of Symptomatic With Hereditary Transthyretin-Mediated Amyloidosis*

It is unclear what criteria could be used to identify hATTR amyloidosis patients who would benefit from treatment with an RNAi-based therapy. The panel discussed that there is no defined threshold for determining when a patient should be considered symptomatic and the situation may be confounded by coexisting conditions, such as occupational carpal tunnel syndrome or diabetic neuropathy. The panel agreed that it is difficult to establish an objective guideline for when to start treatment and that this is best left to the expert opinion of the treating physician.

### *Stage of Polyneuropathy*

Another grey area is whether only patients in certain stages of polyneuropathy would be eligible for one of the upcoming treatments. The trials recruited patients with earlier stages of polyneuropathy who were not confined to a wheelchair. The panel discussed that

patients with advanced polyneuropathy, who are confined to a wheelchair, may still have sensory and motor function in the hands and arms that may be preserved with treatment. More data are required to know if such patients would benefit from treatment.

### *Patients With Previous Liver Transplant*

Although RNAi treatments have not been studied in patients who have undergone liver transplant, the panel indicated that clinicians would consider using an RNAi treatment in such patients if TTR levels remained elevated or if disease continued to progress despite liver transplant. The panel did not discuss a threshold for defining a high TTR level and conceded that the use of RNAi treatments in this patient population is hypothetical, based on the mechanism of action of RNAi, and that more data would be required to determine whether treating such patients is safe and effective.

### *Patients With Cardiomyopathy*

Patients with hATTR polyneuropathy who also present with cardiomyopathy may be prescribed a TTR stabilizer. RNAi treatments have a different mechanism of action and, therefore, could theoretically be used in combination with a TTR stabilizer. However, the panel acknowledged that no data are currently available to support combination therapies.

### *Patients Who Are Presymptomatic*

There is no evidence to confirm whether any treatments for hATTR amyloidosis will delay disease onset in patients who have a genetic mutation for hATTR amyloidosis but who have not yet presented with any clinical symptoms. Presymptomatic individuals are identified in clinical practice when a family member has a diagnosis of hATTR amyloidosis and an individual is willing to be screened for the condition. The panel acknowledged that it is unlikely that the upcoming treatments would be used in presymptomatic patients with a confirmed genetic diagnosis of hATTR amyloidosis because the mutations are not 100% penetrant and not all persons with the mutation will develop symptoms of the disease.

### *Patients Who Are Confined to a Bed or Palliative*

There was consensus among the panel members that patients who are confined to a bed due to loss of mobility or who have progressed to such a degree that they are considered to be undergoing palliative treatment would be unlikely to benefit from treatment with an RNAi agent.

### *Prescribing Physician and Treatment Setting*

Treatments with an IV route of administration should be administered under the care of specialist(s), primarily neurologists and cardiologists, in centres that routinely administer infusions, such as hospitals, university centres, specialty clinics, and private centres.

### *Assessment of Initial Treatment Response*

A clinically meaningful response to treatment could be considered an improvement in symptoms or stabilization of neurologic impairment as assessed clinically. Patients who exhibit a reduced rate of decline may also be responding to treatment, although judging the rate of decrease compared with the natural history of the disease could be challenging as no clear thresholds are available. There was no consensus among the panel of what measure is most suitable to assess initial response to treatment. The mNIS+7 was used in the clinical trials; however, this scale is not used in clinical practice and may be resource intensive to administer. Also, the QST component of the mNIS+7 is not available in all

centres. More general measures will be needed if they are to be implemented in clinical practice.

### *Ongoing Patient Assessments*

Recurrent testing is required to determine whether there has been a response to treatment, although there was no consensus among panel members as to what outcome measures would be suitable for use in clinical practice. Patient-reported outcomes to assess self-care and symptoms, such as pain, are important to monitor during follow-up. Panellists agreed that treatment response should be assessed every six months at a minimum in patients showing slower progression of the disease. In patients with rapidly progressive disease, treatment response may be assessed every three months.

### *Treatment Discontinuation*

Panellists acknowledged that it is difficult to determine when treatment should be discontinued. Continued disease progression may indicate that the patient is not responding to treatment, although disease progression itself is not an indicator of nonresponse. It is possible that while the disease continues to progress, the rate of progression may be slowed down with treatment. The decision to stop treatment should not be based on only one outcome, such as ambulation, because non-ambulatory individuals may still have function in the upper limbs that is important for maintaining acceptable quality of life (e.g., ability to feed oneself). The panel cautioned against using PND staging as the sole outcome for determining treatment discontinuation. Patients who are bedridden or palliative would be unlikely to benefit from treatment. Overall, the panel agreed that there is no objective way of determining benefit and that the decision to discontinue treatment should be left to the treating physician's discretion.

### *Additional Considerations*

There are many unknowns associated with the RNAi treatments that are being developed for hATTR amyloidosis, as previously described. Overall, the clinical experts believe that RNAi treatments offer many advantages over the current standard of care, although direct evidence of superiority is lacking. Given the limitations associated with currently available treatments for hATTR amyloidosis, most patients will likely request the new RNAi treatments — namely, it is highly likely that RNAi treatments will become first-line therapy for hATTR amyloidosis and that there will be a strong desire within the clinical and patient community to treat hATTR amyloidosis patients with polyneuropathy with an RNAi-based therapy, including transitioning patients on current standard of care to an RNAi treatment. Panel members agreed that it will be important to track outcomes and collect data to gain a better understanding of the longer-term safety and efficacy of RNAi treatments and to assist in identifying those patients who are most likely to benefit from such therapy.

# Discussion

## Summary of Available Evidence

One double-blind, parallel-design, placebo-controlled, phase III RCT met the inclusion criteria for the systematic review (the APOLLO study). In this trial, adults diagnosed with FAP with documented TTR mutation were enrolled and randomized (2:1) to patisiran 0.3 mg/kg or placebo IV every three weeks for 18 months (N = 225). Enrolment was limited to those with PND stage IIIB or lower (i.e., must be able to walk with two sticks or crutches) and excluded patients with New York Heart Association functional class III or class IV heart failure, or those who had undergone a liver transplant. The objective was to determine the superiority of patisiran versus placebo on the change from baseline to 18 months on neurological impairment as measured by the mNIS+7. Other secondary outcomes included health-related quality of life, motor strength, disability, gait speed, nutritional status, and autonomic symptoms, which were part of the statistical testing hierarchy.

## Interpretation of Results

### Efficacy

The APOLLO study was not designed to evaluate mortality, cardiac morbidity, or hospitalizations, which were identified as key outcomes in the review protocol and are important outcomes to patients. Although data on cardiac events and hospitalizations were reported, these events were not systematically captured, and instead were extracted from adverse event reports.

The APOLLO study tested the effects of patisiran versus placebo on neurologic impairment (mNIS+7), health-related quality of life (Norfolk QoL-DN), motor strength (NIS-W), disability (R-ODS), gait speed (10MWT), nutritional status (mBMI), and autonomic symptoms (COMPASS 31). For the primary outcome (mNIS+7), statistically significant differences were detected between the patisiran and placebo groups. The mNIS+7 score decreased (improved) or was stable in many patients treated with patisiran, which is not consistent with the natural history of the disease.[8] Muscle strength and QST contributed the most points to the mNIS+7, and while muscle strength testing may be influenced by the patient's motivation in cases of unblinding, motivation would be unlikely to have an effect on sensory testing.[8] The FDA stated that some components of the mNIS+7 are biomarkers with no direct clinical benefit, and changes in motor and sensory function detected by the physician might not be perceptible to the patient or result in improved function in daily activities. However, the clinical experts consulted stated that although the mNIS+7 is not used in clinical practice, components of the composite, such as the NIS-W, may be part of routine neurological assessments.

The key secondary outcomes (Norfolk QoL-DN, NIS-W, R-ODS, 10MWT, mBMI, and COMPASS 31) showed a consistent pattern, with mean scores in the patisiran group remaining stable over 18 months and the scores in the placebo group suggesting a decline in health status. While all key secondary outcomes were statistically significant, the clinical relevance of the differences observed was difficult to evaluate since there is no known MCID for the outcomes (except for the 10MWT). However, given the results of secondary outcomes, such as the Norfolk QoL-DN and R-ODS, these suggest that the differences were relevant to patients. Moreover, the difference between treatment groups in gait speed (0.31 m/s) exceeded the estimated MCID reported in the literature (0.05 m/s).

The APOLLO study examined a number of cardiac biomarkers and echocardiogram parameters to explore the impact of patisiran on cardiac structure and function. hATTR amyloidosis often affects the heart, with amyloid deposits leading to heart failure, arrhythmias, and sudden cardiac death. The cardiac biomarker data had a number of limitations. First, it is unclear if these measures represent direct clinical benefit in patients with hATTR amyloidosis. The FDA reviewer from the Division of Cardiovascular and Renal Products stated that the APOLLO study does not provide any cardiac efficacy data.[8] The imaging and biomarkers reported "do not measure how a patient feels, functions or survives, nor are they known to predict how a patient feels, function or survives and hence do not measure a clinical benefit."[8] Second, the proportion of patients with a history of cardiac disorders appears to differ between groups at baseline, which may bias the cardiac outcome data. There was a planned analysis of a cardiac subgroup but randomization was not stratified for this group; consequently, the distribution of known and unknown confounders may not be balanced. And indeed, imbalances were observed between treatment groups in a number of the baseline characteristics in this subgroup. Statistical testing of these cardiac outcomes was planned for the cardiac subgroup only, but this was outside the statistical testing hierarchy and therefore should be interpreted with consideration of the risk of type I error. In addition, it is unclear if the criteria used to define this group (LV wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension) was clinically relevant, or if other diagnostic criteria should have been used to identify those with cardiomyopathy. Considering the limitations described above, no conclusions could be drawn based on the cardiac biomarker and echocardiogram data reported in APOLLO. The European Medicines Agency initial authorization states patisiran has shown a positive impact on cardiac parameters; however, the FDA approved patisiran for the treatment of polyneuropathy and makes no claims with regard to cardiac efficacy.[30,31] Health Canada approved patisiran for the treatment of polyneuropathy in adults with hATTR amyloidosis.

A potential source of bias in the APOLLO study was the differential losses to the follow-up period, with a higher percentage of placebo patients with missing data than in the patisiran group. The analysis methods assumed that patients were missing at random, which may not be true as the available data suggests that patients who withdrew had worse outcomes than those who remained in the trial. Sensitivity analyses were conducted to test the impact of missing data, including one that assumed patients were missing not at random; although the results of these analyses were similar to the primary analysis, these analyses cannot fully account for the impact of missing data. However, considering the differential losses in the placebo group, it is anticipated that any potential bias would bias toward the null rather than overestimate the treatment effects of patisiran.

With regard to external validity, in APOLLO, the patients enrolled were, on average, 60 years old and predominantly male and white, with a disease onset after 50 years of age. They were classified as stage I or stage II FAP, which excluded any patients who were wheelchair bound with severe sensory, motor, and autonomic involvement. Patients excluded were those who had type I diabetes, type II diabetes for more than five years, or who had experienced New York Heart Association class III or class IV heart failure. Thus, the generalizability to these patients is unknown. Further, there was limited data on subgroups of interest to this review, and as patients with liver transplant were excluded from the study, there is no data on the efficacy of patisiran in this population. The clinical expert panel agreed that an RNAi may be considered in patients who had previously undergone liver transplant if TTR levels remained elevated or if disease continued to progress, but acknowledged that there is no evidence to support this approach and that this represents an evidence gap.

The available RCT evidence was limited to a single placebo-controlled trial with treatment duration of 18 months. Data from two open-label extension studies were available and have been summarized in Appendix 6. The phase II extension study included 27 patients who were treated with patisiran for two years. The phase III extension study enrolled 25 patients who completed the phase II extension, plus 163 patients who completed the APOLLO study. All patients were treated with patisiran 0.3 mg/kg IV every three weeks in this ongoing study. At the one-year data cut-off, outcome data were available for 64 patients (34%) who remained on treatment and had reached that time point. The phase II (ALN-TTR02-003) and phase III (ALN-TTR02-006) extension studies provide preliminary evidence of long-term stabilization of certain efficacy outcomes with patisiran in patients with hATTR amyloidosis. However, both studies are limited by the absence of a comparator group, lack of blinding, and small sample sizes. Although data for the Norfolk QoL-DN, mNIS+7, and other efficacy outcomes are reported, the results are difficult to interpret due to inherent limitations of the extension study — namely, no control group and potential for observer bias in subjective end points. Moreover, these data represent a select patient population, as the reason for patient withdrawal is likely related to poorer outcomes.

The patient populations in the extension studies represented those with broader characteristics than that of APOLLO in that they allowed enrolment of patients who were using a TTR stabilizer concomitantly with patisiran (74% of patients in ALN-TTR02-003 and 6.9% of patients in ALN-TTR02-006) or patients who had more severe disease, as represented by PND stage IV (6.9% of patients in ALN-TTR02-006) and New York Heart Association class III or class IV (7.4% of patients in ALN-TTR02-006). As mentioned previously, the APOLLO study did not allow for concomitant TTR stabilizer use and excluded patients who were confined to a wheelchair or bedridden, and who were New York Heart Association class > 2. According to the panel of clinical experts consulted for this review, patients with hATTR polyneuropathy who also present with cardiomyopathy may be prescribed a TTR stabilizer. However, the panel acknowledged that no data are currently available to support combination therapies. Further, the panel discussed that patients with advanced polyneuropathy, who are confined to a wheelchair, may still have sensory and motor function in the hands and arms that may be preserved with treatment. More data are required to know if such patients would benefit from treatment.

As there was no direct evidence comparing patisiran with other drugs for hATTR amyloidosis, the available indirect evidence was summarized (see Appendix 7). The manufacturer submitted an indirect comparison that compared patisiran with inotersen, based on data from two phase III trials (APOLLO and NEURO-TTR). In this analysis, individual patient data from APOLLO was used to calculate the mNIS+$7_{ionis}$, a composite that used different sensory and autonomic testing than the mNIS+7 in APOLLO but the same NIS-W, NIS-R, and nerve conduction studies. Two indirect comparisons were calculated, one using the Bucher method and a second using matching-adjusted indirect comparison methods. The matching-adjusted indirect comparison is a form of population-adjusted indirect treatment comparison that used individual patient data from APOLLO and matched baseline aggregate data reported in the inotersen trial. Both analyses suggested that patisiran was statistically superior to inotersen for the change from baseline in mNIS+$7_{ionis}$ and the Norfolk QoL-DN scores. Although the differences between treatments were statistically significant, the clinical significance of the differences is unclear, given the lack of MCID for these outcome measures. A second indirect comparison was identified by CADTH that compared patisiran with tafamidis, but due to differences in the patient populations and outcome measures, the results carry a high level of uncertainty and no strong conclusions could be drawn from this analysis.

### Harms

In the APOLLO study, most patients (97%) experienced an adverse event, with diarrhea, peripheral edema, and infusion-related reactions reported most frequently among those who received patisiran. The percentage of patients who reported a serious adverse event was similar for patisiran (37%) and placebo (40%), but the percentage of patients who stopped treatment due to adverse events was lower in the patisiran group than in the placebo group (5% versus 14%). Infusion-related reactions were reported more frequently in the patisiran group than in the placebo group (19% versus 9%); however, only one patisiran patient stopped treatment due to these events and no events met the criteria for a serious adverse event. The most common infusion-related reactions in the patisiran group were back pain, abdominal pain, headache, arthralgia, and dyspnea. Flushing was the most common infusion-related reaction in the placebo group. Some of these adverse events were associated with premedications administered prior to infusions; as a result, the premedication regimen was modified during the course of the study. The manufacturer stated that there was no increase in infusion-related reactions with the reduced dose premedication regimen.

No data were reported on comparative safety in the manufacturer-provided indirect comparison between patisiran and inotersen, and no other comparative safety data for patisiran versus tafamidis or diflunisal were identified in the literature.

No new safety signals were detected in the open-label extension studies; however, these data were limited by the small sample size and lack of control group or blinding. Moreover, the APOLLO study had limited power to detect infrequent adverse events or those with a longer lag time. Considering that patisiran is part of a new drug class and comparative data were limited to a single RCT that was 18 months in duration, additional data are required to determine the safety of the medication in the longer term.

## Conclusions

One double-blind, placebo-controlled, phase III RCT evaluated the safety and efficacy of patisiran in patients with hATTR amyloidosis and polyneuropathy FAP stage I and stage II. After 18 months of treatment, patients treated with patisiran showed statistically significant differences versus those treated with placebo in neurological impairment, measured using the mNIS+7 composite score, and health-related quality of life, based on the Norfolk QoL-DN questionnaire. Statistically significant differences were also demonstrated in favour of patisiran for disability (measured using the R-ODS), gait speed (measured by the 10MWT), unintended weight loss (measured by mBMI), and autonomic symptoms (measured by the COMPASS 31 instrument).

Infusion-related reactions were reported more frequently in the patisiran group than in the placebo group; however, these events rarely required the patient to stop treatment. Considering that patisiran is part of a new drug class and that comparative data were limited to a single placebo-controlled RCT that was 18 months in duration, additional data are required to determine the safety and efficacy of patisiran in the longer term.

No direct evidence was available comparing patisiran with other treatments for hATTR amyloidosis, though an indirect comparison suggests patisiran may be statistically superior to inotersen for the change from baseline in mNIS+$7_{ionis}$ and the Norfolk Qol-DN scores. However, the clinical significance of the differences calculated is unclear, given the lack of MCID for these outcome measures. The indirect comparison provided no data on the comparative safety.

# Appendix 1: Patient Input Summary

*This section was prepared by CADTH staff based on the input provided by patient groups.*

**1. Brief Description of Patient Group(s) Supplying Input**

One patient group, the Canadian Organization for Rare Disorders (CORD), provided input for this submission. CORD is a national network of organizations for patients with rare disorders. It provides a common voice for patients and works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services. CORD completed the patient input with the support of the Canadian Amyloidosis Support Network (CASN). CASN is a non-profit volunteer organization of patients with amyloidosis and their families.

CORD declared financial payment in the amount of $5,000 to $10,000 in the past two years from the manufacturer of patisiran. CORD stated that they received no help from outside their organization for data collection and analysis, or for the completion of the patient group submission.

**2. Condition-Related Information**

Information for this submission was gathered from patients, who were recruited through two networks: Amyloidosis Support Groups, Inc. and CASN. The Amyloidosis Support Groups, Inc. is based in the US and has support groups for patients with amyloidosis in more than 35 cities as well as global patient engagement, including through the CASN. Patients provided input through an online survey, individual interviews, and written testimonials. The online survey was distributed to all members of the amyloidosis networks; however, the instructions targeted patients, and caregivers of patients, with hereditary transthyretin-mediated (hATTR) amyloidosis. Of the 51 responses received, 73% were diagnosed with hATTR amyloidosis, 4% had symptoms consistent with hATTR amyloidosis, 10% had a type of amyloidosis similar to hATTR, and 10% were caregivers for someone with hATTR amyloidosis. Four per cent had no diagnosis or were unsure of the type of amyloidosis. The survey respondents included more males than females (70% and 30%, respectively) and most respondents lived in the US. Of those patients from Canada, 80% lived in Ontario. The majority of respondents were diagnosed between the ages of 60 years and 79 years (53%). Fewer were diagnosed between 40 years and 59 years (36%) or 20 years and 39 years (< 6%). Most respondents had been living with the condition for two to 10 years since their diagnosis.

hATTR amyloidosis is a debilitating condition that affects multiple systems in the body. It results in significant physical damage, pain, and psychological distress, and impacts daily functioning and health-related quality of life. Patients experience symptoms of neuropathy, gastro paralysis, diarrhea, effects on the heart, deterioration of muscles with effects on mobility, and weight loss. In the survey, patients rated symptoms of nerve damage (i.e., tingling, numbness, burning pain, carpal tunnel, and weakness) as the most difficult, with one-third reporting these symptoms having serious impact and one-fifth reporting these symptoms to be incapacitating. The second most difficult symptom was gastrointestinal, with 51% reporting serious or incapacitating effects of gastrointestinal-related sexual dysfunction, sweating, dizziness upon standing, and weight loss. Other gastrointestinal symptoms, such as diarrhea, nausea, constipation, and urinary tract infection, were serious or incapacitating among one-third of respondents. Cardiac symptoms, such as palpitations, arrhythmia, and chest pain, were reported as serious or incapacitating by 40% of patients but were not present or posed minor difficulty in 50% of patients. Other cardiac symptoms,

such as leg swelling, fatigue, shortness of breath, and dizziness, were not present or minor in about 40% of respondents and serious in about 25%.

The symptoms may make daily activities difficult. As stated by one patient, "…there are many times I can't leave the house for fear of diarrhea." One patient with familial amyloidosis described how the condition affected several generations of the family, having to see close family members suffer and succumb to the condition while growing up and, when the patient too was diagnosed, falling into severe depression. Another patient described the progressive nature of the disease: ". . . each day it progresses, requiring changes and adaptation big and small to day to day living. It went from difficulty walking distances to not being able to walk at all in 4 years." The disease affects not only the patient, but also the patient's caregivers and entire family.

**3. Current Therapy-Related Information**

Three patients (one in Canada and two in the US) indicated that they had had a liver transplant and three patients (in the US) reported use of tafamidis in the past. Three patients received inotersen and 29 received patisiran. Most respondents (75%) reported having received a treatment related to hATTR amyloidosis, primarily to manage symptoms related to heart, nerve damage, and inflammation. The most frequently reported treatment (64%) was diflunisal and one-third reported using at least one other medication to reduce inflammation. More than half had used, or were currently using, therapy for cardiac management, such as a diuretic to reduce blood pressure, amiodarone to regulate heartbeat, and warfarin to prevent clots. Patients (40%) also took medication to manage fluid or mineral levels and a small number used antibacterial treatments, home therapies, or green tea extract to manage gastrointestinal symptoms.

Liver transplant was rated as very effective by the Canadian patient and not at all effective by the American patients. Two patients reported that tafamidis was somewhat effective and one patient said it was not at all effective. Treatments for inflammation (i.e., diflunisal) were rated as moderately effective by about 50%, but were mostly regarded as not effective. Among patients taking medications for cardiac management (e.g., blood pressure and arrhythmia), most reported that they worked well or very well, although 12% to 20% reported that the therapies were not at all effective or poorly effective. Treatments to manage fluid levels were rated as moderately effective to not at all effective by 60%.

The currently available treatments for hATTR amyloidosis generally manage symptoms but do not address disease progression. This is the primary unmet need for the treatment of hATTR amyloidosis. As stated by one patient, "…we desperately need drugs that will flush out the added proteins in our system – that would help with all of the symptoms."

**4. Expectations About the Drug Being Reviewed**

Patients who received patisiran experienced a reduction in nerve pain, increase in strength and energy, better appetite, and improved mobility. Patients also reported a slowing or halting of disease progression and felt that they could do more. Patients stated, "I have more energy…I have a more positive outlook on life," "I can move better, easier, stronger…Since I am stronger I know I can now work in other places other than the home," "My mood is better…," and "…I don't have to suffer pain like I used to and less frequent diarrhea and constipation." Side effects included nausea, edema, hot flashes, chills, short headaches, and diarrhea, but these were considered manageable. Fifty percent of patients who received patisiran said they experienced no side effects.

### 5. Additional Information

hATTR amyloidosis is a rare disease and has not received the same amount of attention as diseases that are more common.

# Appendix 2: Literature Search Strategy

## Clinical Literature Search

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | MEDLINE All (1946-present)<br>Embase (1974-present)<br>Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | February 22, 2019 |
| Alerts: | Bi-weekly search updates until June 19, 2019 |
| Study Types: | No search filters were applied |
| Limits: | No date or language limits were used<br>Conference abstracts: excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| MeSH | Medical Subject Heading |
| exp | Explode a subject heading |
| .ti | Title |
| .ab | Abstract |
| .dq | Candidate term word (Embase) |
| .ot | Original title |
| adj# | Requires terms to be adjacent to each other within # number of words (in any order) |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kf | Author keyword heading word (MEDLINE) |
| .kw | Author keyword (Embase); keyword |
| .nm | Name of substance word |
| .pt | Publication type |
| .mp | Mapped term |
| .rn | Registry number |
| .yr | Publication year |
| medall | Ovid database code: MEDLINE All, 1946 to present, updated daily |
| oemezd | Ovid database code; Embase, 1974 to present, updated daily |

| MULTI-DATABASE STRATEGY | |
|---|---|
| 1 | (patisiran* or Onpattro* or aln 18328 or aln18328 or aln ttr02 or alnttr02 or genz 438027 or genz438027 or 50FKX8CB2Y).ti,ab,ot,kf,hw,rn,nm. |
| 2 | 1 use medall |
| 3 | *patisiran/ |
| 4 | (patisiran* or Onpattro* or aln 18328 or aln18328 or aln ttr02 or alnttr02 or genz 438027 or genz438027).ti,ab,kw,dq. |
| 5 | or/3-4 |
| 6 | 5 use oemezd |
| 7 | 6 not (conference review or conference abstract).pt. |
| 8 | 2 or 7 |
| 9 | remove duplicates from 8 |

| OTHER DATABASES | |
|---|---|
| PubMed | A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |
| Trial registries (ClinicalTrials.gov and others) | Same keywords, limits used as per MEDLINE search. |

### Grey Literature

| | |
|---|---|
| Dates for Search: | February 2019 |
| Keywords: | Onpattro (patisiran), hereditary transthyretin-mediathereditary transthyretin-mediated amyloidosis |
| Limits: | No date or language limits used |

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- Internet search.

# Appendix 3: Excluded Studies

## Table 19: Excluded Studies

| Reference | Reason for Exclusion |
|---|---|
| 1. Suhr OB, Coelho T, Buades J, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. Orphanet J Rare Dis. 2015;10:109. | Phase II study |
| 2. Adams D, Suhr OB, Conceicao I, et al. Phase 2 open-label extension (OLE) study of patisiran, an investigational siRNA agent for familial amyloidotic polyneuropathy (FAP). Orphanet J Rare Dis. 2015;10(Supplement1):1-2.<br>3. Clinical Study Report: ALN-TTR02-003. A phase 2, multicenter, open-label, extension study to evaluate the long-term safety, clinical activity, and pharmacokinetics of ALN-TTR02 in patients with familial amyloidotic polyneuropathy who have previously received ALN-TTR02[CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Alnylam Pharmaceuticals, Inc.; 2017 Feb 9.<br>4. Clinical Study Report: ALN-TTR02-006. A multicenter, open-label, extension study to evaluate the long-term safety and efficacy of Patisiran in patients with familial amyloidotic polyneuropathy who have completed a prior clinical study with Patisiran [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Anylam Pharmaceuticals Inc.; 2017 Nov 20. | Not a randomized controlled trial |
| 5. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017;17(1):181. | No outcome data |

# Appendix 4: Detailed Outcome Data

## Table 20: Summary of Baseline Characteristics of Cardiac Subpopulation in APOLLO

| Characteristic | APOLLO | |
|---|---|---|
| | Placebo N = 36 | Patisiran N = 90 |
| Mean age (SD), years | [redacted] | [redacted] |
| Male, n (%) | [redacted] | [redacted] |
| Race, n (%) | | |
| White | [redacted] | [redacted] |
| Asian | [redacted] | [redacted] |
| Other or missing | [redacted] | [redacted] |
| Years since diagnosis of hATTR amyloidosis, mean (SD) | [redacted] | [redacted] |
| Age at hATTR Symptom Onset, n (%) | | |
| < 50 years | [redacted] | [redacted] |
| ≥ 50 years | [redacted] | [redacted] |
| Familial Amyloidotic Polyneuropathy Stage | | |
| 0 | [redacted] | [redacted] |
| I | [redacted] | [redacted] |
| II | [redacted] | [redacted] |
| III | [redacted] | [redacted] |
| Genotype, n (%) | | |
| V30M | [redacted] | [redacted] |
| Non-V30M | [redacted] | [redacted] |
| New York Heart Association Functional Class,[a] n (%) | | |
| I | [redacted] | [redacted] |
| II | [redacted] | [redacted] |
| III or IV | [redacted] | [redacted] |
| Previous Tetramer Stabilizer Use, n (%) | | |
| Tafamidis | [redacted] | [redacted] |
| Diflunisal | [redacted] | [redacted] |
| None | [redacted] | [redacted] |
| NT-proBNP, median IQR[b] | [redacted] | [redacted] |
| Cardiac implanted devices, n (%) | [redacted] | [redacted] |
| Medical history of cardiac disorders, n (%) | [redacted] | [redacted] |
| Cardiac conduction disorders | [redacted] | [redacted] |
| Cardiomyopathies | [redacted] | [redacted] |
| Myocardial disorders | [redacted] | [redacted] |
| Supraventricular arrhythmias | [redacted] | [redacted] |
| Ventricular arrhythmias and cardiac arrest | [redacted] | [redacted] |
| Baseline Cardiovascular Treatment, n (%) | | |
| Beta blockers | [redacted] | [redacted] |
| ACE inhibitors or ARB | [redacted] | [redacted] |

| Characteristic | APOLLO | |
|---|---|---|
| Spironolactone | [redacted] | [redacted] |
| Furosemide | [redacted] | [redacted] |
| Hydrochlorothiazide | [redacted] | [redacted] |
| Torasemide | [redacted] | [redacted] |

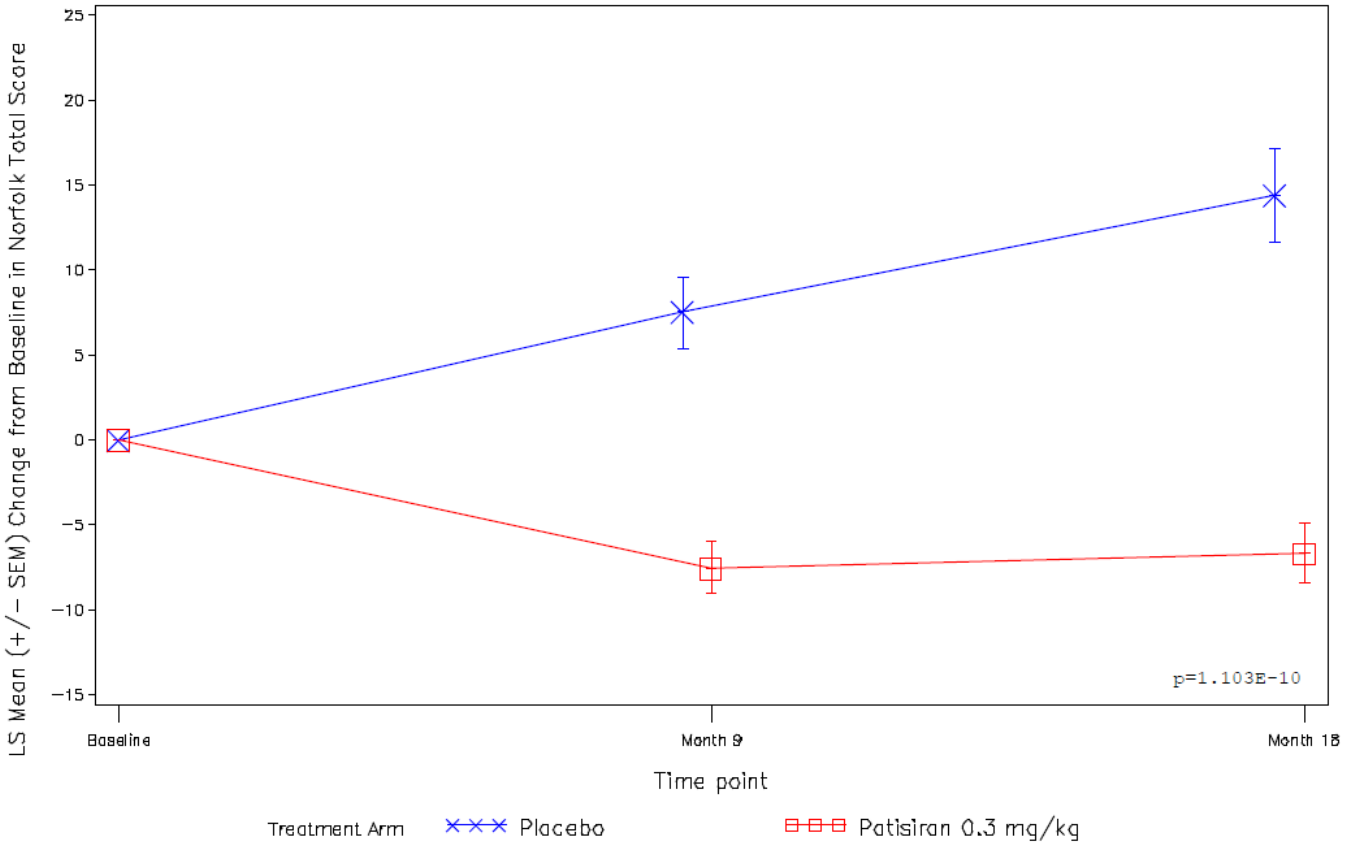
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; hATTR = hereditary transthyretin-mediated; IQR = interquartile range; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; SD = standard deviation; V30M = valine to methionine substitution at position 30.

[a] Class I: no symptoms; class II: symptoms with ordinary physical activity; class III: symptoms with less than ordinary physical activity; class IV: symptoms at rest.

[b] Data converted by the CADTH Common Drug Review based on the following conversion factor: 1 pmol/L = 8.457 pg/mL.[29]

Source: Clinical Study Report for the APOLLO study,[7] Solomon et al. (2019).[21]

## Figure 6: Change in Norfolk Quality of Life-Diabetic Neuropathy Score Over Time in APOLLO Study (Mixed-Effects Model for Repeated Measures, Modified Intention-to-Treat)




LS = least squares; Norfolk = Norfolk Quality of Life-Diabetic Neuropathy; SEM = standard error of the mean.

Source: Clinical Study Report for the APOLLO study.[7]

## Table 21: Sensitivity Analyses for Norfolk Quality of Life-Diabetic Neuropathy in APOLLO Study

| Analysis[a] | Baseline | | Change From Baseline to 18 Months | | LS Mean Difference Patisiran vs. Placebo (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | LS Mean (SE) | | |
| **Multiple Imputation/ANCOVA[a]** | | | | | | |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Patisiran | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **MMRM, Including Post-Alternative Treatment** | | | | | | |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Patisiran | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

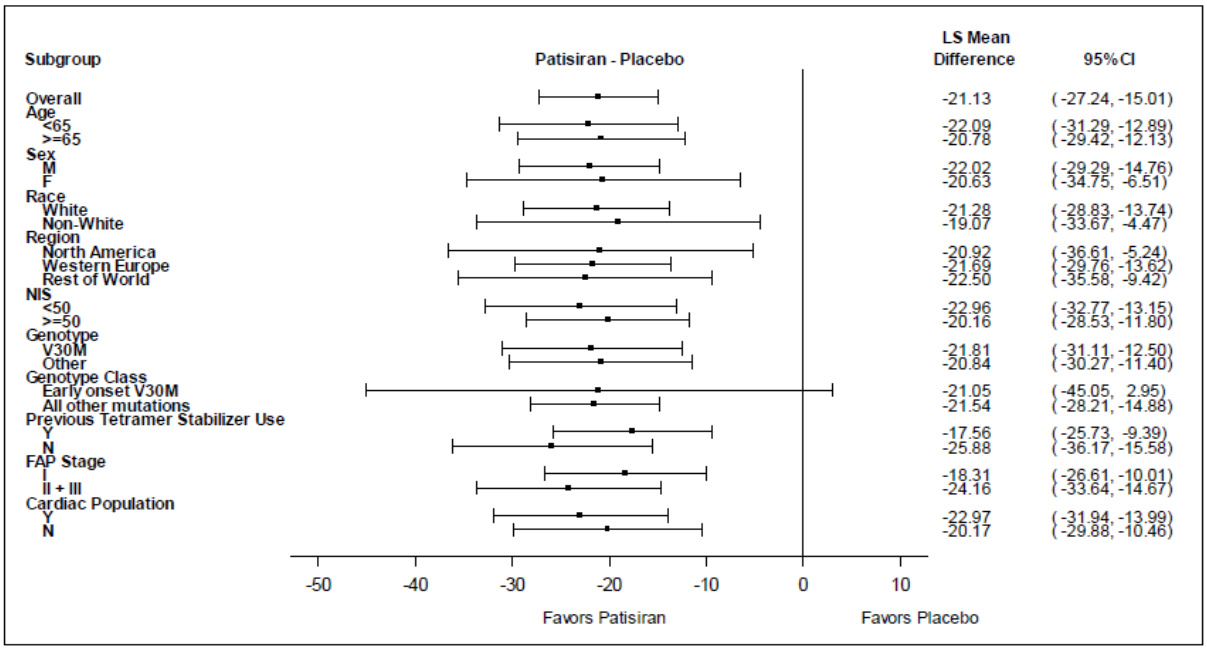
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; MMRM = mixed-effects model for repeated measures; NIS = Neurologic Impairment Score; NR = not reported; SD = standard deviation; SE = standard error; vs. = versus.

[a] See Table 9 for description of analysis methods.

[b] Covariates included baseline score, treatment, genotype, age at hATTR onset, previous tetramer stabilizer use, region, and baseline NIS score.

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 7: Subgroup Analysis for Change From Baseline in Norfolk QoL-DN to Month 18 in APOLLO (Mixed-Effects Model for Repeated Measures, Modified Intention-to-Treat)




CI = confidence interval; F = female; FAP = familial amyloidosis with polyneuropathy; LS = least squares; M = male; N = no; NIS = Neurologic Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; V30M = valine to methionine substitution at position 30; Y = yes.

Note: Analysis of cardiac population was conducted post hoc.

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 8: Observed Change From Baseline in Norfolk Quality of Life-Diabetic Neuropathy for Patients With Missing 18-Month Assessment

**Figure 8 contained confidential information and was removed at the request of the manufacurer.**

Source: Clinical Study Report for the APOLLO study.[7]

## Table 22: Sensitivity Analyses for Change From Baseline in Modified Neurologic Impairment Score +7 in APOLLO Study

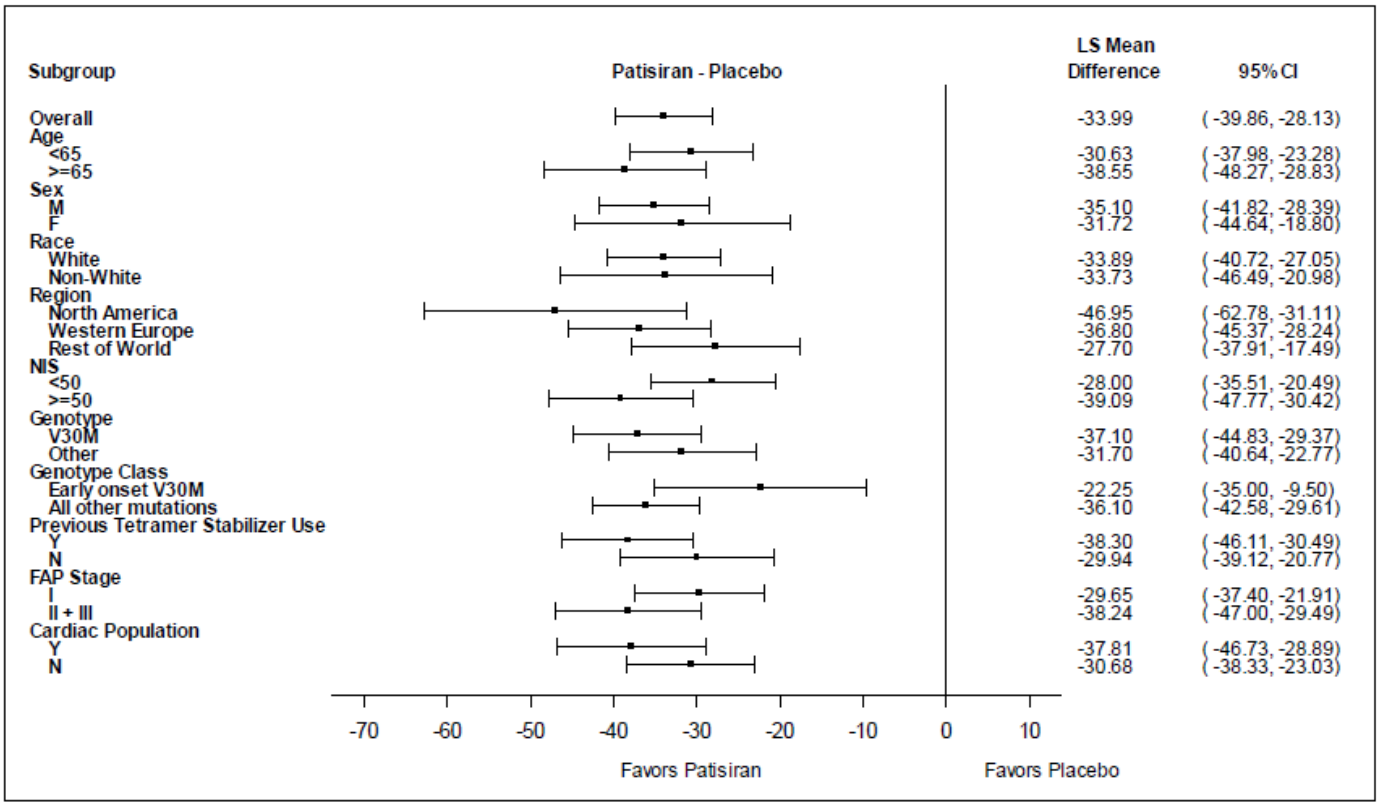
| Analysis mNIS+7 | Baseline | | Change From Baseline to 18 Months | | LS Mean Difference Patisiran vs. Placebo (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | LS Mean (SE) | | |
| **Multiple Imputation / ANCOVA[a]** | | | | | | |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Patisiran | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Pattern-Mixture Model** | | | | | | |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Patisiran | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **MMRM, Including Post-Alternative Treatment** | | | | | | |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Patisiran | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **MMRM — Different Imputation Method for Missing Data** | | | | | | |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Patisiran | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; MMRM = mixed-effects model for repeated measures; mNIS+7 = modified Neurologic Impairment Score +7; NR = not reported; SD = standard deviation; SE = standard error.

[a] [redacted]

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 9: Subgroup Analysis for Change From Baseline in Modified Neurologic Impairment Score +7 to Month 18 in APOLLO (Mixed-Effects Model for Repeated Measures, Modified Intention-to-Treat)

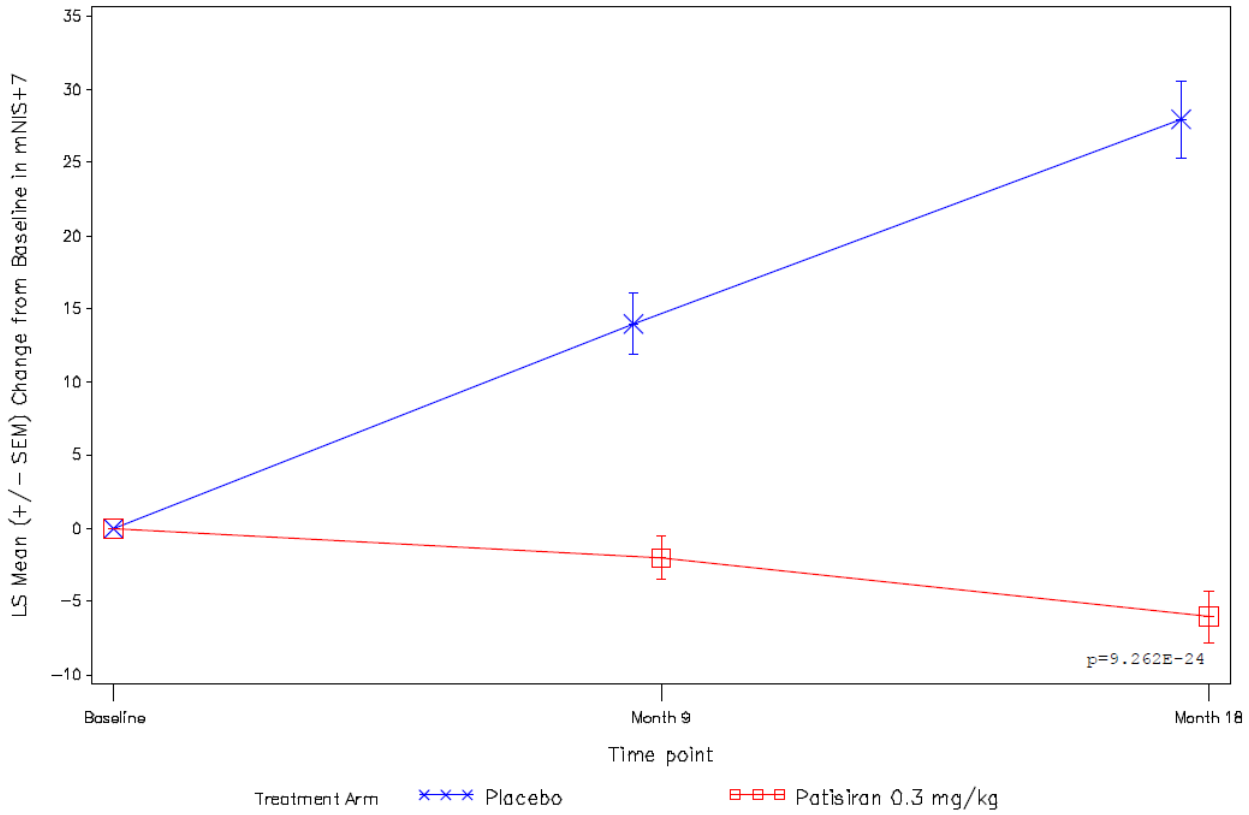



CI = confidence interval; F = female; FAP = familial amyloidosis with polyneuropathy; LS = least squares; M = male; mNIS+7 = modified Neurologic Impairment Score +7; N = no; NIS = Neurologic Impairment Score; V30M = valine to methionine substitution at position 30; Y = yes.

Note: Analysis of cardiac population was conducted post hoc.

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 10: Change in Modified Neurologic Impairment Score +7 Over Time in APOLLO (Mixed-Effects Model for Repeated Measures, Modified Intention-to-Treat)




LS = least squares; mNIS+7 = modified Neurologic Impairment Score +7; SEM = standard error of the mean.

Source: Clinical Study Report for the APOLLO study.[7]

## Table 23: Completeness of Modified Neurologic Impairment Score +7 Data in APOLLO Study

| | Number of Patients (%) | |
|---|---|---|
| | Placebo | Patisiran |
| **Baseline** | [redacted] | [redacted] |
| **Included in MMRM Model** | [redacted] | [redacted] |
| Both month 9 and month 18 data available | [redacted] | [redacted] |
| Month 9 data included but missing month 18 data | [redacted] | [redacted] |
| Censored after month 9 due to alternative treatment initiation | [redacted] | [redacted] |
| **Excluded from MMRM Model** | [redacted] | [redacted] |
| Missing both month 9 and month 18 data | [redacted] | [redacted] |
| Censored before month 9 due to alternative treatment initiation | [redacted] | [redacted] |

MMRM = mixed-effects model for repeated measures.

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 11: Observed Change From Baseline in Modified Neurologic Impairment Score +7 for Patients With Missing 18-Month Assessment

**Figure 11 contained confidential information and was removed at the request of the manufacurer.**

Source: Clinical Study Report for the APOLLO study.[7]

## Figure 12: Cumulative Distribution of the Modified Neurologic Impairment Score +7 Change From Baseline in APOLLO Study (Modified Intention-to-Treat)

**Figure 12 contained confidential information and was removed at the request of the manufacurer.**

Source: Clinical Study Report for the APOLLO study.[7]

## Table 24: Troponin I Results in APOLLO Study

| | mITT Population | | | | Cardiac Subpopulation | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome / Treatment Group | Baseline | | Change From Baseline to 18 Months | | Baseline | | Change From Baseline to 18 Months | |
| | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) |
| **Troponin I (mcg/L)[a,b]** | | | | | | | | |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patisiran | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

mITT = modified intention-to-treat; SD = standard deviation.

[a] Normal range less than 0.10 mcg/L.

[b] The troponin values were reported as < 0.1 mcg/L for 90% of patients and were imputed to be 0.1 mcg/L. As a result of these issues, the effect of patisiran treatment on troponin I cannot be inferred.

Source: Clinical Study Report for the APOLLO study.[7]

# Appendix 5: Description and Critical Appraisal of Outcome Measures

## Aim

To summarize the validity of the following outcome measures:

- Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN)
- EuroQol 5-Dimensions 5-Levels (EQ-5D-5L)
- Modified Neurologic Impairment Score +7 (mNIS+7)
- Rasch-built Overall Disability Scale (R-ODS)
- Composite Autonomic Symptom Score 31 (COMPASS 31)
- polyneuropathy disability (PND) staging
- familial amyloidotic polyneuropathy (FAP) staging
- 10 Metre Walk Test (10MWT)
- modified Body Mass Index (mBMI)
- N-terminal prohormone brain-type natriuretic peptide (NT-proBNP)
- troponin I
- echocardiogram — left ventricular (LV) longitudinal strain
- echocardiogram — LV wall thickness
- echocardiogram — left ventricular ejection fraction (LVEF).

## Findings

### Table 25: Summary of Outcome Measures and Their Measurement Properties

| Instrument | Type | Evidence of Validity | MCID | References |
|---|---|---|---|---|
| **HRQoL** | | | | |
| Norfolk QoL-DN | • Disease-specific HRQoL measure that evaluates the impact of neuropathy on functional status<br>• 35 items, grouped into 5 domains: physical functioning and large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, autonomic neuropathy | Yes | Unknown | Vinik (2014)[6] |
| EQ-5D-5L | • Generic, preference-based measure of HRQoL | Yes[a] | Instrument-defined (Canadian population): 0.037 | Richardson (2016)[32]<br>McClure (2017)[26] |
| **Neurologic Impairment** | | | | |
| mNIS+7 | • Measure of neurological impairment with clinical assessments and neurophysiologic tests | Yes[b] | Unknown | Peripheral Nerve Society (1995)[28]<br>Suanprasert (2014)[33]<br>Dyck (2017)[23] |

| Instrument | Type | Evidence of Validity | MCID | References |
|---|---|---|---|---|
| | • The measure used in APOLLO was a 304-point composite consisting of NIS-W, NIS-R, ∑5 NCS, QST score, and postural blood pressure | | | |
| COMPASS 31 | • Measure of autonomic symptoms<br>• 31 items, grouped into 6 domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, pupillomotor | Yes[a] | Unknown | Sletten (2012)[24]<br>Treister (2015)[25] |
| R-ODS | • Measure of disability, specifically limitations in activities and social participation<br>• 24-item linearly weighted scale | Yes[a] | Unknown | van Nes (2011)[34]<br>Draak (2014)[35]<br>Vanhoutte (2015)[36] |
| **Disability and Functional Status** | | | | |
| PND staging | • Staging of hATTR amyloidosis based on mobility | No | Unknown | Ando (2013)[1] |
| FAP staging | • Staging of hATTR amyloidosis based on mobility and neuropathy | No | Unknown | Ando (2013)[1] |
| 10MWT | • Walking test to assess ability to ambulate | Yes[a] | Survivors of subacute stroke or older adults with mobility disabilities: 0.05 m/s | Perera (2006)[37]<br>Lang (2016)[38]<br>Niu (2017)[39]<br>Mori (2019)[40] |
| **Nutritional Status** | | | | |
| mBMI | • Measure of nutritional status that takes into consideration hypoalbuminemia<br>• mBMI = BMI × albumin | Yes | Unknown | Suhr (1994)[41]<br>Suhr (2005)[42]<br>Franz (2013)[43]<br>Suhr (2014)[44] |
| **Cardiovascular Biomarkers and Echocardiogram** | | | | |
| NT-proBNP | • A marker of cardiac stress and injury<br>• Cardiac biomarker that is released from the heart into the circulation in response to myocardial wall tension and stress | Yes | Unknown | Palladini (2003)[45]<br>Lehrke (2009)[46]<br>Sattianayagam (2012)[47]<br>Cappelli (2014)[48]<br>Kristen (2014)[49]<br>Damy (2016)[50]<br>Grogan (2016)[51]<br>Ternacle (2016)[52]<br>Kristen (2017)[53]<br>Siepen (2018)[54] |
| Troponin I | • A marker of cardiac stress and injury<br>• Cardiac biomarker that is released in response to myocardial injury | Yes | Unknown | Cappelli (2014)[48]<br>Grogan (2016)[51]<br>Kristen (2017)[53] |
| LV longitudinal strain | • A measure of cardiac function<br>• An echocardiogram measure of systolic dysfunction | Yes | Unknown | Stanton (2009)[55]<br>Quarta (2014)[56]<br>Hu (2015)[57]<br>Ternacle (2016)[52]<br>Barros-Gomes (2017)[58]<br>Rocha (2017)[59]<br>Siepen (2018)[54] |

| Instrument | Type | Evidence of Validity | MCID | References |
|---|---|---|---|---|
| LV wall thickness | • A measure of cardiac structure<br>• An echocardiogram measure to identify structural impairment due to remodelling from amyloid infiltrates | Yes | Unknown | Kristen (2007)[60]<br>Sattianayagam (2012)[47] |
| LVEF | • An echocardiogram measure of systolic dysfunction | Yes | Unknown | Ruberg (2012)[3] |

Σ5 NCS = sum of five attributes of nerve conduction studies; 10MWT = 10 metre walk test; BMI = body mass index; COMPASS 31 = Composite Autonomic Symptom Score 31; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FAP = familial amyloidotic polyneuropathy; hATTR = hereditary transthyretin-mediated; HRQoL = health-related quality of life; LV = left ventricular; LVEF = left ventricular ejection fraction; MCID = minimal clinically important difference; mNIS+7 = Modified Neurologic Impairment Score +7; $mNIS+7_{Ionis}$ = modified Neurologic Impairment Score +7 outcome measure used in the phase III randomized controlled trial for inotersen; mBMI = modified body mass index; NIS-R = Neurologic Impairment Score–Reflexes; NIS-W = Neurologic Impairment Score–Weakness; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PND = polyneuropathy disability; QST = quantitative sensory testing; R-ODS = Rasch-built Overall Disability Scale.

[a] Evidence of validity in other disease states. No studies conducted in patients with hATTR amyloidosis.

[b] Validated in the $mNIS+7_{Ionis}$, which differs slightly from the mNIS+7 used in the APOLLO study.

## Health-Related Quality of Life

### *Norfolk Quality of Life-Diabetic Neuropathy*

The Norfolk QoL-DN is a self-administered, patient-reported, disease-specific, quality-of-life instrument that consists of 35 standardized items, grouped into five domains, to assess the impacts of neuropathy on functional status.[7] The five domains are physical functioning and large-fibre neuropathy (15 items), activities of daily living (five items), symptoms (eight items), small-fibre neuropathy (four items), and autonomic neuropathy (three items).[6,22] In the validated tool, patients are asked to recall symptoms over a four-week period; however, for the APOLLO study, the recall period was shortened to one week, as recommended by FDA.[22] Part I of the questionnaire consists of seven symptom items, which are recorded on a binary scale of present (one) or absent (zero).[22] Part II of the questionnaire consists of 28 items to assess activities of daily living, with most responses rated on a five-point Likert scale ranging from zero (not a problem) to four (severe problem). Item 31 is rated on a five-point scale of −two (excellent), −one (very good), zero (good), one (fair), and two (poor). Item 32 is rated on a five-point scale of −two (much better), −one (somewhat better), zero (about the same), one (somewhat worse), and two (much worse).[22] The domains are aggregated with the integer sum to arrive at a total score, with higher scores representing poorer health status. The total score ranges from −four (best quality of life) to 136 (worst quality of life).[22] The instrument was originally developed to assess patients' perceptions of symptoms of nerve fibre damage that occur in diabetic neuropathy.[6] The pattern of neuropathy in hereditary transthyretin-mediated (hATTR) amyloidosis is similar to that of diabetic neuropathy.[6]

The Norfolk QoL-DN was validated in 61 patients with hATTR amyloidosis with the valine to methionine substitution at position 30 (V30M) and stage I to stage III disease from a single study centre in Portugal.[6] The questionnaire was translated into Portuguese and validated linguistically. The patients in this study had stage I (independent ambulation, N = 29), stage II (assistance required to walk, N = 16), or stage III (wheelchair bound or bedridden, N = 16) hATTR amyloidosis. There were, approximately, an equal proportion of men (50.8%) and women (49.2%), and the average age ranged from 39 years for stage I patients to 55 years for stage III patients. According to the clinical experts consulted for this review, the V30M mutation is most common in Canadian patients of Portuguese or Italian descent. The study

results will be generalizable to these patients; however, it may be less generalizable to patients with other types of hATTR mutations or to patients who present with predominant cardiomyopathy. Patients completed the Norfolk QoL-DN at baseline and stage II and stage III patients completed the questionnaire again at four weeks. The scoring range for the Norfolk QoL-DN was −2 to 138. Validity: The Norfolk QoL-DN was correlated with objective measures of neurological function, which included the modified form of Neurologic Impairment Score (NIS), Neuropathy Impairment Score–Lower Limbs (NIS-LL), and quantitative sensory testing (QST). The correlation with NIS followed a quadratic equation, with an initial increase of 1.02 points per unit increase in NIS total score. The five domains of Norfolk QoL-DN correlated strongly with NIS-LL subscales of muscle weakness, reflexes, and sensation (Pearson's correlation coefficient [r] ranged from 0.51 to 0.87).[61] The Norfolk QoL-DN also correlated strongly with small-fibre function as assessed with heat pain threshold (Pearson's r = 0.65) and moderately with cooling detection threshold (Pearson's r = 0.42), and with autonomic function as assessed with heart rate response to deep breathing (Pearson's r = −0.38). Discriminant validity: The Norfolk QoL-DN discriminated between patients with and without disease and between patients with different stages of disease (mean total score [standard deviation, or SD]: healthy volunteers = 2.6 [5.0]; stage I = 21.0 [14.5]; stage II = 73.1 [27.5]; stage III = 95.4 [2.7]; $P < 0.002$). With duration of disease, the Norfolk QoL-DN followed a quadratic equation, with an initial increase of 9.12 points per year of symptom duration and levelling off at about 19 years. Reliability: The instrument was demonstrated to have test–retest reliability as there were no statistically significant differences between the baseline and week 4 assessments in patients with stage II or stage III disease. Aside from small-fibre neuropathy, there were also no statistically significant differences in the individual domains at baseline and week 4.

A minimal clinically important difference (MCID) for the Norfolk QoL-DN was not identified for patients with diabetic neuropathy or hATTR amyloidosis.

### *The EuroQol 5-Dimensions 5-Levels*

The EQ-5D-5L was developed by the EuroQol Group as an improvement to the EuroQol 5-Dimensions 3-Levels to measure small and medium health changes, and reduce ceiling effects.[26,62] The instrument is comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on five levels: level 1 is "no problems," level 2 is "slight problems," level 3 is "moderate problems," level 4 is "severe problems," and level 5 is "extreme problems" or "unable to perform."[26] A total of 3,125 unique health states are possible, with 55555 representing the worst health state and 11111 representing the best state. The corresponding scoring of EQ-5D-5L health states is based on a scoring algorithm that is derived from preference data obtained from interviews using choice-based techniques (e.g., time trade-off) and discrete choice experiment tasks.[26] The lowest and highest score varies, depending on the scoring algorithm used. The anchors are zero (dead) and one (full health); however, negative values are also allowed to represent health states that a population considers worse than death. As an example, a Canadian scoring algorithm results in a score of −0.148 for health state 55,555 (worst health state) and a score of 0.949 for health state 11,111 (best health state).[26] Another component of the EQ-5D-5L is a visual analogue scale, which asks respondents to rate their health on a visual scale from zero (worst health imaginable) to 100 (best health imaginable).[26]

Richardson et al. examined various instruments, including the EQ-5D-5L, in respondents who were healthy and who had a chronic disease (i.e., arthritis, asthma, cancer,

depression, diabetes, hearing loss, and heart disease) through an online survey in Australia, Canada, Germany, Norway, the UK, and the US.[32] Discriminant validity: The mean EQ-5D-5L differed between healthy respondents and respondents with a chronic disease (0.88 in healthy respondents and range of 0.09 to 0.29 in respondents with chronic disease). Construct validity: The EQ-5D-5L was strongly correlated with the physical component of the Short Form (36) Health Survey (average across all disease states, r = 0.66), moderately correlated with the psychosocial content of the mental component of the Short Form (36) Health Survey, the Capabilities Instrument, and the Subjective Well-Being Instrument of the UK Office for National Statistics (average across all disease states, r = 0.48), and moderately correlated with preference measures of visual analogue scale and time trade-off on own health state (average across all disease states, r = 0.43).

McClure et al. (2017) obtained MCIDs for the EQ-5D-5L by calculating the average absolute difference between the index score of the baseline health state and the index score of all single-level transitions from the baseline state.[26] A single-level transition was defined as a change in a single dimension to the level that is the next worse or next better, while holding all other dimensions constant. Such single-level transitions across all 3,125 health states were averaged to arrive at MCIDs for various countries by applying country-specific scoring algorithms. For Canada, transitions between level 3 and level 4 were excluded from the average to form a constant distribution of MCID values across the range of baseline scores. This analysis resulted in a Canadian-specific MCID of 0.037.[26]

No studies were identified that examined the validity, reliability, or MCID of the EQ-5D-5L in patients with hATTR amyloidosis.

## Neurologic Impairment

### *Modified Neurologic Impairment Score +7*

The mNIS+7 used in APOLLO is a 304-point composite measure to assess neurological impairment. It consists of clinical assessments (NIS component) and neurophysiologic tests (+7 component).[7] The components of the mNIS+7 are (1) NIS–Weakness (NIS-W) and decrease of NIS–Reflexes (NIS-R), which are based on physical examination of the lower limbs, upper limbs, and cranial nerves; (2) electrophysiological measures of small- and large-nerve fibre function to determine the sum of five attributes of nerve conduction studies ($\Sigma$5 NCS), which are ulnar compound muscle action potential (CMAP), ulnar sensory nerve action potential (SNAP), sural SNAP, tibial CMAP, and peroneal CMAP; (3) sensory testing of touch pressure by body surface area and heat pain by body surface area to determine the QST score; and (4) postural blood pressure to assess autonomic function.[7] NIS-W is the sum of the cranial nerve components (third nerve, sixth nerve, facial weakness, palate weakness, tongue weakness) and muscle weakness in 19 areas (respiratory, neck flexion, shoulder abduction, elbow flexion, brachioradialis, elbow extension, wrist flexion, wrist extension, finger flexion, finger spread, thumb abduction, hip flexion, hip extension, knee flexion, knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors).[22] It is assessed separately for the right and left sides of the body and each component is scored on a scale of 0 to 4 (0 = normal, 1 = 25% weak, 2 = 50% weak, 3 = 75% weak, 3.25 = movement against gravity, 3.5 = movement against gravity eliminated, 3.75 = muscle flicker, no movement, and 4 = paralysis), with a total score range of 0 to 192.[22] NIS-R is the sum of five reflexes (biceps brachii, triceps brachii, brachioradialis, quadriceps femoris, and triceps surae). It is assessed separately for the right and left sides of the body and each component is scored on a scale of 0 to 2 (0 = normal, 1 = decreased,

3 = absent). Adjustments are made for the age of patients and the total score ranges from 0 to 20.[22] QST is scored up to 80 points, ∑5 NCS is scored up to 10 points, and postural blood pressure is scored up to two points.[22] The NIS-W and QST components are weighted more heavily because sensorimotor neuropathy is prominent in hATTR amyloidosis.[22] A higher score on the mNIS+7 indicates worse neurological function.

The mNIS+7 was developed specifically for polyneuropathy in patients with hATTR amyloidosis. Suanprasert et al. (2014) conducted a retrospective review of 97 untreated patients with hATTR at the Mayo Clinic, Rochester, US, to determine the kind, severity, and distribution of polyneuropathy signs and nerve tests, the ability of the Neurologic Impairment Score +7 (NIS+7) to represent these signs and tests, and modifications needed to the NIS+7 to better measure polyneuropathy.[33] The NIS+7 differs from the mNIS+7 in that it includes NIS-sensation; it does not include QST, the ∑5 NCS consists of a different set of attributes (i.e., sural SNAP, tibial motor distal latency, peroneal CMAP, peroneal motor nerve conduction velocity, and peroneal motor nerve distal latency), it includes vibration detection threshold to assess large nerve fibre function, and it includes heart rate response to deep breathing to assess autonomic function rather than postural blood pressure.[7] The study found that NIS-sensation did not adequately measure sensation loss, large-fibre sensory dysfunction was over-emphasized over small sensory-fibre dysfunction, heart rate decrease with deep breathing did not adequately assess autonomic dysfunction, and the attributes of the ∑5 NCS could not all be evaluated in patients with hATTR amyloidosis.[33] The authors suggested that the evaluation of polyneuropathy in patients with hATTR amyloidosis could be improved by modifying the NIS+7 in the following aspects: replace vibration detection threshold with QST, replace heart rate response to deep breathing with postural blood pressure or Q-sweat, and replace the five nerve tests of ∑5 NCS with the modified set of five nerve tests described previously.[33] To evaluate the mNIS+7 accurately and reliably, the authors recommended that assessments be conducted by specially trained experts.[33]

The performance of a different version of the mNIS+7, the mNIS+7$_{ionis}$, was evaluated by Dyck et al. (2017).[23] The mNIS+7$_{ionis}$ differs from the mNIS+7 in that it includes NIS-sensation and assesses autonomic dysfunction with heart rate decrease with deep breathing rather than postural blood pressure. The differences and similarities of the mNIS+7, mNIS+7$_{ionis}$, and the NIS are presented in Table 25. Baseline assessments of neuropathy signs (NIS), NIS+7, mNIS+7$_{ionis}$, PND score, Norfolk QoL-DN, Dyck/Rankin score, Neuropathy Symptom and Change score, and the Short Form (36) Health Survey were evaluated in the first 100 patients enrolled in the NEURO-TTR trial (inotersen versus placebo). Validity: The mNIS+7$_{ionis}$ was correlated strongly with the Norfolk QoL-DN, PND stage, the Dyck/Rankin score, and the Neuropathy Symptom and Change score (Spearman's rank correlation r ≥ 0.5 or r ≤ −0.5).[23,61] The mNIS+7$_{ionis}$ was weakly to strongly correlated with the Short Form (36) Health Survey ([r ≥ 0.5 or r ≤ −0.5] or [r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5]).[23] The following provides the correlations for components of the mNIS+7$_{ionis}$ that matched those used in the APOLLO trial. The NIS-W was weakly to strongly correlated with Norfolk QoL-DN and Short Form (36) Health Survey ([r ≥ 0.5 or ≤ −0.5 or [r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > -0.5]), and strongly correlated with PND stage, the Dyck/Rankin score, and the Neuropathy Symptom and Change score (r ≥ 0.5 or r ≤ −0.5).[23,61] The ∑5 NCS was not significantly correlated with Norfolk QoL-DN, the Neuropathy Symptom and Change score, or Short Form (36) Health Survey, and was weakly to strongly correlated with PND stage and the Dyck/Rankin score (r ≥ 0.25 to < 0.5 or r ≤ −0.25 to r > −0.5).[23,61] The QST touch pressure was strongly correlated with Norfolk QoL-DN (r ≥ 0.5 or r ≤ −0.5), and weakly to strongly correlated with PND stage, the

Dyck/Rankin score, and the Short Form (36) Health Survey ([ ≥ 0.5 or r ≤ −0.5] or [r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5]).[23,61] The QST heat pain was not significantly correlated with any of the measures.[23] Reliability: Test–retest reproducibility of ∑5 NCS, which was assessed in the same way as in the APOLLO trial, was high (Krippendorff's alpha = 0.98).[23] Test–retest reproducibility for QST was lower (Krippendorff's alpha = 0.57; 0.44 for touch pressure and 0.65 for heat pain).[23] The repeat tests were conducted within a day or a few days of the first test by the same examiners and, therefore, may have been influenced by recall.

## Table 26: Comparison of the mNIS+7, mNIS+7$_{ionis}$, and NIS

| Component | mNIS+7 (Points)[a] | mNIS+7$_{ionis}$ (Points)[b] | NIS (Points) |
|---|---|---|---|
| NIS-W | 192 | 192 | 192 |
| NIS-Sensation | NA | 32 | 32 |
| NIS-R | 20 | 20 | 20 |
| Quantitative sensory testing | 80 | 80 | NA |
| ∑5 NCS | 10 | 18.6 | NA |
| Postural blood pressure | 2 | NA | NA |
| Heart rate with deep breathing | NA | 3.7 | NA |
| **Total points[c]** | 304 | 346.3 | 244 |

Σ5 NCS = sum of five attributes of nerve conduction studies; mNIS+7 = modified Neurologic Impairment Score; mNIS+7$_{ionis}$ = modified Neurologic Impairment Score (ionis definition); NA = not applicable; NIS = Neurologic Impairment Score; NIS-R = Neurologic Impairment Score–Reflexes; NIS-W = Neurologic Impairment Score–Weakness.

[a] Primary outcome for the APOLLO study (patisiran).

[b] Primary outcome for the NEURO-TTR study (inotersen).

[c] Higher points indicate greater neurologic impairment.

Source: CADTH Common Drug Review submission.[22]

No studies were identified that examined the MCID of the mNIS+7. For the NIS in patients with diabetic polyneuropathy, the Peripheral Nerve Society proposed that a mean difference between groups of two points was meaningful, as a change of two points represents a 50% change in sensation or muscle stretch reflexes and a 25% change in muscle strength.[28] However, this value was based on the smallest degree of change that a physician could detect, rather than on any distribution or anchor-based statistical technique. Considering that the mNIS+7 score includes other components that are not part of the NIS, it is unclear if the two-point difference can be applied to the mNIS+7.

*Composite Autonomic Symptom Score-31*

COMPASS 31 is a patient-reported measure to assess changes in autonomic symptoms. It consists of 31 questions that evaluate six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor.[7] The COMPASS 31 was developed from the original Autonomic Symptom Profile questionnaire, which consists of 169 questions, and the 84-item COMPASS to create a more simplified and time-efficient instrument.[24] Questions include either yes or no answers (scored as one or zero), present or not present (scored as zero or one), frequency of symptoms as "rarely or never," "occasionally or sometimes," "frequently or a lot of the time," and "almost always or constantly" (scored as zero, one, two, and three, respectively), severity of symptoms as "mild," "moderate," and "severe" (scored as one, two, and three, respectively), and time course of symptoms (scored zero to three, with zero representing improvement, one no

change, two some worsening, and three much worsening).[24] The scoring for changes in bodily function depended on the individual question.[24] Scores range from zero to 100, with higher scores representing more severe symptoms.[25]

The COMPASS 31 was validated in 66 patients with and without small-fibre polyneuropathy from the Massachusetts General Hospital.[25] The questionnaire was completed twice at two week intervals. Validity: Internal consistency of the items was demonstrated, with Cronbach's alpha of 0.919 for the entire questionnaire. The domains of orthostatic intolerance, vasomotor, gastrointestinal, and pupillomotor had good internal consistency (Cronbach's alpha of 0.869 to 0.910). However, the domain of bladder had low internal consistency (Cronbach's alpha of 0.598) and the domain of secretomotor had unacceptable internal consistency (Cronbach's alpha of 0.246). The COMPASS 31 was compared with the gold standard of autonomic function testing that assesses cardiovagal, adrenergic, and sudomotor functions. The total scores were moderately correlated (Spearman's correlation of 0.474). A strong correlation was observed with sudomotor function (Spearman's correlation of 0.608); however, correlation was weak with adrenergic (0.148) and cardiovagal (−0.103) functions. The COMPASS 31 was also compared with the short-form McGill Pain Questionnaire, the Short Form (36) Health Survey, and a zero to 10 numeric pain scale. Correlations were strong for all comparisons (0.815, −0.754, and 0.622, respectively). Discriminant validity: The COMPASS 31 was statistically different between patients with small-fibre neuropathy and patients without (total score of 38.8 and 19.6, respectively). In receiver operating characteristic analysis, COMPASS 31 demonstrated fair diagnostic accuracy with an area under the curve of 0.749. Reliability: Test–retest reliability was acceptable with Spearman's correlation of 0.886.

No studies were identified that examined the validity, reliability, or MCID of the COMPASS 31 in patients with hATTR amyloidosis.

## Disability and Functional Status

*Rasch-built Overall Disability Scale*

The R-ODS (also known as inflammatory R-ODS) consists of a 24-item linearly weighted scale to measure disability, specifically limitations in activity and social participation.[7] The questions are rated on a three-level scale: zero (unable to perform), one (able to perform but with difficulty), and two (able to perform without difficulty).[22] The total score ranges from zero (maximal disability) to 48 (no disability).[22] The scale was developed for patients with immune-mediated neuropathies — namely, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and gammopathy-related polyneuropathy.[34]

The validity and reliability of the R-ODS was examined in 294 patients with Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and gammopathy-related polyneuropathy from the Netherlands.[34] Validity: The correlation of the R-ODS with the Overall Disability Sum Score was evaluated. The intra-class correlation coefficient was 0.85, which demonstrated good external construct validity. Reliability: The Person Separation Index was determined to measure internal reliability and an index > 0.7 was considered acceptable. The resulting index was 0.97, which demonstrated acceptable internal reliability. Test–retest reliability was tested by comparing assessments completed at baseline and two to four weeks later; test–retest reliability was found to be good. A study of 137 patients with Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and gammopathy-related polyneuropathy found that the correlation coefficient for multivariate analysis from a regression model between R-ODS and self-rating

of health status on a EuroQol thermometer that ranged from zero (worst state) to 100 (best state) was 0.61, 0.42, and 0.30, respectively.[35] Another study examined the correlation between R-ODS and a EuroQol thermometer in 114 patients with Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy.[36] The Spearman's correlation coefficients were strong for both conditions (Spearman's correlation coefficients = 0.79 and 0.60, respectively).

No studies were identified that examined the validity, reliability, or MCID of the R-ODS in patients with hATTR amyloidosis. A 34-item Familial Amyloid Polyneuropathy scale was developed by Pruppers et al. (2015) with tests of validity and reliability; it is unclear why this disease-specific instrument was not utilized in the APOLLO study.[63]

*Polyneuropathy Disability Staging*

PND is classified according to the following stages.[1]

- Stage 0: No symptoms
- Stage I: Sensory disturbances but preserved walking capability
- Stage II: Impaired walking capacity but ability to walk without a stick or crutches
- Stage IIIA: Walking with the help of one stick or crutch
- Stage IIIB: Walking with the help of two sticks or crutches
- Stage IV: Confined to a wheelchair or bedridden

The PND classifies hATTR amyloidosis based on mobility only and does not consider autonomic dysfunction.

*Familial Amyloidotic Polyneuropathy Staging*

FAP is classified according to the following stages.[1]

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

*10 Metre Walk Test*

The 10MWT test is conducted to assess a patient's ability to ambulate without assistance from another person, although ambulatory aids such as canes and walkers are permitted.[7] The test measures functional mobility and walking speed in meters per second over the short distance.

The 10MWT was evaluated in patients with Charcot-Marie-Tooth disease, which is an inherited neurological disorder.[40] One study included 34 patients from a neuromuscular clinic in China.[39] Patients were administered the 10MWT along with the Overall Neuropathy Limitation Scale to assess motor function of the limbs, the Functional Disability Scale to assess motor function of the lower extremities, and the Berg Balance Scale to assess balance. Validity: The 10MWT was strongly correlated with motor function of the limbs (Pearson's r = −0.529 and −0.611), moderately to strongly correlated with motor function of

the lower extremities (r = −0.481 and −0.574), and strongly correlated with balance (r = −0.612 and −0.697). Discriminant validity: Compared with healthy controls, patients had significantly lower velocities on the 10MWT (1.03 m/s versus 1.31 m/s). Another study included 53 patients with Charcot-Marie-Tooth disease type 1A from Italian centres that specialized in hereditary neuropathies.[40] Patients underwent a 10MWT, a subjective evaluation of walking ability with the 12-item Walking Scale (Walk12), assessment of lower limb strength with a dynamometer, assessment of balance with the Berg Balance Scale and the Short Physical Performance Battery, and evaluation of quality of life with the Short Form (36) Health Survey. Validity: The 10MWT exhibited strong correlation with both measures of balance (Spearman's rank correlation coefficients of −0.64 and −0.55), moderate correlation with the Walk12 scale (Spearman's rank correlation coefficient of 0.39), and moderate correlation with lower limb strength (Spearman's correlation coefficients of −0.50 and −0.34). With respect to the Short Form (36) Health Survey, the 10MWT was strongly correlated with physical functioning (Spearman's correlation coefficient of −0.55); moderately correlated with role physical (−0.41), general health (−0.35), and role emotional (−0.36); and was not significantly correlated with bodily pain, vitality, social functioning, or mental health.

The test–retest reliability of the 10MWT was evaluated by Lang et al. (2016) in patients with Parkinson disease.[38] The 10MWT was administered to 35 patients over two sessions that were held five to 14 days apart. Gait speed was measured with a hand-held stopwatch by two testers. Reliability: The intra-class correlation coefficients were 0.92 for comfortable gait speed and 0.96 for fast gait speed, demonstrating excellent test–retest reliability.

The magnitude of a meaningful change (decline) in gait speed on a 10MWT among 100 adults who were survivors of a subacute stroke was examined with an anchor-based technique.[37] The anchors were two items from the Short Form (36) Health Survey physical function scale — ability to walk one block and ability to climb one flight of stairs. A minimally significant change for both questions of the Short Form (36) Health Survey was established as a change of one level based on the literature. The corresponding mean difference in 10 m gait speed was 0.01 m/s for decline in one level for climbing one flight of stairs and 0.10 m/s for decline in one level for walking a block. The authors also calculated meaningful change based on distribution techniques in 100 older adults with mobility disabilities and 100 survivors of subacute stroke, and found corresponding changes in gait speed of 0.05 m/s and 0.06 m/s for the two populations, respectively. After assessing the results of both anchor and distribution-based techniques in all patients, the authors recommended that 0.05 m/s change in gait speed represents a small meaningful change.

No studies were identified that examined the validity, reliability, or MCID of the 10MWT in patients with hATTR amyloidosis.

## Nutritional Status

*Modified Body Mass Index*

Patients with hATTR amyloidosis are affected by wasting; in these circumstances, body mass index overestimates clinical status. A more accurate measure is the mBMI, which corrects for hypoalbuminemia and edema, and is calculated by the product of body mass index and serum albumin.[44] Among 27 patients with hATTR amyloidosis in Sweden, the mBMI was strongly correlated with number of years before death (r = 0.89) and to the duration of gastrointestinal symptoms (r = −0.66).[41] The mBMI was also correlated with PND score ($P$ = 0.009).[41] Among 21 patients with hATTR amyloidosis who had had a liver

transplant, preoperative mBMI < 700 kg g/L $m^2$ was associated with significantly lower overall survival compared with mBMI ≥ 700 kg g/L $m^2$ after transplant (median survival of 5.2 months versus 78.8 months).[43] Another study compared the survival of patients with hATTR amyloidosis who received a liver transplant as part of an earlier series when severely malnourished patients were accepted (N = 34) and a later series of patients who were selected based on mBMI > 600 kg g/L $m^2$ (N = 27) in Sweden.[42] Survival was significantly prolonged in the later series of patients who had mBMI > 600 kg g/L $m^2$.[42]

## Cardiovascular Biomarkers and Echocardiogram

Patients with hATTR polyneuropathy may also present with cardiomyopathy due to amyloid deposits in the heart. Cardiac manifestations of the disease include arrhythmias, heart failure, and sudden cardiac death. The degree to which polyneuropathy or cardiomyopathy is present depends on the genetic mutation (e.g., the V30M mutation produces predominant polyneuropathy whereas V122I mutation produces predominant cardiomyopathy), geographic location, and the individual.[1] Therefore, although patisiran is indicated specifically for hATTR polyneuropathy, the CADTH Common Drug Review has evaluated the evidence available for the following cardiac outcomes, which were exploratory in APOLLO.

*N-terminal Prohormone Brain-Type Natriuretic Peptide*

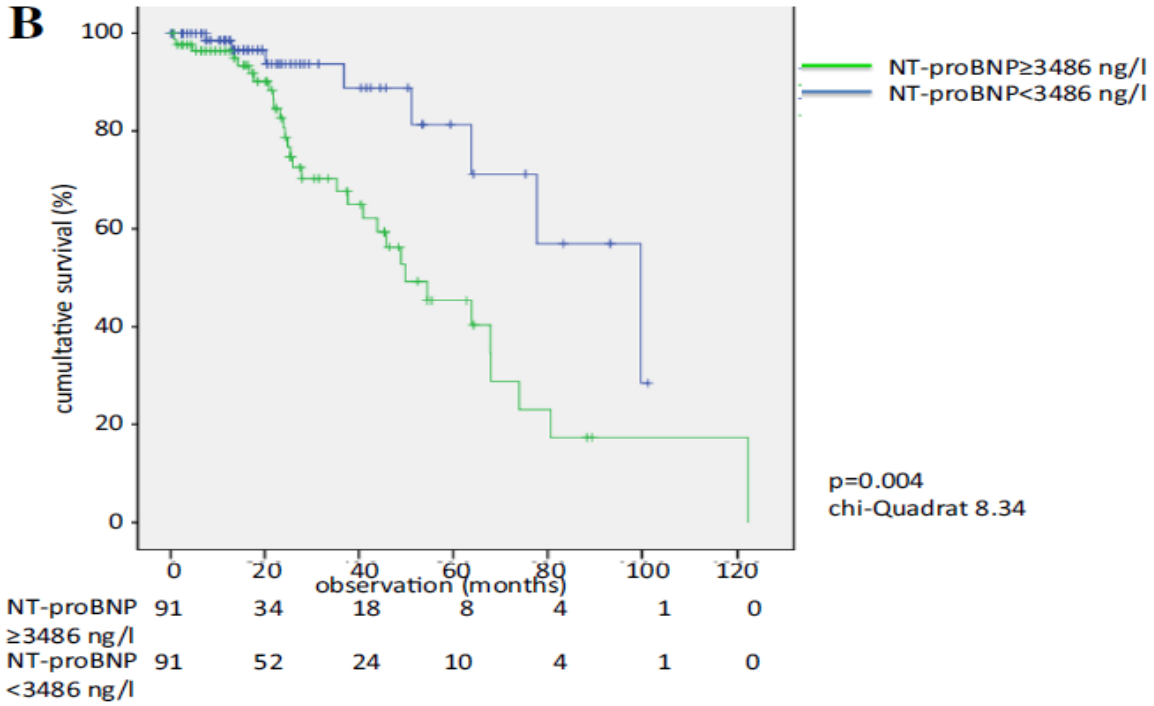
NT-proBNP is a cardiac biomarker that is released from the heart into the circulation in response to an increase in myocardial wall tension and stress.[22] NT-proBNP was measured with a chemiluminescence assay, with a normal value less than 144.63 pmol/L.[7] The biomarker has been validated as a marker of cardiac stress and injury in patients with transthyretin amyloidosis (hereditary and wild-type) and light-chain amyloidosis.[45,48,49,52] Evidence has also shown that it is a valid surrogate marker for mortality in patients with hATTR amyloidosis.[47,53]

In a large cohort study of 1,617 patients with transthyretin amyloidosis (1,452 with hereditary and 165 with wild-type), factors associated with survival were examined.[53] Over 1.2 years of follow-up, 115 patients died. Mortality rates increased with NT-proBNP quartile (first quartile = 1.7%, second quartile = 5.2%, third quartile = 21.7%, and fourth quartile = 71.3%). Patients with higher NT-proBNP quartile also presented with lower Karnofsky Performance Status index, mBMI, and renal function. NT-proBNP was weakly correlated with mBMI (r = −0.236), moderately correlated with left atrial diameter (r = 0.337), and strongly correlated with septal thickness (r = 0.654) and LV posterior wall thickness (r = 0.649). In the Cox proportional hazards model, predictors of survival in patients with hATTR amyloidosis were age, mBMI, mutation (V30M), brain natriuretic peptide, and NT-proBNP (first quartile to third quartile pooled versus fourth quartile). In 60 patients with hATTR amyloidosis of the Thr60Ala mutation, NT-proBNP was significantly associated with survival in univariate (hazard ratio = 0.39; 95% CI, 0.16 to 0.96 for < 3,383 pg/mL versus ≥ 3,383 pg/mL) and multivariate (hazard ratio = 0.17; 95% CI, 0.03 to 0.92 for < 3,383 pg/mL versus ≥ 3,383 pg/mL) analyses.[47]

A prognostic staging system for patients with wild-type transthyretin amyloidosis was developed based on factors that affected overall survival.[51] Among 260 patients, multivariate predictors of mortality were age, ejection fraction, pericardial effusion, troponin, and NT-proBNP. The staging system included thresholds of 0.05 ng/mL for troponin and 3,000 pg/mL for NT-proBNP, and were chosen based on the association with death. The age- and sex-adjusted hazard ratio for NT-proBNP threshold of 3,000 pg/mL was 2.2 (95%

CI, 1.36 to 3.60). The four-year overall survival estimates were 57% for stage I (both values below threshold), 42% for stage II (one value above threshold), and 18% for stage III (both values above threshold). Siepen et al. (2018) examined predictors of mortality in 191 patients with wild-type transthyretin amyloidosis.[54] In multivariable analyses, NT-proBNP was a predictor of mortality (hazard ratio = 1.0, *P* = 0.018). The Kaplan–Meier survival curves for patients with NT-proBNP < 3,486 pg/mL and ≥ 3,486 pg/mL are shown in Figure 13.

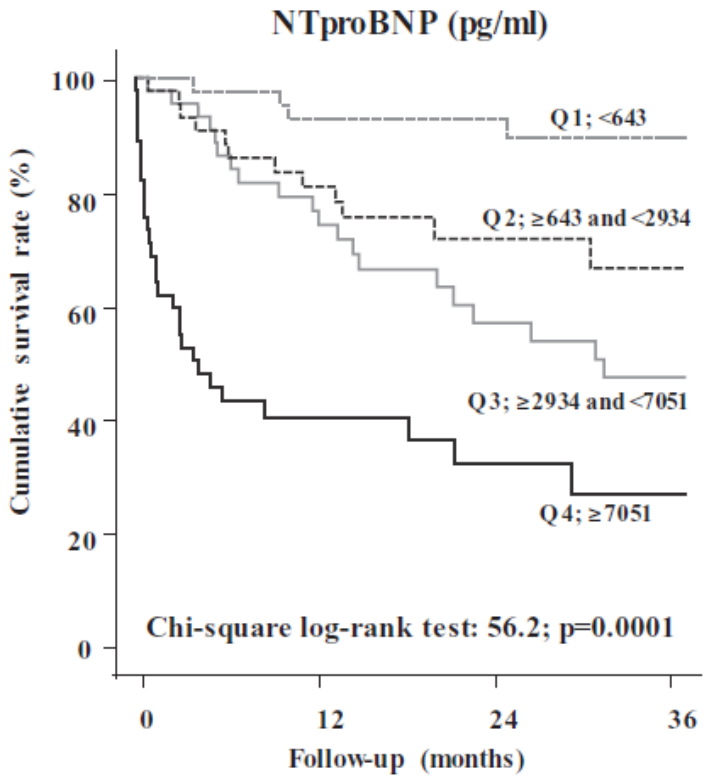
## Figure 13: Kaplan–Meier Curves for a NT-proBNP Threshold




Source: Reprinted with permission from Springer Nature. Clinical Research in Cardiology: Predictors of survival stratification in patients with wild-type cardiac amyloidosis, aus dem Siepen F, Bauer R, Voss A, et al., 2017.[54]

Damy et al. examined predictors of mortality in 198 patients with cardiac amyloidosis (118 light-chain amyloidosis, 57 with hATTR amyloidosis, and 23 with wild-type transthyretin amyloidosis).[50] In multivariate analysis among the subset of patients with transthyretin amyloidosis, NT-proBNP was a significant predictor of mortality. When the three types of amyloidosis were combined, significant predictors of mortality were age, cardiac output, and NT-proBNP. Figure 14 provides the Kaplan–Meier curves showing survival by different thresholds of NT-proBNP for all types of amyloidosis combined.

## Figure 14: Kaplan–Meier Curves for Various NT-proBNP Thresholds




Source: Reprinted with permission of the publisher (Taylor & Francis Ltd) Amyloid: Identification of prognostic markers in transthyretin and AL cardiac amyloidosis. Damy T, Jaccard A, Guellich A, et al. 2016.[50]

In another study of 79 patients with cardiac amyloidosis (26 light-chain amyloidosis, 36 hATTR, and 17 wild-type transthyretin amyloidosis), NT-proBNP significantly increased the risk of major adverse cardiac events (hazard ratio = 8.00; 95% CI, 2.67 to 23.93).[52] The optimal cut-off value for predicting major adverse cardiac events was a NT-proBNP value of 4,000 pg/mL.[52]

Among 152 patients with light-chain amyloidosis, NT-proBNP differed significantly between those with and without heart involvement (median: 507.8 pmol/L or 4,294 pg/mL versus 22.1 pmol/L or 187 pg/mL).[45] The death rate below and above a threshold of 152 pmol/L (1,285 pg/mL), which was the value at which sensitivity, specificity, and accuracy were optimal for the diagnosis of heart involvement, was 7.6 per 100 person-years and 72.2 per 100 person-years, respectively.[45] A study of 27 patients with light-chain amyloidosis and seven patients with hATTR amyloidosis also found that NT-proBNP was significantly higher in patients with cardiac involvement compared with those without (2,931 pg/mL versus 177 pg/mL).[46] In receiver operating characteristic curve analysis, a threshold of < 2,426.5 pg/mL was the optimal predictor for event-free survival.[46] NT-proBNP was found to predict right ventricle dysfunction in 76 patients with light-chain amyloidosis, with best sensitivity and specificity at a threshold of 2,977 pg/mL.[48] Among 185 patients with light-chain amyloidosis, NT-proBNP levels were significantly higher with several indicators of cardiac disease severity, such as New York Heart Association classification, QRS width on electrocardiogram, and septal thickness.[49] Over a follow-up of 28 months, 84 patients died;

these patients had higher NT-proBNP compared with survivors (10,966 pg/mL versus 4,453 pg/mL).[49] In univariate analyses, NT-proBNP was a significant predictor of survival; however, in a multivariable model that included other biomarkers, such as troponin and pro-atrial natriuretic peptide, NT-proBNP was not a significant determinant of mortality.[49]

*Troponin I*

Cardiac troponin I is a biomarker that is released in response to myocardial injury.[22] It was measured with a chemiluminescence assay, with normal values less than 0.10 mcg/L.[7] In a large cohort study of 1,617 patients with transthyretin amyloidosis (1,452 with hereditary and 165 with wild-type), factors associated with survival were examined.[53] Over 1.2 years of follow-up, 115 patients died. Mortality rates increased with troponin I and troponin T quartile (first quartile = 6.5%, second quartile = 14.5%, third quartile = 33.9%, and fourth quartile = 45.2%).[53] Patients with higher levels of troponin I or troponin T had lower Karnofsky Performance Status index, mBMI, and renal function.[53] Troponin I was moderately correlated with septal thickness (r = 0.348) and LV posterior wall thickness (r = 0.434).[53] A prognostic staging system for patients with wild-type transthyretin amyloidosis was developed based on factors that affected overall survival.[51] Among 260 patients, multivariate predictors of mortality were age, ejection fraction, pericardial effusion, troponin, and NT-proBNP. The staging system included thresholds of 0.05 ng/mL for troponin and 3,000 pg/mL for NT-proBNP, and were chosen based on the association with death. The age- and sex-adjusted hazard ratio for troponin threshold of 0.05 ng/mL was 2.34 (95% CI, 1.46 to 3.76). The four-year overall survival estimates were 57% for stage I (both values below threshold), 42% for stage II (one value above threshold), and 18% for stage III (both values above threshold). In patients with light-chain amyloidosis (N = 76), troponin I predicted right ventricle involvement, with a cut-off value of 0.085 ng/L having a sensitivity and specificity of 85% and 90%, respectively.[48]

Although a large cohort study in patients with hATTR amyloidosis found that mortality risk increased with increasing troponin I quartile, in adjusted Cox proportional hazards models, troponin was not statistically significant (possibly because there were too many missing observations). In patients with wild-type transthyretin amyloidosis, troponin was a significant predictor in an adjusted model; however, it is unclear if this result can be translated to patients with hATTR amyloidosis. Therefore, it is unclear based on this evidence if troponin I is correlated with mortality in patients with hATTR amyloidosis.

*Echocardiogram — Left Ventricular Longitudinal Strain*

LV longitudinal strain is a measure of impaired systolic function.[22] Normal values are further from zero (i.e., negative); as values approach zero, this indicates abnormality.[7] Therefore, a negative change indicates improvement whereas a positive change indicates worsening.

In one study, LV longitudinal strain was examined in 14 patients with hATTR amyloidosis with the V30M mutation (six with cardiac amyloidosis, four with extracardiac amyloidosis, and four without amyloidosis) and a control group of 14 healthy individuals without the mutation or cardiovascular disease.[59] The mean basal longitudinal strain, apical longitudinal strain (two chambers, three chambers, and four chambers), and mean longitudinal tension were all significantly higher (i.e., further from normal) compared with patients with extracardiac amyloidosis; aside from three-chamber longitudinal strain, these measures were also higher compared with patients who had the V30M mutation but no disease.

In another study conducted in 172 patients with cardiac amyloidosis (80 light-chain amyloidosis, 36 hATTR amyloidosis, and 56 wild-type transthyretin amyloidosis), global

longitudinal strain was strongly correlated with LVEF (r = −0.55) and moderately correlated with LV wall thickness (r = 0.34).[56] In multivariable analysis, each incremental 1% increase in global LV longitudinal strain significantly increased risk of mortality from any cause (hazard ratio = 1.1; 95% CI, 1.01 to 1.19).[56] In another study of 79 patients with cardiac amyloidosis (26 light-chain amyloidosis, 36 hATTR amyloidosis, and 17 wild-type transthyretin amyloidosis), LV longitudinal strain correlated with cardiac amyloid burden, as assessed with late gadolinium enhancement on cardiac magnetic resonance (correlation not provided) and as assessed histologically in three hearts (r = 0.72).[52] Siepen et al. (2018) examined predictors of mortality in 191 patients with wild-type transthyretin amyloidosis and found that while global longitudinal strain was a significant predictor in univariate analysis, it lost significance in multivariate analysis.[54]

Global LV longitudinal systolic strain was assessed in 24 patients with light-chain amyloidosis.[57] Over a median follow-up of 487 days, 16 patients died. In these patients, global longitudinal systolic strain decreased significantly from baseline (−10 ± 5% versus −12 ± 4%). Global longitudinal systolic strain was also strongly correlated with higher NT-proBNP at baseline (r = −0.677). In univariate analysis, global longitudinal systolic strain was significantly associated with all-cause mortality (hazard ratio = 1.17; 95% CI, 1.02 to 1.35). However, statistical significance was lost in a multivariate model adjusted for age, gender, New York Heart Association class, and high-dose melphalan with autologous stem cell transplant (hazard ratio = 0.98; 95% CI, 0.67 to 1.45). In a larger study of 150 patients with light-chain amyloidosis (63 with cardiac amyloidosis and 87 without cardiac amyloidosis), global longitudinal strain was a significant predictor of survival in a multivariate Cox model (hazard ratio = 2.68; 95% CI, 1.07 to 7.13 for global longitudinal strain ≥ −14.81).[58]

The association between global longitudinal strain and mortality was examined in 546 patients undergoing echocardiography for known or suspected LV impairment.[55] Global longitudinal strain was calculated from three standard apical views using 2D speckle tracking. Over a period of about five years, 91 patients died. Global longitudinal strain was significantly associated with mortality in nested Cox models (hazard ratio = 1.45; 95% CI, 1.19 to 1.77) and added to the predictive power of other clinical variables as measured by model $\chi^2$. Intra-class correlation coefficients for interobserver variability and intraobserver variability were 0.916 and 0.922, respectively, demonstrating good agreement.[55]

While the evidence suggests that LV longitudinal strain is correlated with measures of cardiac dysfunction and cardiac amyloidosis, there is insufficient evidence to correlate this outcome with mortality in patients with hATTR amyloidosis, as the studies include a small number of patients with hATTR amyloidosis and the data are conflicting.

*Echocardiogram — Left Ventricular Wall Thickness*

LV wall thickness is assessed by echocardiogram to identify structural impairment due to remodelling from amyloid infiltrates.[22] In 60 patients with hATTR amyloidosis of the Thr60Ala mutation, which causes cardiomyopathy as the predominant feature of hATTR,[1] LV posterior wall thickness was significantly associated with survival in univariate (hazard ratio = 0.42; 95% CI, 0.18 to 0.95 for < 17 mm versus ≥ 17 mm) and multivariate (hazard ratio = 0.17; 95% CI, 0.03 to 0.97 for < 17 mm versus ≥ 17 mm) analyses.[47] Among 39 patients with light-chain amyloidosis, LV wall thickness progression was higher in patients who died compared with survivors (2.02 ± 0.85 mm/month versus 0.19 ± 0.03 mm/month).[60] Progression of LV wall thickness was associated with survival in univariate and multivariate analyses.[60]

The evidence suggests that LV wall thickness is correlated with survival in patients with amyloidosis, although there were no data available for patients with hATTR mutations that cause predominant polyneuropathy, such as V30M.

*Echocardiogram — Left Ventricular Ejection Fraction*

LVEF is assessed by echocardiogram to measure systolic dysfunction.[22] Patients with wild-type amyloidosis (N = 18) and amyloidosis due to mutation of transthyretin protein with isoleucine at position 122 (N = 11), which is a mutation that causes cardiomyopathy as the predominant feature of hATTR,[1] were prospectively evaluated every six months, for up to two years, by Ruberg et al. (2012).[3] A LVEF < 50% was significantly associated with mortality in univariate analysis (hazard ratio = 4.12; 95% CI, 1.24 to 13.6).[3]

There is currently insufficient data to correlate LVEF with mortality in patients with hATTR amyloidosis.

# Appendix 6: Summary of Extension Studies

## Aim

To review the efficacy and harms data reported from the open-label extensions of the phase II trial (Study ALN-TTR02-003)[64] and ongoing phase III trial (ALN-TTR02-006)[65] of patisiran for hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy in adults.

## Phase II Open-Label Extension (ALN-TTR02-003)

### Study and Phase Design

The parent study (ALN-TTR02-002) of this open-label extension was an open-label, multi-centre, multiple-ascending dose phase II trial. The primary objective of ALN-TTR02-002 was to evaluate safety and tolerability of multiple patisiran doses in adult patients with hATTR amyloidosis.[66] The study included 29 patients, 26 of whom completed the study. Patients received an initial dose of 10 mcg/kg patisiran, followed by a second higher dose (50 mcg/kg, 150 mcg/kg, or 300 mcg/kg) three or four weeks later. At least one treatment-emergent adverse event was experienced by 23 patients (approximately 79%); the highest incidence was in the group that received 50 mcg/kg or 300 mcg/kg every four weeks and 300 mcg/kg every three weeks. Most treatment-emergent adverse events were mild to moderate in severity and there were no deaths. The study concluded that two consecutive doses of patisiran, separated by a three- or four-week interval, were well tolerated.

ALN-TTR02-003 was a multi-centre, open-label, phase II extension study of ALN-TTR02-002 in adult patients with hATTR amyloidosis.[64] The primary objective of the extension study was to evaluate long-term safety of patisiran for up to two years. Secondary objectives of interest to this review were to evaluate long-term changes from baseline in the modified Neurologic Impairment Score +7 composite (mNIS+7), quality of life (EuroQol 5-Dimensions [EQ-5D]), disability (Rasch-built Overall Disability Scale [R-ODS]), motor function impacting activities of daily living (10 metre walk test), and nutritional status (modified body mass index [mBMI]). Tertiary objectives of interest to this review included ambulation (familial amyloidotic polyneuropathy [FAP] stage and polyneuropathy disability [PND] score), symptoms of autonomic neuropathy (Composite Autonomic Symptom Score 31 [COMPASS 31] questionnaire), and cardiac structure and function in patients with pre-existing cardiac amyloid involvement (echocardiograms, serum troponin I and N-terminal prohormone brain-type natriuretic peptide [NT-proBNP]). All-cause and cardiovascular mortality, hospitalizations, and cardiovascular morbidity were not evaluated.

The extension study included patients from ALN-TTR02-002 who received and tolerated patisiran; these patients were permitted to receive patisiran for up to an additional two years. Prior to entry into the extension study, there was an initial 28-day screening period, followed by a two-year treatment period, and then at least a 21-day follow-up period after the last dose. The interval between the time of completion of the parent study and entry into the extension study was not restricted. The time between the last dose of patisiran in the parent study and the first dose in the extension study ranged from 169 days to 512 days. Patients with a liver transplant were excluded. Patients received patisiran 0.3 mg/kg every three weeks by intravenous (IV) infusion and remained at the clinic for one to six hours after the infusion for observation. Premedications (i.e., dexamethasone, acetaminophen, histamine-1 receptor blocker and histamine-2 receptor blocker) were administered to

prevent infusion-related reactions. Study assessments were conducted at outpatient visits every six months.

Baseline was defined as the last non-missing value prior to the first dose of patisiran in the extension study. For mNIS+7 and the 10 metre walk test, baseline was the average of screening and baseline assessments. The full analysis set was the primary set for clinical activity assessment and included all patients who were enrolled. The safety analysis set was used in the reporting of harms and included patients in the full analysis set who received at least one dose of the study drug. The cardiac subgroup included patients with left ventricular (LV) wall thickness ≥ 13 mm on baseline echocardiogram, and no history of uncontrolled hypertension or aortic valve disease. Numbers, with percentages, were reported for harms and the PND stage, and summary statistics of observed values and changes from baseline were reported for other efficacy outcomes.

Patients who tolerated patisiran during this extension study were eligible to continue treatment under another extension study protocol (ALN-TTR02-006); otherwise, they returned for a second follow-up visit 56 days after the last dose.

## Results

### *Patient Disposition*

The parent study enrolled 29 patients and, of these, 27 were enrolled in the open-label extension study (see Table 27). The full analysis set and safety analysis set included all 27 patients. Twenty-five patients (92.6%) completed the extension study phase (i.e., completed year 2 efficacy assessments, a 21-day follow-up visit after the last dose, or a 56-day follow-up visit after the last dose). One patient died of myocardial infarction prior to the end of the extension study visit and one patient withdrew from the study due to an adverse event of gastroesophageal cancer. The cardiac subgroup included 11 patients.

**Table 27: Patient Disposition in Study ALN-TTR02-003**

| | ALN-TTR02-003 |
|---|---|
| Enrolled, N (%) | 27 (100) |
| Treated, N (%) | 27 (100) |
| Completed, N (%) | 25 (92.6) |
| Withdrawals, N (%) | 2 (7.4) |
| AE | 1 (3.7) |
| Death | 1 (3.7) |
| FAS, N (%) | 27 (100) |
| Safety, N (%) | 27 (100) |
| Cardiac subgroup, N (%) | 11 (40.7) |

AE = adverse event; FAS = full analysis set.

Source: ALN-TTR02-003 Clinical Study Report.[64]

Table 28 provides the baseline characteristics of patients in the full analysis set. The mean age of patients was 57.9 years at screening, 66.7% of patients were male, and all were white. The valine to methionine substitution at position 30 (V30M) was present in 74.1%. The majority were FAP stage I, unimpaired ambulation (88.9%) and PND stage I, sensory disturbances but preserved walking capability (55.6%). Most patients were classified as New York Heart Association class I (70.4%). At study entry, 48.1% were on concomitant

tafamidis and 25.9% on diflunisal. The mean age of patients in the cardiac subgroup was 68.8 years at screening and eight patients were male. Eight patients had the V30M mutation and, at study entry, five patients each were on concomitant tafamidis or diflunisal.

## Table 28: Baseline Characteristics in Study ALN-TTR02-003

| | ALN-TTR02-003 N = 27 |
|---|---|
| Age, mean (SD), years | 57.9 (15.4) |
| Male, N (%) | 18 (66.7) |
| White, N (%) | 27 (100) |
| V30M mutation, N (%) | 20 (74.1) |
| Years since hATTR amyloidosis diagnosis, mean (SD) | 2.7 (1.4) |
| FAP Stage, N (%) | |
| I (unimpaired ambulation) | 24 (88.9) |
| II (assistance with ambulation required) | 3 (11.1) |
| III (wheelchair bound or bedridden) | 0 (0) |
| PND Score, N (%) | |
| I | 15 (55.6) |
| II | 9 (33.3) |
| IIIA | 2 (7.4) |
| IIIB | 1 (3.7) |
| IV | 0 (0) |
| NYHA Class, N (%)[a] | |
| I | 19 (70.4) |
| II | 7 (25.9) |
| III | 0 (0) |
| IV | 0 (0) |
| Concomitant TTR Stabilizer Use, N (%)[b] | |
| Diflunisal | 7 (25.9) |
| Tafamidis | 13 (48.1) |

FAP = familial amyloidotic polyneuropathy; hATTR = hereditary transthyretin-mediated; NYHA = New York Heart Association; PND = polyneuropathy disability; SD = standard deviation; TTR = transthyretin.

[a] Missing in one patient.

[b] At study entry.

Source: ALN-TTR02-003 Clinical Study Report.[64]

### *Drug Exposure*

Patients received patisiran for a mean period of 24.7 months in the extension study (range: 19 to 25 months) and the mean number of doses received was 34.6 (see Table 29).

## Table 29: Drug Exposure in Study ALN-TTR02-003

| | ALN-TTR02-003 N = 27 |
|---|---|
| Total duration of exposure, mean (SD) (months) | [redacted] |
| **Number of Patients With Total Duration** | |
| ≥ 12 Months, N (%) | [redacted] |
| ≥ 18 Months, N (%) | [redacted] |
| ≥ 24 Months, N (%) | [redacted] |
| Total number of doses, mean (SD) | [redacted] |
| Number of patients with dose reduction, N (%) | [redacted] |
| Number of patients without missing doses, N (%) | [redacted] |
| Number of Patients With Missing Doses | |
| 1 missing dose, N (%) | [redacted] |
| 2 missing doses, N (%) | [redacted] |
| ≥ 3 missing doses, N (%) | [redacted] |

SD = standard deviation.

Source: ALN-TTR02-003 Clinical Study Report.[64]

*Harms*

Treatment-emergent adverse events were defined as any adverse event that started during or after the administration of the study drug up to 28 days following the last dose. Table 30 provides a summary of events. All except one patient experienced at least one adverse event. Most adverse events were mild (22.2%) to moderate (55.6%) in severity. Seven patients (25.9%) experienced 18 serious adverse events. Two patients died, one due to gastroesophageal cancer and one due to myocardial infarction.

## Table 30: Treatment-Emergent Adverse Events in Study ALN-TTR02-003

| | ALN-TTR02-003 N = 27 |
|---|---|
| At least 1 AE, N (%) | 26 (96.3) |
| At least 1 SAE, N (%) | 7 (25.9) |
| At least 1 AE leading to discontinuation, N (%) | 2 (7.4) |
| Death | 2 (7.4) |

AE = adverse event; SAE = serious adverse event.

Source: ALN-TTR02-003 Clinical Study Report.[64]

Adverse events that occurred in 15% or more of patients (≥ five patients) were flushing (25.9%), diarrhea (22.2%), infusion-related reactions (22.2%), nasopharyngitis (22.2%), urinary tract infection (22.2%), vomiting (22.2%), wound (22.2%), and nausea (18.5%). Six patients reported infusion-related reactions, which included flushing (five patients), burning sensation (two patients), dyspnea (two patients), and headache (one patient). The infusion-related reactions were all mild in severity and none resulted in study discontinuation. The incidence of infusion-related reactions and number of symptoms decreased over time. A serious adverse event of osteonecrosis occurred in two patients and all other serious adverse events occurred in one patient. One patient had a serious adverse event of atrioventricular block. Five patients reported ocular events, which included reduced visual

acuity in two patients and blurred vision in one patient. Anti-drug antibodies were found in one patient.

*Efficacy*

In Table 31, the health-related quality of life measures, EQ-5D and EuroQol Visual Analogue Scale, are provided. The mean change [standard error of the mean (SEM)] in EQ-5D from baseline to 24 months was −0.01 (0.02) and was stable over 24 months. It was also similar among patients who used a concomitant transthyretin (TTR) stabilizer and those who did not. The mean change (SEM) in the EuroQol Visual Analogue Scale was 1.7 (2.53) (mean change −0.3 [SEM 2.31] in patients using a TTR stabilizer and 7.1 [6.97] in patients not using a TTR stabilizer) and was stable over 24 months.

## Table 31: Health-Related Quality of Life Outcomes in Study ALN-TTR02-003

| | EQ-5D (N = 27) | EQ-VAS (N = 27) |
|---|---|---|
| **Baseline** | | |
| n | 27 | 27 |
| Mean (SD) | 0.78 (0.14) | 67.9 (17.85) |
| Range | 0.31 to 1.00 | 30 to 98 |
| **Month 24** | | |
| n | 26 | 27 |
| Mean (SD) | 0.76 (0.16) | 69.3 (20.59) |
| Range | 0.28 to 1.00 | 25 to 98 |
| **Change From Baseline** | | |
| n | 26 | 26 |
| Mean (SEM) | −0.01 (0.02) | 1.7 (2.53) |
| Range | −0.22 to 0.17 | −25 to 30 |

EQ-5D = EuroQol 5-Dimensions; EQ-VAS = EuroQol Visual Analogue Scale; SD = standard deviation; SEM = standard error of the mean.

Source: ALN-TTR02-003 Clinical Study Report.[64]

The mean change (SEM) in mNIS+7 from baseline to 24 months was −6.95 (2.03), which suggested stabilization or improvement in neuropathy (see Table 32) and was similar among patients who received or did not receive a concomitant TTR stabilizer. A decrease in mNIS+7 started at six months, with mean change from baseline (SEM) of −1.33 (2.04); the decrease was maintained from six months to 24 months (mean changes [SEM] from baseline at 12 months, 18 months, and 24 months were −3.26 [2.29], −0.88 [2.69], and −6.95 [2.03], respectively). For most patients (74.1%), mNIS+7 either did not change or decreased at 24 months. The mean values of the individual components of mNIS+7 were stable or decreased over 24 months (mean change from baseline [SEM] = 1.23 [1.43] for Neurologic Impairment Score–Weakness, −0.48 [0.53] for Neurologic Impairment Score–Reflexes, −7.4 [2.04] for quantitative sensory testing, −0.19 [0.18] for the sum of five attributes of nerve conduction studies, and −0.10 [0.06] for postural blood pressure). The mean change (SEM) in COMPASS 31 was 1.32 (1.80) and a similar change was observed in all six domains.

## Table 32: Neurological Impairment Outcomes in Study ALN-TTR02-003

| | mNIS+7 (N = 27) | COMPASS 31 (N = 27) |
|---|---|---|
| **Baseline** | | |
| n | 27 | 27 |
| Mean (SD) | 53.02 (35.63) | 15.85 (13.34) |
| Range | 2.00 to 122.50 | 0.0 to 46.1 |
| **Month 24** | | |
| n | 26 | 26 |
| Mean (SD) | 48.04 (33.38) | 16.40 (15.88) |
| Range | 3.00 to 127.75 | 0.0 to 53.1 |
| **Change From Baseline** | | |
| n | 26 | 26 |
| Mean (SEM) | −6.95 (2.03) | 1.32 (1.80) |
| Range | −34.63 to 15.38 | −15.8 to 24.0 |

COMPASS 31 = Composite Autonomic Symptom Score 31; mNIS = modified Neurologic Impairment Score; SD = standard deviation; SEM = standard error of the mean.

Source: ALN-TTR02-003 Clinical Study Report.[64]

Table 33 presents the disability outcome of R-ODS. The R-ODS changed by a mean (SEM) of −1.8 (0.83) from baseline to 24 months and was similar with and without a TTR stabilizer.

## Table 33: Disability Outcome in Study ALN-TTR02-003

| | R-ODS (N = 27) |
|---|---|
| **Baseline** | |
| n | 26 |
| Mean (SD) | 38.1 (8.61) |
| Range | 15 to 48 |
| **Month 24** | |
| n | 26 |
| Mean (SD) | 36.1 (10.44) |
| Range | 15 to 48 |
| **Change From Baseline** | |
| n | 25 |
| Mean (SEM) | −1.8 (0.83) |
| Range | −14 to 8 |

R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation; SEM = standard error of the mean.

Source: ALN-TTR02-003 Clinical Study Report.[64]

The mean change (SEM) in gait speed on the 10 metre walk test was 0.03 (0.04) m/s overall (see Table 34). The mean change (SEM) was 0.06 (0.05) m/s in patients using TTR stabilizer and −0.02 (0.06) in patients not using TTR stabilizer.

## Table 34: Motor Function Outcome in Study ALN-TTR02-003

| | 10 Metre Walk Test (Gait Speed, m/s) (N = 27) |
|---|---|
| **Baseline** | |
| n | 22 |
| Mean (SD) | 1.14 (0.79) |
| Range | 0.4 to 2.2 |
| **Month 24** | |
| n | 26 |
| Mean (SD) | 1.24 (0.09) |
| Range | 0.4 to 2.1 |
| **Change From Baseline** | |
| n | 21 |
| Mean (SEM) | 0.03 (0.04) |
| Range | −0.4 to 0.3 |

SD = standard deviation; SEM = standard error of the mean.

Source: ALN-TTR02-003 Clinical Study Report.[64]

Most patients (74.1%) showed no change in PND score from baseline to 24 months (see Table 35). In five patients (18.5%), however, the score worsened, with four patients transitioning from PND I to PND II and one patient transitioning from PND II to PND IIIA. One patient improved from PND IIIA to PND II. Similarly, most patients (85.2%) maintained a stable FAP stage from baseline to 24 months. Three patients (11.1%) experienced FAP stage progression.

## Table 35: Ambulation Outcome in Study ALN-TTR02-003

| PND Score (N = 27) | | FAP Stage (N = 27) | |
|---|---|---|---|
| **Baseline, n (%)** | | **Baseline, n (%)** | |
| Stage I | [redacted] | [redacted] | [redacted] |
| Stage II | [redacted] | [redacted] | [redacted] |
| Stage IIIA | [redacted] | [redacted] | [redacted] |
| Stage IIIB | [redacted] | | |
| Stage IV | [redacted] | | |
| **Month 24, n (%)** | | **Month 24, n (%)** | |
| Stage I | [redacted] | [redacted] | [redacted] |
| Stage II | [redacted] | [redacted] | [redacted] |
| Stage IIIA | [redacted] | [redacted] | [redacted] |
| Stage IIIB | [redacted] | | |
| Stage IV | [redacted] | | |
| **Change from Baseline, n (%)** | | **Change from Baseline, n (%)** | |
| Worsened | [redacted] | [redacted] | [redacted] |
| No Change | [redacted] | [redacted] | [redacted] |
| Improved | [redacted] | [redacted] | [redacted] |

FAP = familial amyloidotic polyneuropathy; PND = polyneuropathy disability.

Source: ALN-TTR02-003 Clinical Study Report.[64]

The mean change (SEM) in mBMI was −60.76 (34.86) kg/m$^2$ × albumin g/L (see Table 36). In patients using or not using TTR stabilizer, the mean change (SEM) was −77.60 (39.78) kg/m$^2$ × albumin g/L and −15.86 (74.21) kg/m$^2$ × albumin g/L, respectively. The mBMI was stable during the first year, with a mean change (SEM) at 12 months of 1.94 (21.02) kg/m$^2$ × albumin g/L, but then started to decrease subsequently to the second year, as shown in Table 36.

## Table 36: Nutritional Status Outcome in Study ALN-TTR02-003

| | mBMI (kg/m$^2$ × Albumin g/L) (N = 27) |
|---|---|
| **Baseline** | |
| n | 27 |
| Mean (SD) | 1,030.49 (168.64) |
| Range | 728.6 to 1,379.6 |
| **Month 24** | |
| n | 22 |
| Mean (SD) | 976.46 (199.53) |
| Range | 573.4 to 1,354.5 |
| **Change From Baseline** | |
| n | 22 |
| Mean (SEM) | −60.76 (34.86) |
| Range | −368.8 to 258.9 |

mBMI = modified body mass index; SD = standard deviation; SEM = standard error of the mean.

Source: ALN-TTR02-003 Clinical Study Report.[64]

Among the cardiac subgroup, the mean change (SEM) in troponin I and NT-proBNP were −0.09 (0.08) mcg/L and −49.6 (170.83) ng/L, respectively (see Table 37). Changes in echocardiogram parameters are also shown in Table 37.

## Table 37: Cardiac Outcomes in Study ALN-TTR02-003 (Cardiac Subgroup)

| | Troponin I (mcg/L) (N = 11) | NT-proBNP (ng/L) (N = 11) | EF (N = 11) | LV Wall Thickness (N = 11) | Average Peak Longitudinal Strain (N = 11) |
|---|---|---|---|---|---|
| **Baseline** | | | | | |
| n | 8 | 9 | 11 | 11 | 11 |
| Mean (SEM) | 0.14 (0.08) | 809.8 (246.68) | 62.46 (2.63) | 1.58 (0.06) | −16.64 (1.32) |
| Range | 0.03 to 0.69 | 105 to 2,070 | 40.71 to 75.66 | 1.34 to 1.92 | −23.0 to −9.2 |
| **Month 24** | | | | | |
| n | 10 | 10 | 10 | 10 | 10 |
| Mean (SEM) | 0.06 (0.02) | 726.0 (244.63) | 62.89 (3.66) | 1.47 (0.07) | −16.53 (0.87) |
| Range | 0.03 to 0.21 | 56 to 2,565 | 37.75 to 76.45 | 1.13 to 1.89 | −19.8 to −11.8 |
| **Change From Baseline** | | | | | |
| n | 8 | 8 | 10 | 10 | 10 |
| Mean (SEM) | −0.09 (0.08) | −49.6 (170.83) | 0.63 (1.45) | −0.08 (0.05) | 0.85 (0.89) |
| Range | −0.66 to 0.03 | −986 to 807 | −8.15 to 6.84 | −0.41 to 0.08 | −4.1 to 5.1 |

EF = ejection fraction; LV = left ventricular; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; SEM = standard error of the mean.

Source: ALN-TTR02-003 Clinical Study Report.[64]

## Phase III Open-Label Extensions (ALN-TTR02-006)

### Study and Phase Design

ALN-TTR02-006 is an ongoing, open-label, single-arm extension study that included patients with hATTR amyloidosis with polyneuropathy who completed and tolerated the study drug in the phase II extension study ALN-TTR02-003 or the pivotal phase III study ALN-TTR02-004 (the APOLLO study). Patients were from 19 countries in Europe, North America (including four sites in Canada), South America, and Asia. Patients in study ALN-TTR02-003 received open-label patisiran for two years. Patients in the APOLLO study were randomized to patisiran or placebo for 18 months and remained blinded to treatment received during APOLLO (i.e., patisiran or placebo) throughout the ALN-TTR02-006 extension study phase. Patients were excluded from using concominant diflunisal or tafamidis, unless previously allowed in the parent study. All patients in ALN-TTR02-006 received at least one other concomitant medication during the study, with the most frequent being retinol. The objectives of the extension study were to investigate the safety and efficacy of patisiran after long-term dosing of up to five years. Efficacy outcomes of relevance to the review were health-related quality of life (EQ-5D, Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QoL-DN]), the mNIS+7, COMPASS 31, R-ODS, 10 metre walk test, PND and FAP stage, mBMI, and cardiac outcomes. The mNIS+7 was assessed two times independently at least 24 hours apart, but no more than seven days apart. All-cause and cardiovascular mortality and hospitalizations were not evaluated.

The first visit of the extension study occurred about three weeks after the last dose of patisiran in the parent study. Baseline was defined as the last visit in the parent study or, if more than 45 days had elapsed, as the first visit of the extension study phase. Patients received 0.3 mg/kg patisiran IV infusion every three weeks. Premedications (i.e., dexamethasone, acetaminophen, histamine-1 receptor blocker and histamine-2 receptor blocker) were administered prior to infusion to prevent infusion-related reactions. Efficacy assessments were conducted 52 weeks post-baseline and every year thereafter. Safety assessments were conducted 12 weeks, 26 weeks, and 52 weeks during the first year and every year thereafter. The data presented here is for a 52-week follow-up from an interim cut-off date of July 14, 2017.

The full analysis set was the primary set for analysis of efficacy and included all patients who were enrolled in ALN-TTR02-006. The safety analysis set included patients in the full analysis set who received at least one dose of patisiran in this study. Numbers, with percentages, were reported for harms involving PND stage, FAP stage, and New York Heart Association classification. Summary statistics of observed values and changes from baseline were reported for other efficacy outcomes. The data are presented separately for patients from study ALN-TTR02-003, and for patients from the placebo and patisiran arms of the APOLLO study. In the following text, these groups are referred to as patients from “ALN-TTR02-003,” “ALN-TTR02-004 (placebo),” and “ALN-TTR02-004 (patisiran),” respectively.

#### *Results*

**Patient Disposition**

At data cut-off, all 25 patients who completed the phase II extension study (ALN-TTR02-003) and 163 of 169 patients who completed the phase III randomized trial (ALN-TTR02-004, the APOLLO study) were enrolled in ALN-TTR02-006 (see Table 38). Six patients from

ALN-TTR02-004 did not enter this study because of patient decision (N = 1), death after study completion (N = 2), serious adverse event of colon cancer (N = 1), and treatment not completed (N = 2). At the time of data cut-off, no patient had completed this phase III extension study and 11 patients had withdrawn from the study due to adverse events, death, and patient decision. Of the five deaths that led to study withdrawal, four occurred in patients who had received placebo in study ALN-TTR02-004 and one death occurred in a patient who had received patisiran in study ALN-TTR02-004. The cause of death in the patient who had received patisiran was worsening amyloidosis. The full analysis set includes 188 patients; however, at the time of data cut-off, efficacy data at week 52 was available for only 64 patients. The safety set includes 184 patients; four patients from ALN-TTR02-004 (patisiran) who were enrolled in ALN-TTR02-003 had not yet received a dose of patisiran during the open-label extension at the time of data cut-off.

## Table 38: Patient Disposition in Study ALN-TTR02-006

| | From ALN-TTR02-003 | From ALN-TTR02-004 (placebo) | From ALN-TTR02-004 (patisiran) | Total |
|---|---|---|---|---|
| Enrolled, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Treated, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Ongoing, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Week 52 efficacy | [redacted] | [redacted] | [redacted] | [redacted] |
| Completed, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Withdrawals, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Reason For Withdrawals | | | | |
| AE | [redacted] | [redacted] | [redacted] | [redacted] |
| Death | [redacted] | [redacted] | [redacted] | [redacted] |
| Patient decision | [redacted] | [redacted] | [redacted] | [redacted] |
| FAS, N (%)[a] | [redacted] | [redacted] | [redacted] | [redacted] |
| Safety, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |

AE = adverse event; FAS = full analysis set.

[a] At time of data cut-off of this interim analysis, week 52 efficacy data were available for 64 patients.

Source: ALN-TTR02-006 Clinical Study Report.[65]

Table 39 shows the baseline characteristics of patients in study ALN-TTR02-006. The mean age of patients in the total full analysis set was 61.3 years, 73.9% of patients were male, and 79.3% were white. The mean time since diagnosis was about four years. The V30M mutation was present in 46.3% of patients. Tetramer stabilizers were used concomitantly by 13 patients (6.9%), of whom 5.3% were on tafamidis (10 patients from ALN-TTR02-003) and 1.6% on diflunisal (two patients from ALN-TTR02-004 [placebo] and one patient from ALN-TTR02-003). At baseline, patients in the placebo group of ALN-TTR02-004 had more severe disease characteristics than patients who had previously received patisiran in ALN-TTR02-004 or ALN-TTR02-003 (mean mNIS+7 = 100.08 versus 77.74 versus 45.7 points; mean Norfolk QoL-DN score = 73.5 versus 56.0 versus not available; mean gait speed = 0.54 versus 0.85 versus 1.26 m/s, respectively). Patients who previously received patisiran in ALN-TTR02-003 had less advanced disease, with the majority at a score of PND I (40.0%) or PND II (52.0%) at baseline. More patients from the placebo and patisiran groups of ALN-TTR02-004 had a score of PND III or PND IV (67.5% and 49.1%, respectively).

## Table 39: Baseline Characteristics in Study ALN-TTR02-006

| | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) | Total (N = 188) |
|---|---|---|---|---|
| Age, mean (SD), years | 58.5 (15.09) | 63.7 (10.91) | 61.1 (12.33) | 61.3 (12.46) |
| Male, N (%) | 17 (68.0) | 33 (76.7) | 89 (74.2) | 139 (73.9) |
| White, N (%) | 25 (100) | 28 (65.1) | 25 (100) | 149 (79.3) |
| V30M mutation, N (%) | 18 (72.0) | 21 (48.8) | 48 (40.0) | 87 (46.3) |
| Years since hATTR diagnosis, mean (SD) | 4.91 (1.41) | 4.22 (3.64) | 3.75 (2.61) | 4.01 (2.78) |
| **PND Score, N (%)** | | | | |
| I | 10 (40.0) | 5 (11.6) | 27 (22.5) | 42 (22.3) |
| II | 13 (52.0) | 9 (20.9) | 30 (25.0) | 52 (27.7) |
| IIIA | 1 (4.0) | 8 (18.6) | 28 (23.3) | 37 (19.7) |
| IIIB | 1 (4.0) | 15 (34.9) | 24 (20.0) | 40 (21.3) |
| IV | 0 (0) | 6 (14.0) | 7 (5.8) | 13 (6.9) |
| NYHA Class, N (%) | | | | |
| I | 19 (76.0) | 17 (39.5) | 53 (45.7) | 89 (47.3) |
| II | 4 (16.0) | 21 (48.8) | 56 (48.3) | 81 (43.1) |
| III | 2 (8.0) | 3 (7.0) | 6 (5.2) | 11 (5.9) |
| IV | 0 (0) | 2 (4.7) | 1 (0.9) | 3 (1.6) |
| **Concomitant TTR Stabilizer Use, N (%)[a]** | | | | |
| Diflunisal | [redacted] | [redacted] | [redacted] | [redacted] |
| Tafamidis | [redacted] | [redacted] | [redacted] | [redacted] |

NYHA = New York Heart Association; PND = polyneuropathy disability; SD = standard deviation; TTR = transthyretin; V30M = valine to methionine substitution at position 30.

[a] Used for at least two weeks within the first month following the first dose of patisiran in study ALN-TTR02-006.

Source: ALN-TTR02-006 Clinical Study Report.[65]

### Drug Exposure

Table 40 provides details of exposure to patisiran in ALN-TTR02-006. Among the 184 patients who received a dose of patisiran as of the data cut-off date, the mean duration of treatment was nine months.

Patients from ALN-TTR02-003 (N = 25) were previously exposed to patisiran for 24 months in the parent study and were treated for an additional mean duration of 16.2 months in the current study as of data cut-off. Patients from ALN-TTR02-004 (placebo) (N = 43) were newly treated with patisiran for a mean duration of 7.1 months. Patients from ALN-TTR02-004 (patisiran) (N = 116) were previously exposed to patisiran for 18 months in study ALN-TTR02-004 and were treated for an additional mean duration of 8.1 months in the current study.

## Table 40: Drug Exposure in Study ALN-TTR02-006

| | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 116) | Total (N = 184) |
|---|---|---|---|---|
| Total duration of exposure, mean (SD), months | [redacted] | [redacted] | [redacted] | [redacted] |
| **Number of Patients on Drug** | | | | |
| ≥ 12 months, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥ 18 months, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥ 24 months, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| Total number of doses, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Number of patients with no missing doses, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Number of Patients With Missing Doses** | | | | |
| 1 missing dose, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| 2 missing doses, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥ 3 missing doses, N (%) | [redacted] | [redacted] | [redacted] | [redacted] |

NR = not reported; SD = standard deviation.

Source: ALN-TTR02-006 Clinical Study Report.[65]

### Harms

Safety outcomes are presented for the total safety analysis set as well as separately for patients from study ALN-TTR02-003, and for patients from ALN-TTR02-004 (placebo) and ALN-TTR02-004 (patisiran).

Table 41 provides a summary of treatment-emergent adverse events. At least one adverse event was reported by the majority of patients (78.3%). Most adverse events were mild or moderate in severity. None of the adverse events led to study withdrawal. However, adverse events leading to study drug discontinuation occurred in 11.6% of patients from ALN-TTR02-004 (placebo) and 5.2% of patients from ALN-TTR02-004 (patisiran). Serious adverse events were experienced by 42 patients (22.8%) and led to discontinuation of the study drug in 11 patients (6.0%). No serious adverse events were of anaphylaxis or severe hypersensitivity. Six patients (3.3%) died prior to the data cut-off date. Three deaths of patients from ALN-TTR02-004 (placebo) were classified as cardiovascular events by an external independent adjudication committee; one of these deaths was a sudden death. One patient from the patisiran group died of a cardiovascular event. In addition, after the data cut-off date, four patients died — one in the placebo group and three in the patisiran group.

## Table 41: Treatment-Emergent Adverse Events in Study ALN-TTR02-006

| | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 116) | Total (N = 184) |
|---|---|---|---|---|
| At least 1 AE, N (%) | 25 (100) | 34 (79.1) | 85 (73.3) | 144 (78.3) |
| At least 1 SAE, N (%) | 4 (16.0) | 13 (30.2) | 25 (21.6) | 42 (22.8) |
| At least 1 AE leading to study withdrawal, N (%) | 0 | 0 | 0 | 0 |
| Death | 0 | 4 (9.3) | 2 (1.7) | 6 (3.3) |

AE = adverse event; SAE = serious adverse event.

Source: ALN-TTR02-006 Clinical Study Report.[65]

Adverse events that occurred in at least 10% of patients from ALN-TTR02-004 (placebo) were infusion-related reactions (25.6%), peripheral edema (25.6%), diarrhea (18.6%), and urinary tract infection (16.3%). In patients from ALN-TTR02-004 (patisiran), the only adverse event that occurred in at least 10% was falls (10.3%). Adverse events that occurred in at least 10% of patients from ALN-TTR02-003 were flushing (20.0%), peripheral edema (16.0%), nasopharyngitis (16.0%), and urinary tract infection (12.0%). The most common serious adverse event was asthenia (three patients), followed by cardiac disorders (two patients each experienced cardiac amyloidosis, cardiac arrest, cardiac failure, congestive cardiac failure, and a conduction disorder), cellulitis, hip fracture, syncope, and chronic kidney disease (two patients each). At least one infusion-related reaction occurred in 19 patients (10.3%) (8% in patients from ALN-TTR02-003, 25.6% in patients from ALN-TTR02-004 [placebo], and 5.2% in patients from ALN-TTR02-004 [patisiran]). All infusion-related reactions were mild or moderate in severity and none led to study withdrawal. When assessed over time, infusion-related reactions were slightly more frequent during the first three months in patients from the placebo group. Ocular events occurred in three patients (12.0%) from ALN-TTR02-003, seven patients (16.3%) from ALN-TTR02-004 (placebo), and seven patients (6.0%) in ALN-TTR02-004 (patisiran). No patient tested positive for anti-drug antibodies in the screening assay.

**Efficacy**

In the open-label extension study, efficacy assessments were available for 64 patients at week 52 at the time of data cut-off.

Health-related quality of life measures are provided in

Table 42. The Norfolk QoL-DN was administered to patients in ALN-TTR02-004 and during the phase III extension study. Patients from ALN-TTR02-004 (placebo) experienced a mean change (standard deviation [SD]) of −10.2 (16.3) points and patients from ALN-TTR02-004 (patisiran) experienced a mean change (SD) of −1.8 (10.7) points at week 52. The mean change could not be assessed for patients from ALN-TTR02-003 because the Norfolk QoL-DN was administered to only one patient in that study. The mean change (SD) in EQ-5D-5L was −0.02 (0.11) in patients from ALN-TTR02-003, 0.03 (0.23) in patients from ALN-TTR02-004 (placebo), and 0.01 (0.15) in patients from ALN-TTR02-003 (patisiran). Mean changes (SDs) in the EuroQol Visual Analogue Scale were 0.6 (9.6), 4.5 (24.1), and −1.5 (11.4) in patients from ALN-TTR02-003, ALN-TTR02-004 (placebo), and ALN-TTR02-004 (patisiran), respectively.

## Table 42: Health-Related Quality of Life Outcomes in Study ALN-TTR02-006

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| **Norfolk QoL-DN** | Baseline | | | |
| | n | 1 | 43 | 116 |
| | Mean (SD) | 34.0 (NA) | 73.5 (27.7) | 56.0 (30.9) |
| | Week 52 | | | |
| | n | 15 | 10 | 30 |
| | Mean (SD) | 40.7 (30.1) | 67.1 (31.9) | 53.7 (28.5) |
| | Change from baseline | | | |
| | n | 0 | 10 | 30 |
| | Mean (SD) | NA | −10.2 (16.3) | −1.8 (10.7) |
| **EQ-5D-5L** | Baseline | | | |
| | n | 25 | 43 | 116 |
| | Mean (SD) | 0.77 (0.17) | 0.45 (0.23) | 0.64 (0.23) |
| | Week 52 | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | 0.75 (0.16) | 0.45 (0.24) | 0.67 (0.20) |
| | Change from baseline | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | −0.02 (0.11) | 0.03 (0.23) | 0.01 (0.15) |
| **EQ-VAS** | Baseline | | | |
| | n | 25 | 43 | 116 |
| | Mean (SD) | 69.1 (21.0) | 45.8 (20.5) | 57.2 (21.3) |
| | Week 52 | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | 68.9 (20.4) | 47.0 (27.5) | 49.7 (20.3) |
| | Change from baseline | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | 0.6 (9.6) | 4.5 (24.1) | −1.5 (11.4) |

EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; EQ-VAS = EuroQol Visual Analogue Scale; NA = not applicable; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; SD = standard deviation.

Source: ALN-TTR02-006 Clinical Study Report.[65]

Table 43 provides data for neuropathy-related outcomes. For mNIS+7, patients from ALN-TTR02-004 (placebo) experienced a mean change (SD) of −1.31 (9.86) points from baseline (i.e., improvement), whereas patients from ALN-TTR02-004 (patisiran) and ALN-TTR02-003 experienced a mean change (SD) of 1.48 (14.02) and 2.47 (13.28) points (i.e., worsening), respectively. The largest improvement in COMPASS 31 occurred in ALN-TTR02-004 (placebo), with a mean change (SD) of −10.34 (11.55) points.

## Table 43: Neurological Impairment Outcomes in Study ALN-TTR02-006

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| **mNIS+7** | Baseline | | | |
| | n | 25 | 43 | 116 |
| | Mean (SD) | 45.66 (31.64) | 100.08 (43.74) | 77.74 (43.70) |
| | Week 52 | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | 48.49 (37.97) | 99.65 (44.39) | 81.53 (39.17) |
| | Change From Baseline | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | 2.47 (13.48) | −1.31 (9.86) | 1.48 (14.02) |
| **COMPASS 31** | Baseline | | | |
| | n | 25 | 43 | 116 |
| | Mean (SD) | 15.93 (15.12) | 35.82 (18.04) | 26.13 (17.36) |
| | Week 52 | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | 13.38 (12.00) | 33.70 (18.09) | 22.42 (14.83) |
| | Change From Baseline | | | |
| | n | 24 | 10 | 30 |
| | Mean (SD) | −1.80 (7.64) | −10.34 (11.55) | 0.00 (10.10) |

COMPASS 31 = Composite Autonomic Symptom Score 31; mNIS+7 = modified Neurologic Impairment Score +7; SD = standard deviation.

Source: ALN-TTR02-006 Clinical Study Report.[65]

Table 44 provides the disability outcome of R-ODS. Mean changes (SD) in R-ODS were −1.0 (3.6), 1.0 (3.5), and −1.3 (4.4), in patients from ALN-TTR02-003, ALN-TTR02-004 (placebo), and ALN-TTR02-004 (patisiran), respectively.

## Table 44: Disability Outcome in Study ALN-TTR02-006

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| **R-ODS** | Baseline | | | |
| | n | 25 | 43 | 116 |
| | Mean (SD) | 36.7 (10.3) | 20.4 (12.5) | 29.2 (12.7) |
| | Week 52 | | | |
| | n | 23 | 10 | 30 |
| | Mean (SD) | 36.3 (11.1) | 22.3 (11.1) | 29.2 (11.6) |
| | Change from baseline | | | |
| | n | 23 | 10 | 30 |
| | Mean (SD) | −1.0 (3.6) | 1.0 (3.5) | −1.3 (4.4) |

R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation.

Source: ALN-TTR02-006 Clinical Study Report.[65]

Table 45 shows the data for motor function assessments. The mean change (SD) in the 10 metre walk test was similar among all groups (−0.065 [0.192] m/s in patients from ALN-TTR02-003, −0.058 [0.105] m/s in patients from ALN-TTR02-004 [placebo], and −0.055 [0.161] m/s in patients from ALN-TTR02-004 [patisiran]). Five patients in ALN-TTR02-004 (placebo) did not perform the test at week 52 and their results were imputed as zero.

## Table 45: Motor Function Outcome in Study ALN-TTR02-006

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| **10 metre walk test (m/s)** | Baseline | | | |
| | n | 25 | 43 | 116 |
| | Mean (SD) | 1.262 (0.413) | 0.541 (0.376) | 0.848 (0.498) |
| | Week 52 | | | |
| | n | 24 | 11 | 30 |
| | Mean (SD) | 1.212 (0.432) | 0.367 (0.322) | 0.882 (0.475) |
| | Change From Baseline | | | |
| | n | 24 | 11 | 30 |
| | Mean (SD) | −0.065 (0.192) | −0.058 (0.105) | −0.055 (0.161) |

SD = standard deviation.

Source: ALN-TTR02-006 Clinical Study Report.[65]

In most patients, PND did not change from baseline to week 52 (see Table 46). A few patients experienced disease progression at week 52 (N = 4, 1, and 5 in patients from ALN-TTR02-003, ALN-TTR02-004 [placebo], and ALN-TTR02-004 [patisiran], respectively) or disease improvement (one patient from ALN-TTR02-003 and five patients from ALN-TTR02-004 [patisiran]). Similarly, FAP did not change in most patients at week 52. It worsened in five patients (one patient each from ALN-TTR02-003 and ALN-TTR02-004 [placebo], and three patients from ALN-TTR02-004 [patisiran]) and improved in one patient from the ALN-TTR02-004 (patisiran).

## Table 46: Ambulation Outcome in Study ALN-TTR02-006

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| **PND** | Baseline, n (%) | 25 | 43 | 116 |
| | Stage 0 | 0 (0) | 0 (0) | 0 (0) |
| | Stage I | 10 (40.0) | 5 (11.6) | 27 (23.3) |
| | Stage II | 13 (52.0) | 9 (20.9) | 30 (25.9) |
| | Stage IIIA | 1 (4.0) | 8 (18.6) | 28 (24.1) |
| | Stage IIIB | 1 (4.0) | 15 (34.9) | 24 (20.7) |
| | Stage IV | 0 (0) | 6 (14.0) | 7 (6.0) |
| | Week 52, n (%) | 24 | 10 | 30 |
| | Stage 0 | 0 (0) | 0 (0) | 0 (0) |
| | Stage I | 10 (41.7) | 1 (10.0) | 5 (16.7) |
| | Stage II | 9 (37.5) | 0 (0) | 8 (26.7) |
| | Stage IIIA | 3 (12.5) | 1 (10.0) | 7 (23.3) |

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| | Stage IIIB | 2 (8.3) | 7 (70.0) | 8 (26.7) |
| | Stage IV | 0 (0) | 1 (10.0) | 2 (6.7) |
| | Change From Baseline, n (%) | 24 | 10 | 30 |
| | Worsened | 4 (16.7) | 1 (10.0) | 5 (16.7) |
| | No Change | 19 (79.2) | 9 (90.0) | 20 (66.7) |
| | Improved | 1 (4.2) | 0 (0) | 5 (16.7) |
| **FAP** | Baseline, n (%) | 25 | 43 | 116 |
| | Stage 0 | 0 (0) | 0 (0) | 0 (0) |
| | Stage I | 20 (80.0) | 12 (27.9) | 48 (41.4) |
| | Stage II | 5 (20.0) | 25 (58.1) | 61 (52.6) |
| | Stage III | 0 (0) | 6 (14.0) | 7 (6.0) |
| | Week 52, n (%) | 24 | 10 | 30 |
| | Stage 0 | 0 (0) | 0 (0) | 0 (0) |
| | Stage I | 18 (75.0) | 1 (10.0) | 9 (30.0) |
| | Stage II | 6 (25.0) | 8 (80.0) | 19 (63.3) |
| | Stage III | 0 (0) | 1 (10.0) | 2 (6.7) |
| | Change From Baseline, n (%) | 24 | 10 | 30 |
| | Worsened | 1 (4.2) | 1 (10.0) | 3 (10.0) |
| | No Change | 23 (95.8) | 9 (90.0) | 26 (86.7) |
| | Improved | 0 (0) | 0 (0) | 1 (3.3) |

FAP = familial amyloidotic polyneuropathy; PND = polyneuropathy disability.

Source: ALN-TTR02-006 Clinical Study Report.

Nutritional status, measured by mBMI, is presented in Table 47. The mean change indicated improvement in all groups. The degree of improvement varied, with the largest change occurring in patients from ALN-TTR02-003 (mean change [SD]: 42.8 [114.3] kg/m$^2$ × albumin g/L). Patients from ALN-TTR02-005 (patisiran) experienced a mean change (SD) of 29.3 (77.5) kg/m$^2$ × albumin g/L and patients from ALN-TTR02-004 (placebo) experienced a mean change (SD) of 17.0 (161.9) kg/m$^2$ × albumin g/L.

## Table 47: Nutritional Status Outcome in Study ALN-TTR02-006

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| **mBMI (kg/m$^2$ × Albumin g/L)** | Baseline | | | |
| | n | 25 | 43 | 116 |
| | Mean (SD) | 1,002.3 (173.8) | 876.0 (228.5) | 971.5 (225.3) |
| | Week 52 | | | |
| | n | 24 | 10 | 28 |
| | Mean (SD) | 1,046.2 (182.9) | 880.5 (218.6) | 1,055.5 (176.4) |

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| | Change From Baseline | | | |
| | n | 24 | 10 | 28 |
| | Mean (SD) | 42.8 (114.3) | 17.0 (161.9) | 29.3 (77.5) |

mBMI = modified body mass index; SD = standard deviation.

Source: ALN-TTR02-006 Clinical Study Report.[65]

Cardiac outcomes are shown in Table 48. Patients in ALN-TTR02-004 (patisiran) experienced the greatest increase in NT-proBNP at week 52 (mean change [SD]: 180.44 [958.11] pmol/L). The mean change (SD) in patients from ALN-TTR02-003 and ALN-TTR02-004 (placebo) were 5.19 (21.43) pmol/L and 9.56 (262.10) pmol/L, respectively. The mean change in troponin I was not calculated in the interim analysis because most patients had troponin I < 0.1 mcg/L. The mean change in LV wall thickness was negative in all groups (−0.053 [0.162] cm in patients from ALN-TTR02-003, −0.196 [0.114] cm in patients from ALN-TTR02-004 [placebo], and −0.185 [0.189] cm in patients from ALN-TTR02-004 [patisiran]). LV ejection fraction increased in patients from ALN-TTR02-003 (mean change [SD]: 0.185% [8.835%]) and ALN-TTR02-004 (placebo) (1.573% [13.451%]), and decreased in ALN-TTR02-004 (patisiran) (−2.127% [5.595%]). LV strain increased in all groups (1.37% [4.60%] in patients from ALN-TTR02-003, 1.09% [2.95%] in patients from ALN-TTR02-004 [placebo], and 1.63% [3.33%] in patients from ALN-TTR02-004 [patisiran]).

## Table 48: Cardiac Outcomes in Study ALN-TTR02-006

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| **NT-proBNP (pmol/L)** | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| **LV wall thickness (cm)** | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |

| | | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|---|
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| **LVEF (%)** | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| **LV strain (%)** | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] | [redacted] | [redacted] |

LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; SD = standard deviation.
Source: ALN-TTR02-006 Clinical Study Report.[65]

Table 49 provides change from baseline in New York Heart Association classifications. Data were available for only a small proportion of patients at week 52. The majority of patients experienced no change from baseline. A few patients worsened (12.5% in patients from ALN-TTR02-003, 1% in patients from ALN-TTR02-004 [placebo], and 7% in patients from ALN-TTR02-004 [patisiran]). Improvement occurred in 3% of patients from ALN-TTR02-003 and ALN-TTR02-004 (placebo), and 5% of patients from ALN-TTR02-004 (patisiran).

## Table 49: New York Heart Association Classification in Study ALN-TTR02-006

| | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|
| Baseline, n (%) | [redacted] | [redacted] | [redacted] |
| I | [redacted] | [redacted] | [redacted] |
| II | [redacted] | [redacted] | [redacted] |
| III | [redacted] | [redacted] | [redacted] |
| IV | [redacted] | [redacted] | [redacted] |
| Week 52 change, n (%) | [redacted] | [redacted] | [redacted] |

| | From ALN-TTR02-003 (N = 25) | From ALN-TTR02-004 (Placebo) (N = 43) | From ALN-TTR02-004 (Patisiran) (N = 120) |
|---|---|---|---|
| Worsened | [redacted] | [redacted] | [redacted] |
| No change | [redacted] | [redacted] | [redacted] |
| Improved | [redacted] | [redacted] | [redacted] |

Source: ALN-TTR02-006 Clinical Study Report.[65]

## Summary

The phase II ALN-TTR02-003 and phase III ALN-TTR02-006 extension studies provide preliminary evidence of long-term stabilization of certain efficacy outcomes with patisiran in patients with hATTR amyloidosis, although both studies are limited by the absence of a comparator group, lack of blinding, and small sample sizes. No new safety signals emerged from the studies. The patient populations in the extension studies either allowed enrolment of patients who were using a TTR stabilizer concomitantly with patisiran (74% of patients in ALN-TTR02-003 and 6.9% of patients in ALN-TTR02-006) or patients who had more severe disease, as represented by PND stage IV (6.9% of patients in ALN-TTR02-006) and New York Heart Association class III or class IV (7.4% of patients in ALN-TTR02-006). In these two respects, the extensions differed from the pivotal parent study, APOLLO, which did not allow for concomitant TTR stabilizer use and excluded patients who were confined to a wheelchair or bedridden and who were New York Heart Association class > 2.

The phase II ALN-TTR02-003 study evaluated a small number of patients over two years (N = 27). Neuropathy, as measured by the mNIS+7, was stable in patients who were either using or not using a concomitant TTR stabilizer. EQ-5D and the EuroQol Visual Analogue Scale were also stable and most patients experienced no change in PND or FAP stage. However, nutritional status, while stable during the first year, did decrease subsequently to the second year. All except one patient experienced an adverse event and there were two deaths.

The phase III ALN-TTR02-006 study evaluated a larger number of patients from various countries over a longer duration, with over three years of patisiran exposure in 24 patients from a phase II study and over two years of exposure in 30 patients from the patisiran arm of the pivotal phase III study, APOLLO. ALN-TTR02-006 is still ongoing and, at the time of the interim analysis, only about 35% of enrolled patients had completed 52-week efficacy assessments. In this subset, efficacy outcomes were stable, with most patients experiencing no change in PND or FAP stage. Most patients experienced an adverse event, and there were six deaths prior to data cut-off and an additional four deaths after data cut-off. This extension study will be following patients for a total of five years and the final results will provide evidence to determine whether disease outcomes remain stable with long-term patisiran treatment.

# Appendix 7: Summary of Indirect Comparisons

## Introduction and Background

There is an absence of head-to-head studies comparing patisiran against other therapies in the study population in the CADTH Common Drug Review. Indirect treatment comparisons (ITCs) that include patisiran can provide information on the comparative effectiveness of this drug to other therapies. The objective of this appendix was to summarize and critically appraise the evidence available regarding the indirect comparative efficacy of patisiran to other treatments of hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy in adult patients in any available ITC.

## Methods

The manufacturer submitted one ITC that was reviewed, summarized, and critically appraised.[22] In addition, the CADTH Common Drug Review conducted an independent literature search for published ITCs that compared patisiran with other relevant comparators for the treatment of adult patients with hATTR amyloidosis; one ITC was identified.

## Description of Indirect Treatment Comparisons Identified

Table 50 presents the population, interventions, comparisons, outcomes, and study design criteria for the ITCs included in this review.

### Table 50: Populations, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion

| | Manufacturer-Submitted ITC[22] | Planté-Bordeneuve (2019)[67] |
|---|---|---|
| **Population** | Populations or subgroups enrolling at least 80% patients per treatment group with hATTR amyloidosis with polyneuropathy | ≥ 80% of patients with hATTR amyloidosis with polyneuropathy |
| **Intervention** | **Interventions included in the ITC**<br>Patisiran | **Interventions included in the ITC**<br>Patisiran |
| **Comparators** | Inotersen | Tafamidis |
| **Outcomes** | **Outcomes assessed in the ITC**<br>• Change from baseline on mNIS+$7_{ionis}$ score, mean change difference (95% CI)<br>• Change from baseline on Norfolk QoL-DN score, mean change difference (95% CI)<br>• Change from baseline on mNIS+$7_{ionis}$ ≤ 0, % risk difference (95% CI)<br>• Change from baseline on Norfolk QoL-DN ≤ 0, % risk difference (95% CI)<br>• Improvement or no change in PND score, % risk difference (95%CI)<br>• Change from baseline on mNIS+$7_{ionis}$ ≤ 0, RR (95% CI)<br>• Change from baseline on Norfolk QoL-DN ≤ 0, RR (95% CI) | **Outcomes assessed in the ITC**<br>• NIS-LL<br>• Norfolk QoL-DN<br>• mBMI |

| | Manufacturer-Submitted ITC[22] | Planté-Bordeneuve (2019)[67] |
|---|---|---|
| | • Improvement or no change in PND score, RR (95% CI)<br>• Change from baseline on mNIS+7$_{ionis}$ ≤ 0, OR (95%CI)<br>• Change from baseline on Norfolk QoL-DN ≤ 0, OR (95%CI)<br>• Improvement or no change in PND score, OR (95%CI) | |
| **Study design** | **Studies included in the ITC**<br>• Randomized controlled trials | **Studies included in the ITC**<br>• Randomized controlled trials |
| **Other** | Studies from any country | Published in English |

CI = confidence interval; hATTR = hereditary transthyretin-mediated; ITC = indirect treatment comparison; mNIS+7$_{ionis}$ = modified Neurologic Impairment +7 outcome measure used in the phase III randomized controlled trial for inotersen; NIS-LL = Neuropathy Impairment Score–Lower Limbs; mBMI = modified body mass index; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; OR = odds ratio; PND = polyneuropathy disability; RR = risk ratio.

Source: Manufacturer-submitted ITC and Planté-Bordeneuve (2019).[22,67]

## Review and the Manufacturer-Submitted Indirect Treatment Comparison

### *Objectives and Rationale*

The objective of the manufacturer-submitted ITC was to conduct an indirect comparison between patisiran and inotersen for the treatment of hATTR amyloidosis with polyneuropathy. The lack of head-to-head studies comparing these two treatments was provided as a rationale for conducting the ITC. The ITC analyses focused on clinical efficacy outcomes as measured through the mean change from baseline on modified Neurologic Impairment Score +7 ionis score (mNIS+7$_{ionis}$), mean change from baseline on Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN), percentage of patients with mNIS+7$_{ionis}$ change of zero or less from baseline, percentage of patients with Norfolk QoL-DN change of zero or less from baseline, and percentage of patients with no change from baseline on the polyneuropathy disability (PND) score.

## Methods for Manufacturer-Submitted Indirect Treatment Comparison

### *Study Eligibility and Selection Process*

The manufacturer-submitted ITC focused on comparing patisiran and inotersen for the treatment of hATTR amyloidosis with polyneuropathy. No other treatments were considered. The manufacturer-submitted ITC conducted a systematic literature search to identify treatments of hATTR amyloidosis with polyneuropathy and treatments of transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy. The search strategy utilized was not provided in the submission. The search was conducted on several bibliographic databases: Embase, MEDLINE, the Cochrane Library, Econlit, and PsycINFO. The search strategy was executed on December 13, 2018. Conference abstracts and grey literature were also searched to supplement the systematic literature search. The inclusion and exclusion criteria allowed the inclusion of any study design (observational or experimental). One reviewer was responsible for screening studies and extracting data. Although the manufacturer-submitted ITC provides a table-based flow chart of the number of included reports in each stage of the screening (41 reports included for polyneuropathy and one report included for cardiomyopathy), it is not clear how these reports have informed the ITC or the number of studies that these reports inform, as the analysis solely focused on two trials: the APOLLO trial for patisiran and the NEURO-TTR trial for inotersen.

In addition, it is not clear how the ATTR report that was included was relevant to the analysis. No assessment of the quality of the included studies was provided.

The manufacturer-submitted ITC utilized the APOLLO and NEURO-TTR trials to provide the indirect analysis between patisiran and inotersen. The individual patient data from the APOLLO trial were utilized in the matching-adjusted indirect comparison (MAIC). The manufacturer justified the use of the MAIC based on the potential differences in the baseline characteristics between the two trials that may influence the outcome. The MAIC is a form of population-adjusted ITC that uses individual patient data from trials of one treatment (patisiran) and matched baseline aggregate data reported in a comparator trial (inotersen).

*Data Extraction*

The manufacturer-submitted ITC provided detailed information regarding the study design, patients' baseline characteristics, results, and the overall conduct of each of the APOLLO and NEURO-TTR trials. It is not clear how many reviewers were involved in extracting data from these two trials but the manufacturer-submitted ITC reported that one reviewer was responsible for screening and data extraction of the retrieved reports from the systematic literature search. In addition, it is also not clear how many of the retrieved results directly informed the two included trials and if any other eligible trials were identified. Both trials were double-blind, randomized, phase III, placebo-controlled trials. Patients in both trials were randomized on a 2:1 ratio to active and placebo groups, respectively.

Noticeable differences between the two trials include the following:

- **Different assessment time points:** APOLLO outcomes were measured at 18 months versus 15 months in the NEURO-TTR trial.
- **Variations in the definition of the main outcome measure:** The APOLLO primary end point was reported using the mNIS+7 while the NEURO-TTR trial primary end point was reported using the mNIS+$7_{ionis}$. These two outcomes differ in their assessment of scoring sensation and autonomic function. The mNIS+$7_{ionis}$ composites score is computed from six components: motor strength or weakness, reflexes, sensation, quantitative sensory testing, nerve conduction studies, and heart rate decrease with deep breathing. The mNIS+7 differs in that it uses different nerve conduction test scoring, it does not include the NIS-sensation, and uses postural blood pressure instead of heart rate decrease with deep breathing (see Table 26).
- **Differences in the extent and distribution of missing data:** In the NEURO-TTR trial, 22% of patients in the inotersen group and 13% of patients in the placebo group discontinued, whereas in the APOLLO trial, 7% and 38% of patients discontinued in the patisiran and placebo groups, respectively.
- **Differences in the baseline characteristics:** The primary difference across trials is in the percentage of patients in FAP stage I and stage II, where more patients in the APOLLO trial were classified as stage II compared with NEURO-TTR. Other differences in baseline characteristics also existed, including sex, race and baseline mNIS+$7_{ionis}$ score. Table 51 provides an overview of baseline characteristics in both trials.

## Table 51: Included Studies and Select Patient Characteristics

| Characteristics | APOLLO Trial | | NEURO-TTR Trial | |
|---|---|---|---|---|
| | Patisiran N = 148 | Placebo N = 76 | Inotersen N = 112 | Placebo N = 60 |
| Age, years (SD) | 59.6 (12.0) | 62.0 (10.8) | 59.0 (12.5) | 59.5 (14.0) |
| Male | 73.6% | 75.0% | 68.7% | 68.3% |
| Race | | | | |
| White | 76.4% | 64.5% | 93.8% | 88.3% |
| Black | 2.7% | 1.3% | 2.7% | 1.7% |
| Asian | 18.2% | 32.9% | 0.9% | 5.0% |
| Other | 2.7% | 1.3% | 2.7% | 5.0% |
| BMI (SD) | [redacted] | [redacted] | 24.0 (4.9) | 24.2 (4.9) |
| mBMI (SD) | 969.7 (210.5) | 989.5 (215.6) | 1,011.1 (228.0) | 1,050.0 (228.0) |
| Comorbidity and Concomitant Treatment | | | | |
| Cardiomyopathy | 60.8% | 46.1% | 67.0% | 55.0% |
| Previous treatment with tafamidis or diflunisal | 52.7% | 52.6% | 56.3% | 60.0% |
| Disease Characteristics | | | | |
| FAP Stage | | | | |
| FAP stage I | 45.3% | 48.7% | 66.1% | 70.0% |
| FAP stage II | 54.7% | 50.0% | 33.9% | 30.0% |
| FAP stage III | 0.0% | 1.3% | 0.0% | 0.0% |
| V30M mutation | 37.8% | 51.3% | 50.0% | 55.0% |
| mNIS+7$_{ionis}$ score (SD)[a] | [redacted] | [redacted] | 79.2 (37.0) | 74.8 (39.0) |
| Norfolk QoL-DN score (SD) | 59.6 (28.2) | 55.5 (24.3) | 48.2 (27.5) | 48.7 (26.7) |

BMI = Body Mass Index; ITC = indirect treatment comparison; mBMI = modified BMI; mNIS+7 $_{ionis}$ = modified Neurologic Impairment +7 outcome measure used in the phase III randomized controlled trial for inotersen; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; FAP = familial amyloid polyneuropathy; SD = standard deviation; V30M = valine to methionine substitution at position 30.

[a]APOLLO mNIS+7$_{ionis}$ score was calculated from individual patient data.

Source: Manufacturer-submitted ITC.[22]

### *Comparators*

The manufacturer-submitted ITC compared patisiran 0.3 mg per kg of body weight once every three weeks intravenously to inotersen 300 mg weekly subcutaneous injections. Inotersen is an antisense oligonucleotide that is indicated for the treatment of stage I or stage II polyneuropathy in adult patients with hATTR amyloidosis.[22] No other comparators were included in the analysis. As such, other [redacted] treatments such as tafamidis or diflunisal were not considered in the analysis.

### *Outcomes*

The primary efficacy outcome in both trials was based on changes in the mNIS+7 from baseline. However, in the APOLLO study, the primary outcome measure was reported using the mNIS+7 while in the NEURO-TTR trial, the primary outcome measure was reported using the mNIS+7$_{ionis}$. In NEURO-TTR, a co-primary outcome was the Norfolk QoL-DN total score change from baseline, which is a secondary outcome in the APOLLO trial. In addition, APOLLO reported outcomes at 18 months — its treatment duration — as

opposed to 15 months in the NEURO-TTR trial. The ITC aimed to conduct an analysis on the following outcomes:

- mean change from baseline on mNIS+7$_{ionis}$
- mean change from baseline on Norfolk QoL-DN
- percentage of patients with change from baseline on mNIS+7$_{ionis}$ ≤ 0
- percentage of patients with change from baseline on Norfolk QoL-DN ≤ 0
- percentage of patients with improvement or no change from baseline on PND score.

Confidence intervals of 95% were provided with mean changes for continuous outcomes and odds ratio and relative risk for binary outcomes.

### *Quality Assessment of Included Studies*

No quality assessment was reported in the manufacturer-submitted ITC.

### *Evidence Network*

While the manufacturer did not provide a graphic representation of the evidence network, two trials were included; they share the placebo group as the common comparator.

## Indirect Comparison Methods

The manufacturer-submitted ITC [redacted]

- [redacted]

[redacted]

## Results

[redacted]

[redacted]

## Table 52: Bucher and Matching-Adjusted Indirect Comparison Results of Patisiran Versus Inotersen Under the 15-Month APOLLO Extrapolated Results and 18-Month Observed Results

| Outcome | Bucher Method | | MAIC Method | |
|---|---|---|---|---|
| | Month 15 vs. Month 15 | Month 15 vs. Month 18 | Month 15 vs. Month 15 | Month 15 vs. Month 18 |
| Change from baseline on mNIS+7$_{ionis}$ score, mean change difference (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline on Norfolk QoL-DN score, mean change difference (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline on mNIS+7$_{ionis}$ ≤ 0, % risk difference (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline on Norfolk QoL-DN ≤ 0, % risk difference (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Improvement or no change in PND score, % risk difference (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline on mNIS+7$_{ionis}$ ≤ 0, RR (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline on Norfolk QoL-DN ≤ 0, RR (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Improvement or no change in PND score, RR (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline on mNIS+7$_{ionis}$ ≤ 0, OR (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline on Norfolk QoL-DN ≤ 0, OR (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |

| Outcome | Bucher Method | | MAIC Method | |
|---|---|---|---|---|
| | Month 15 vs. Month 15 | Month 15 vs. Month 18 | Month 15 vs. Month 15 | Month 15 vs. Month 18 |
| Improvement or no change in PND score, OR (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |

CI = confidence interval; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; mNIS+7$_{ionis}$ = modified Neurologic Impairment +7 outcome measure used in the phase III randomized controlled trial for inotersen; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PND = polyneuropathy disability; OR = odds ratio; RR = risk ratio; vs. = versus.

Source: Manufacturer-submitted ITC.[22]

## Critical Appraisal

The systematic review portion of the manufacturer-submitted ITC suffers from several limitations and lack of reporting key items. Only one reviewer conducted the screening and abstracting process, which increases the potential for human error in both stages of the process. The manufacturer-submitted ITC did not provide the search strategy or information regarding how the included report informed the analysis. In addition, the manufacturer-submitted ITC did not provide information about whether an assessment of the quality of the included studies was conducted.

The manufacturer-submitted ITC provided a detailed outline of the differences in the APOLLO and NEURO-TTR trials and attempted to provide methods to ensure that both trials were sufficiently similar to allow valid indirect comparison. The manufacturer-submitted ITC utilized the individual patient data from the APOLLO trial to harmonize the definition of the key efficacy outcome in both trials and calculate a common efficacy outcome for both trials. It also extrapolated the APOLLO efficacy results at 15 months to harmonize assessment time points, considering the rapid deteriorating nature of the disease. The manufacturer-submitted ITC also transparently reported the issues related with missing data in both studies and provided results using imputed and non-imputed data sets. A major advantage of the MAIC method is the use of the individual patient-level data through a weighting method to ensure that potential confounding variables are matched in the manufacturer-sponsored trials with that of the comparison arm from selected published trials. However, the MAIC does not adjust for unobserved or unreported variables and the choice of variables to adjust for should be largely driven by evidence that the adjusted variables are indeed potential effect modifiers. In this case, the manufacturer-submitted ITC reports that there is no evidence in the literature to support the effect of potential confounders. To address this issue, the manufacturer sought clinical expert guidance and also assessed the differences in cross-trial baseline characteristics. A disadvantage of the MAIC is the reduction in statistical power, which may lead to higher uncertainty in the results. The manufacturer-submitted ITC also provided the results under the Bucher indirect method, which does not adjust for differences in baseline characteristics and assumes clinical homogeneity.

While the manufacturer-submitted ITC approach to harmonize the assessment time points in both trials through extrapolating the 15-month results in the APOLLO trial is a valid approach, it also adds a level of uncertainty in the data as the indirect model is based on extrapolated data from a statistical model that needs to be assessed for validity. The manufacturer-submitted ITC did not provide the results and diagnostics of the statistical model used to extrapolate the 15-month APOLLO results. Therefore, indirect comparison between two different assessment time points carries a high level of uncertainty, especially in a disease area with potential rapid progression. [redacted]

[redacted]

Considering that the patient dropout rate in the APOLLO study was imbalanced, with more patients withdrawing from the placebo group than the patisiran group, and considering that the patient dropout rate in the NEURO-TTR study showed an imbalance where more patients dropped out of the active arm, the direction of bias due to missing data in each study is different and it is not clear how this will affect the results in the ITC. Overall, the imbalance of dropouts within and across the studies violates the assumption of homogeneity between the studies and poses potential concerns for the assumption of transitivity. Considering these risks, the imputed data set provides a more appropriate approach, using a conservative method to missing data, and we only reported the results calculated from the imputed data set.

[redacted]

An important limitation in the manufacturer-submitted ITC is the inclusion of only inotersen as a comparison. The addition of other treatments (tafamidis or diflunisal) could have helped with some of the statistical power issues that resulted in the wide confidence interval. They also may have provided indirect information for the comparison and allowed a better assessment of the benefits of patisiran with other treatment options. In addition, the manufacturer-submitted ITC did not conduct an analysis of the safety outcomes.

## Review of Planté-Bordeneuve (2019)

### *Objectives and Rationale*

The objective of Planté-Bordeneuve (2019) was to indirectly compare the clinical effectiveness of patisiran and tafamidis in patients with hATTR amyloidosis with polyneuropathy. Included studies were randomized controlled trials with > 80% of patients with hATTR amyloidosis with polyneuropathy.

### Methods

Planté-Bordeneuve (2019) conducted a systematic review and indirect comparison of patisiran and tafamidis, using the Bucher method.

### *Systematic Review*

A search strategy was performed on several bibliographic databases (MEDLINE, Embase, the Cochrane Library, and Econlit) and supplemented with a grey literature search. The search was performed on April 19, 2017. Two reviewers screened the retrieved literature reports and any discrepancies were resolved by a third reviewer. The search strategy was limited to tafamidis as the authors reported that unpublished data from the APOLLO trial (for patisiran) were available to them and they did not conduct a systematic literature search for patisiran.

### *Data Extraction*

It is unclear how many reviewers were involved in the data extraction process. The authors report extracting baseline characteristics and outcome measures for included trials. Table 53 presents a summary of baseline characteristics of both included trials.

## Table 53: Baseline Characteristics of the Trials Included in the Indirect Treatment Comparison

| | Patisiran APOLLO (*n* = 225) | Tafamidis Fx-005 (*n* = 125) |
|---|---|---|
| Age, mean (years) | | |
| Treatment arm | 59.6 | 39.8 |
| Placebo arm | 62.2 | 38.4 |
| Sex, male (%) | | |
| Treatment arm | 73.6 | 50.0 |
| Placebo arm | 75.3 | 42.6 |
| V30M (%) | | |
| Treatment arm | 37.8 | 100.0 |
| Placebo arm | 51.9 | 100.0 |
| Disease duration, mean (SD) (months) | | |
| Treatment arm | 28.7 (39.1) | 47.0 (48.4) |
| Placebo arm | 31.2 (38.9) | 34.7 (32.9) |
| FAP Stage 1 patients (%) | | |
| Treatment arm | 45.3 | 100.0[a] |
| Placebo arm | 48.1 | 100.0[a] |
| FAP Stage 2 patients (%) | | |
| Treatment arm | 54.7 | 0 |
| Placebo arm | 50.6 | 0 |
| FAP Stage 3 patients (%) | | |
| Treatment arm | 0.0 | 0.0 |
| Placebo arm | 1.3 | 0.0 |
| Prior hATTR amyloidosis pharmacotherapy (%) | | |
| Treatment arm | 52.7 | 0.0 |
| Placebo arm | 53.2 | 0.0 |

Source: Reprinted with permission of the publisher (Taylor & Francis Ltd). Expert Opinion on Pharmacotherapy v. 20 (4): An indirect treatment comparison of the efficacy of patisiran and tafamidis for the treatment of hereditary transthyretin-mediated amyloidosis with polyneuropathy. Violaine Planté-Bordeneuve, Hollis Lin, et al. Mar 4, 2019.

### *Comparators*

The authors compared patisiran with tafamidis (20 mg daily). No other treatments were included.

### *Outcomes*

The authors reported the aim was to present the comparative clinical efficacy using mean differences at 18 months for Neuropathy Impairment Score–Lower Limbs (NIS-LL), Norfolk

QoL-DN, and mBMI, and odds ratios for NIS-LL response (threshold for response not defined in the publication).

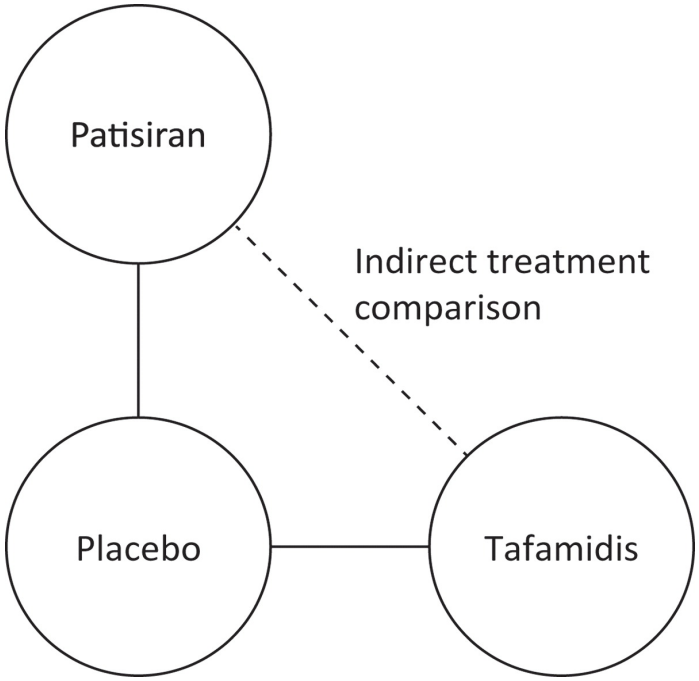
*Quality Assessment*

The authors did not report conducting a quality assessment of the included trials.

*Evidence Network*

Two trials were included with a common placebo arm as shown in Figure 15.

**Figure 15: Evidence Network Diagram**




Source: Reprinted with permission of the publisher (Taylor & Francis Ltd). Expert Opinion on Pharmacotherapy v. 20 (4): An indirect treatment comparison of the efficacy of patisiran and tafamidis for the treatment of hereditary transthyretin-mediated amyloidosis with polyneuropathy. Violaine Planté-Bordeneuve, Hollis Lin, et al., March 4, 2019.

*Meta-Analysis and Indirect Comparison*

The authors reported using the Bucher method to analyze the indirect result of comparing patisiran with tafamidis.

## Results

Two trials were included: APOLLO and Fx-005. APOLLO was a randomized, placebo-controlled, phase III trial of patisiran while Fx-005 was a randomized, placebo-controlled, phase II/III trial of tafamidis. Both measured the clinical efficacy outcome at 18 months. APOLLO enrolled 225 patients and Fx-005 enrolled 125 patients. The Fx-005 trial only included patients with FAP stage I. Other notable differences in the baseline characteristics of both included trials were age, sex, percentage of patients with valine to methionine substitution at position 30 mutation (V30M), duration of the disease, and prior therapy (see Table 53). The primary outcome in APOLLO was measured through the mNIS+7 while Fx-

005 was measured through the NIS-LL outcome. The authors derived the NIS-LL values for the APOLLO trial from the mNIS+7 components; however, it is unclear how they did so. The authors do not describe the extent of missing data in each trial and methods used to address missing data.

It is unclear if the analysis was only conducted on APOLLO patients with FAP stage I. However, the authors report their base-case analysis only for patients with FAP stage I and sensitivity and subgroups analyses, using the modified intention-to-treat (mITT) population, using only data from patients with FAP stage I and V30M, and using only data from patients with FAP stage I who are treatment naïve. Consistently and across most subgroups, the results of the ITC show a statistically significant difference in favour of patisiran. The base-case analysis shows a difference in mean change from baseline to month 18 in the NIS-LL outcome of −5.49 (95% CI, −10.01 to −0.97), an odds ratio of NIS-LL response of 3.23 (95% CI, 0.93-11.29), a difference in mean change from baseline to month 18 in Norfolk QoL-DN of –13.10 (95% C, –23.55 to –2.66), and a difference in mean change from baseline to month 18 of 47.40 (95%CI , –7.70 to 102.50).

### Critical Appraisal of Planté-Bordeneuve (2019)

The main limitation that poses a threat to the internal validity of the study is the differences in the baseline characteristics between the two included trials. This should be considered in light of the primary efficacy result in the manufacturer-submitted ITC, which showed differences in the point estimates and the confidence interval between the Bucher and MAIC methods. These differences in baseline characteristics raise questions regarding the validity of the assumption of clinical homogeneity in the Bucher method. The baseline characteristics indicate that patients enrolled in the APOLLO trials were at a more advanced stage of the disease than those in the Fx-005 trial. In addition to the differences in the baseline clinical characteristics, there were methodological differences between the two trials where Fx-005 was an open-label trial as opposed to the double-blind design of the APOLLO trial. These clinical and methodological differences in the included trials translate to high uncertainty in the results. Other limitations include a restricted search strategy that only focused on tafamidis. As such, the authors did not conduct a full systematic review of all the drugs of interest, potentially missing relative data. The authors also did not report how the screening and data extraction processes were conducted. In addition, the authors did not report on missing data and how missing data were handled. This is especially important as both of the included trials have reported a relatively high percentage of patients not completing the study.

## Discussion and Conclusion

The manufacturer-submitted ITC conducted a Bucher indirect comparison and MAIC between patisiran and inotersen and included two phase III randomized controlled trials: APOLLO and NEURO-TTR. The manufacturer identified key differences between the two studies and attempted to harmonize the outcome definition and the assessment time points between the two trials. The manufacturer used individual patient data from APOLLO to conduct a MAIC to further adjust baseline characteristics. In addition, the manufacturer provided results using imputed and non-imputed data. Using the imputed data set is likely the better approach due to the high degree of missing data in both trials and the unbalanced distribution of patient discontinuation within and across the included trials. Matching the definition of the mNIS+7 outcomes between the two studies was also necessary to provide valid and interpretable estimates of the indirect comparative clinical

efficacy. Harmonizing the outcome assessment end points between the two trials is also necessary to achieve homogeneity between the two trials and to allow more valid indirect comparison. However, the manufacturer-extrapolated assessment outcome in the APOLLO trial also led to an added layer of uncertainty as any potential residual deviance or error from the additional extrapolation statistical model is added to the uncertainty of the results of the indirect comparison. The MAIC method may have not been necessary as the manufacturer-submitted ITC did not provide evidence of confounders. [redacted]. The use of the MAIC method can be advantageous in adjusting for potential differences in the baseline characteristics. However, it also results in decreased statistical power and a break of randomization.

[redacted] An important limitation in the manufacturer-submitted ITC is the inclusion of only inotersen as a comparison. [redacted] In addition, the manufacturer-submitted ITC did not conduct analyses of the safety outcomes.

The literature search conducted by the CADTH Common Drug Review identified an ITC by Planté-Bordeneuve (2019), which attempted to provide an indirect efficacy comparison between patisiran and tafamidis using the Bucher method. The results are, overall, statistically significant in favour of patisiran. However, the included trials show profound differences in baseline characteristics and study design, posing high uncertainty regarding the internal validity of the results.

# References


1. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis.* 2013;8(31): no pagination.
2. Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. *Neurology.* 2015;85(8):675-682.
3. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J.* 2012;164(2):222-228.e221.
4. Schmidt HH, Waddington-Cruz M, Botteman MF, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle Nerve.* 2018;57(5):829-837.
5. Onpattro (patisiran): lipid complex solution; 2 mg/mL patisiran (as patisiran sodium); intravenous [product monograph] Amsterdam (NL): Alnylam Netherlands B.V.; 2019 June 7.
6. Vinik EJ, Vinik AI, Paulson JF, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst.* 2014;19(2):104-114.
7. Clinical study report: ALN-TTR02-004. APOLLO: a phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of patisiran (ALN-TTR02) in transthyretin (TTR)- mediated polyneuropathy (familial amyloidotic polyneuropathy-FAP) [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Alnylam Pharmaceuticals, Inc; 2017 Nov 20.
8. Center for Drug Evaluation Research. Multi-discipline review. *Onpattro (patisiran) intravenous. Company: Alnylam Pharmaceuticals, Inc. Application No.:210922. Approval date: 08/10/2018 (FDA approval package)*. Rockville (MD): U. S. Food and Drug Administration (FDA); 2018: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210922Orig1s000MultiR.pdf. Accessed 2019 Apr 9.
9. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol.* 2016;29 Suppl 1:S14-26.
10. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol.* 2016;68(2):161-172.
11. Suhr OB, Larsson M, Ericzon BG, Wilczek HE. Survival after transplantation in patients with mutations other than Val30Met: extracts from the FAP world transplant registry. *Transplantation.* 2016;100(2):373-381.
12. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation.* 2015;99(9):1847-1854.
13. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA.* 2013;310(24):2658-2667.
14. Tegsedi (inotersen): 284 mg inotersen / 1.5 mL per syringe [189 mg inotersen / mL (as inotersen sodium)] injection[product monograph]. 2018: https://pdf.hres.ca/dpd_pm/00047651.PDF. Accessed 2019 Apr 29.
15. Committee for Medicinal Products for Human Use. Assessment report: Vyndaqel (tafamidis meglumine) *(European public assessment report)*. London (GB): European Medicines Agency; 2011 Sep 22: https://www.ema.europa.eu/en/documents/assessment-report/vyndaqel-epar-public-assessment-report_en.pdf. Accessed 2019 Apr 29.
16. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2018;379(11):1007-1016.
17. Foldrx Pharms. Prescribing information: Vyndaquel (tafamidis meglumine) and Vyndamax (tafamidis). Silver Spring (MD): U.S. Food and Drug Administration; 2019 May 3: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211996s000,212161s000lbl.pdf. Accessed 2019 June 21.
18. Product Information: Vyndaqel (tafamidis meglumine). *(European public assessment report)*. London (GB): European Medicines Agency; 2011 Nov 18: https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf. Accessed 2019 Apr 29.
19. Diflunisal: 250 mg and 500 mg tablets [product monograph]. Vaughan (ON): AA Pharma Inc; 2014: https://pdf.hres.ca/dpd_pm/00024729.PDF. Accessed 2019 Apr 29.
20. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):11-21.
21. Solomon SD, Adams D, Kristen A, et al. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. *Circulation.* 2019;139(4):431-443.
22. CDR submission: Onpattro (patisiran), concentrate for solution for infusion 2 mg/mL [CONFIDENTIAL manufacturer's submission]. Amsterdam (NL): Alnylam Netherlands BV; 2019 Jan 24.
23. Dyck PJ, Kincaid JC, Dyck PJB, et al. Assessing mNIS+7Ionis and international neurologists' proficiency in a familial amyloidotic polyneuropathy trial. *Muscle Nerve.* 2017;56(5):901-911.
24. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. *Mayo Clin Proc.* 2012;87(12):1196-1201.

25. Treister R, O'Neil K, Downs HM, Oaklander AL. Validation of the composite autonomic symptom scale 31 (COMPASS-31) in patients with and without small fiber polyneuropathy. *Eur J Neurol.* 2015;22(7):1124-1130.

26. McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health.* 2017;20(4):644-650.

27. Yazaki M, Tokuda T, Nakamura A, et al. Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin. *Biochem Biophys Res Commun.* 2000;274(3):702-706.

28. Diabetic polyneuropathy in controlled clinical trials: consensus report of the Peripheral Nerve Society. *Ann Neurol.* 1995;38(3):478-482.

29. Cleland JG, McMurray JJ, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *J Am Coll Cardiol.* 2009;54(20):1850-1859.

30. Alnylam Pharmaceuticals Inc. Prescribing information: Onpattro (patisiran) lipid complex injection, for intravenous use Silver Spring (MD): U.S. Food and Drug Administration; 2018: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf. Accessed 2019 May 23.

31. Committee for Medicinal Products for Human Use. Summary of opinion: Onpattro (patisiran) [initial authorisation]. *(European public assessment report)*. London (GB): European Medicines Agency; 2018: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-onpattro_en.pdf. Accessed 2019 May 23.

32. Richardson J, Iezzi A, Khan MA, Chen G, Maxwell A. Measuring the sensitivity and construct validity of 6 utility instruments in 7 disease areas. *Med Decis Making.* 2016;36(2):147-159.

33. Suanprasert N, Berk JL, Benson MD, et al. Retrospective study of a TTR FAP cohort to modify NIS+7 for therapeutic trials. *J Neurol Sci.* 2014;344(1-2):121-128.

34. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology.* 2011;76(4):337-345.

35. Draak TH, Vanhoutte EK, van Nes SI, et al. Changing outcome in inflammatory neuropathies: Rasch-comparative responsiveness. *Neurology.* 2014;83(23):2124-2132.

36. Vanhoutte EK, Draak TH, Gorson KC, et al. Impairment measures versus inflammatory RODS in GBS and CIDP: a responsiveness comparison. *J Peripher Nerv Syst.* 2015;20(3):289-295.

37. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc.* 2006;54(5):743-749.

38. Lang JT, Kassan TO, Devaney LL, Colon-Semenza C, Joseph MF. Test-retest reliability and minimal detectable change for the 10-meter walk test in older adults with Parkinson's disease. *J Geriatr Phys Ther.* 2016;39(4):165-170.

39. Niu HX, Wang RH, Xu HL, et al. Nine-hole peg test and ten-meter walk test for evaluating functional loss in Chinese Charcot-Marie-Tooth disease. *Chin Med J.* 2017;130(15):1773-1778.

40. Mori L, Prada V, Signori A, et al. Outcome measures in the clinical evaluation of ambulatory Charcot-Marie-Tooth 1A subjects. *Eur J Phys Rehabil Med.* 2019;55(1):47-55.

41. Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J Intern Med.* 1994;235(5):479-485.

42. Suhr OB, Friman S, Ericzon BG. Early liver transplantation improves familial amyloidotic polyneuropathy patients' survival. *Amyloid.* 2005;12(4):233-238.

43. Franz C, Hoffmann K, Hinz U, et al. Modified body mass index and time interval between diagnosis and operation affect survival after liver transplantation for hereditary amyloidosis: a single-center analysis. *Clin Transplant.* 2013;27 Suppl 25:40-48.

44. Suhr OB, Conceicao IM, Karayal ON, Mandel FS, Huertas PE, Ericzon BG. Post hoc analysis of nutritional status in patients with transthyretin familial amyloid polyneuropathy: impact of tafamidis. *Neurol Ther.* 2014;3(2):101-112.

45. Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation.* 2003;107(19):2440-2445.

46. Lehrke S, Steen H, Kristen AV, et al. Serum levels of NT-proBNP as surrogate for cardiac amyloid burden: new evidence from gadolinium-enhanced cardiac magnetic resonance imaging in patients with amyloidosis. *Amyloid.* 2009;16(4):187-195.

47. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J.* 2012;33(9):1120-1127.

48. Cappelli F, Baldasseroni S, Bergesio F, et al. Biohumoral markers as predictor of right ventricular dysfunction in AL Amyloidosis. *Amyloid.* 2014;21(2):97-102.

49. Kristen AV, Biener M, Hegenbart U, et al. Evaluation of the clinical use of midregional pro-atrial natriuretic peptide (MR-proANP) in comparison to N-terminal pro-B-type natriuretic peptide (NT-proBNP) for risk stratification in patients with light-chain amyloidosis. *Int J Cardiol.* 2014;176(3):1113-1115.

50. Damy T, Jaccard A, Guellich A, et al. Identification of prognostic markers in transthyretin and AL cardiac amyloidosis. *Amyloid.* 2016;23(3):194-202.

51. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol.* 2016;68(10):1014-1020.

52. Ternacle J, Bodez D, Guellich A, et al. Causes and consequences of longitudinal LV dysfunction assessed by 2d strain echocardiography in cardiac amyloidosis. *JACC Cardiovasc Imaging.* 2016;9(2):126-138.

53. Kristen AV, Maurer MS, Rapezzi C, Mundayat R, Suhr OB, Damy T. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - report from the Transthyretin Amyloidosis Outcome Survey (THAOS). *PLoS One.* 2017;12(4):e0173086.

54. Siepen FAD, Bauer R, Voss A, et al. Predictors of survival stratification in patients with wild-type cardiac amyloidosis. *Clin Res Cardiol.* 2018;107(2):158-169.

55. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging.* 2009;2(5):356-364.

56. Quarta CC, Solomon SD, Uraizee I, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation.* 2014;129(18):1840-1849.

57. Hu K, Liu D, Nordbeck P, et al. Impact of monitoring longitudinal systolic strain changes during serial echocardiography on outcome in patients with AL amyloidosis. *Int J Cardiovasc Imaging.* 2015;31(7):1401-1412.

58. Barros-Gomes S, Williams B, Nhola LF, et al. Prognosis of light chain amyloidosis with preserved LVEF: added value of 2d speckle-tracking echocardiography to the current prognostic staging system. *JACC Cardiovasc Imaging.* 2017;10(4):398-407.

59. Rocha AM, Ferreira SG, Nacif MS, Ribeiro ML, Freitas MR, Mesquita CT. Speckle tracking and transthyretin amyloid cardiomyopathy. *Arq Bras Cardiol.* 2017;108(1):21-30.

60. Kristen AV, Perz JB, Schonland SO, et al. Rapid progression of left ventricular wall thickness predicts mortality in cardiac light-chain amyloidosis. *J Heart Lung Transplant.* 2007;26(12):1313-1319.

61. Cohen J. A power primer. *Psychol Bull.* 1992;112(1):155-159.

62. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20(10):1727-1736.

63. Pruppers MH, Merkies IS, Faber CG, Da Silva AM, Costa V, Coelho T. The Val30Met familial amyloid polyneuropathy specific Rasch-built overall disability scale (FAP-RODS(©) ). *J Peripher Nerv Syst.* 2015;20(3):319-327.

64. Clinical Study Report: ALN-TTR02-003. A phase 2, multicenter, open-label, extension study to evaluate the long-term safety, clinical activity, and pharmacokinetics of ALN-TTR02 in patients with familial amyloidotic polyneuropathy who have previously received ALN-TTR02 [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Alnylam Pharmaceuticals, Inc; 2017 Feb 9.

65. Clinical Study Report: ALN-TTR02-006. A multicenter, open-label, extension study to evaluate the long-term safety and efficacy of Patisiran in patients with familial amyloidotic polyneuropathy who have completed a prior clinical study with Patisiran [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Anylam Pharmaceuticals Inc.; 2017 Nov 20.

66. Clinical Study Report: ALN-TTR02-002. A phase 2, open-label. multi-dose, dose escalation trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous infusions of ALN-TTR02 in patients with TTR amyloidosis [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Alnylam Pharmaceuticals, Inc.; 2015.

67. Planté-Bordeneuve V, Lin H, Gollob J, et al. An indirect treatment comparison of the efficacy of patisiran and tafamidis for the treatment of hereditary transthyretin-mediated amyloidosis with polyneuropathy. *Expert Opin Pharmacother.* 2019;20(4):473-481.