Canadian Journal of Health Technologies
April 2024 Volume 4 Issue 4

CADTH Reimbursement Review

Vutrisiran (Amvuttra)

Sponsor: Alnylam Pharmaceuticals BV
Therapeutic area: Hereditary transthyretin-mediated amyloidosis

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Abbreviations

10MWT	10-metre walk test
AE	adverse event
ATTR	transthyretin-mediated amyloidosis
CI	confidence interval
COMPASS	Composite Autonomic Symptom Score
COMPASS 31	31 question Composite Autonomic Symptom Score
CrI	credible interval
EMA	European Medicines Agency
FAP	familial amyloid polyneuropathy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
H_1	histamine-1 receptor antagonist
hATTR	hereditary transthyretin-mediated amyloidosis
hATTR-PN	hereditary transthyretin-mediated amyloidosis with polyneuropathy
ITC	indirect treatment comparison
LS	least squares
mBMI	modified body mass index
MCID	minimal clinically important difference
MMRM	mixed models for repeated measures
mNIS+7	modified Neuropathy Impairment Score + 7
NIS	Neuropathy Impairment Score
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NYHA	New York Heart Association
OR	odds ratio
PND	polyneuropathy disability
RCT	randomized controlled trial
R-ODS	Rasch-built Overall Disability Score
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
TAC	TTR Amyloidosis Canada
TEAE	treatment-emergent adverse event
TTR	transthyretin

UTI	urinary tract infection
wtATTR	wild-type transthyretin-mediated amyloidosis

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Vutrisiran (Amvuttra), 25 mg, prefilled syringe, administered via subcutaneous injection
Sponsor	Alnylam Pharmaceuticals BV
Indication	For the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	October 18, 2023
Recommended dose	Vutrisiran (Amvuttra) is supplied as a single-use prefilled syringe that contains 25 mg of vutrisiran and is administered as subcutaneous injection once every 3 months

hATTR = hereditary transthyretin-mediated amyloidosis; NOC = Notice of Compliance.

Source: Sponsor's Summary of Clinical Evidence.[1]

Introduction

Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare, autosomal dominant, genetically inherited disease characterized by debilitating progression and myriad serious clinical implications. Originating from a mutation in the *TTR* gene, the disease culminates in the formation of unstable monomers and transthyretin (TTR) fragments, which misfold into amyloid fibril deposits that accumulate in multiple organs. The major systems affected include the peripheral nervous system, leading to polyneuropathy, and the cardiac system, resulting in cardiomyopathies. The malfunctioning *TTR* gene causes the destabilization of the normally tetrameric TTR protein, which the liver produces for its functional activity.

hATTR often progresses rapidly and leads to worsening sensorimotor neuropathy, a condition that damages the patient's sensory and motor nerves, leading to escalating disability over time. Beyond sensorimotor neuropathy, the disease can also instigate a progressive autonomic neuropathy. This condition affects the nerves controlling the body's automatic functions, such as digestion, leading to gastrointestinal impairment, weight loss, and cachexia.[2] The life expectancy of patients with hATTR with polyneuropathy (hATTR-PN) ranges from 10 to 15 years following the time of symptoms developing.[3] Median survival from the time of diagnosis for patients with hATTR-PN is 4.7 years.[4]

Although hATTR-PN is ultra-rare, affecting an estimated 10,000 individuals globally, certain regions where the disease is endemic, like Portugal, and Sweden, exhibit higher prevalence rates (as high as 50 per 100,000 inhabitants).[3,5] In Canada, the exact prevalence is unknown due to a lack of published data.

The disease also manifests as the cardiac variant known as hATTR cardiomyopathy). In this form, TTR amyloid fibrils infiltrate the myocardium, leading to extracellular amyloid deposits and consequent restrictive cardiomyopathy and congestive heart failure. Symptoms are typical of restrictive cardiac disease, including dyspnea, orthostatic hypotension, and syncope.

There are 2 primary treatments authorized for market use in Canada for managing hATTR-PN: patisiran and inotersen. Both these therapies have received a positive CADTH recommendation.[6,7] Additionally, tafamidis meglumine (Vyndaqel), a TTR tetramer stabilizer, has been indicated for use in patients with ATTR who present primarily with cardiomyopathy.[8] The primary goal of hATTR treatments is to decelerate disease progression because there is no cure for neuropathy. Current treatments come with significant risks, and there is inconsistency in clinical outcomes between cardiac and neurologic responses.

The objective of this Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of vutrisiran, 25 mg, administered as subcutaneous (SC) injection once every 3 months for the treatment of stage 1 or stage 2 polyneuropathy in adults with hATTR. Vutrisiran has not been previously reviewed by CADTH.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

CADTH received 1 patient group submission from TTR Amyloidosis Canada (TAC). TAC is a not-for-profit organization dedicated to educating and supporting patients living with all forms of transthyretin amyloidosis. TAC primarily represents patients, caregivers, families, and some volunteer health workers in Canada, but also has members in the US, UK, and other European countries.

TAC provided input based on qualitative interviews conducted with patients who had experience with both vutrisiran and patisiran. The interviewees mentioned that vutrisiran is more convenient compared to patisiran because the administration is less frequent (every 3 months versus every 3 weeks), less time consuming (3 hours for patisiran injection procedure, plus travel time), and the route of administration is SC rather than IV. Patients stated that they were able to learn how to administer a SC injection, which freed them from having to rely on an infusion network, preinjection therapy and clinic visits, the need of a caregiver for clinic visits, and miss a workday.

Furthermore, the interviewees found that vutrisiran may decrease the pharmacoeconomic burdens of illness related to hATTR; avoiding the need for IV administration and keeping patients away from hospital centres may benefit overburdened health systems and protect frail immunocompromised patients. The interviewees also believed that risk of falls may be lessened, which could lead to fewer hospital visits and a better maintenance of quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The primary goal of hATTR treatments is to decelerate disease progression because there is no cure for neuropathy. Current treatments come with significant risks, and there's inconsistency in clinical outcomes between cardiac and neurologic responses. Moreover, there is a lack of comprehensive data on functional outcomes and overall patient quality of life, underscoring the unmet needs in this area.

According to the clinical experts consulted by CADTH, vutrisiran would likely be offered as first-line treatment to most patients with hATTR-PN. However, there is little evidence supporting its use for patients who have previously undergone liver transplant or received other genetic therapies, such as inotersen, or a comparable genetic therapy, such as patisiran. Although there is potential in combining therapies, evidence for treatment combinations is lacking. Vutrisiran might not revolutionize the treatment landscape, but it may offer enhanced convenience.

Vutrisiran is most effective for patients with a confirmed hATTR diagnosis with established presence of neuropathy. The best candidates resemble those in the related clinical trial. Improved access to accurate and reliable testing would help in proper diagnosis. Although all patients with neuropathy might benefit, those with rapidly progressing neuropathy may see the most significant improvements.

As noted by the clinical experts consulted by CADTH, treatment efficacy for hATTR is evaluated using specific metrics, including mortality reduction and serious complication rates. Neuropathy outcomes, autonomic symptoms, and several neuropathy scales provide insights into disease progression and patient experience. Continuous clinical assessments ensure accurate monitoring of the patient's treatment response. In addition, it is common to monitor TTR levels in patients as part of monitoring response to treatment. The timing of assessments depends on the severity of disease. If patients are asymptomatic or minimally symptomatic, yearly assessment is acceptable; in patients with more active disease, assessment every 3 or 6 months is appropriate.

According to the clinical experts consulted by CADTH, therapy might be halted when adverse effects outweigh the benefits. Decisions are based on patient tolerance, willingness, potential therapeutic efficacy, and whether neuropathy progression aligns with the expected course. Treatment effectiveness is indicated by improvements in several neuropathic and autonomic symptoms.

Given the similarities between hATTR-PN and other neuromuscular conditions, it is optimal to have clinicians proficient in the management of patients with neuropathy as primary caregivers, according to the clinical experts consulted by CADTH. Care can be provided in hospitals or clinics with the right resources to address advanced neuropathy, including cardiac and autonomic symptoms.

Clinician Group Input

One clinician from the Amyloidosis Program of Calgary submitted input to CADTH in the form of a letter. The clinician expressed that the dosing and regimen of vutrisiran presents an improvement over the currently approved patisiran in that treatment is only administered every 3 months, rather than every 3 weeks.

In addition, the clinician noted that vutrisiran has the potential to improve patients' quality of life while attenuating disease progression.

Drug Program Input

Drug program input elicited questions regarding the need for any additional tools, measures, and assessments for patients receiving vutrisiran.

Clinical Evidence

Systematic Review

Description of Studies

A sponsor-submitted systematic review identified 2 studies: HELIOS-A and APOLLO. HELIOS-A was a phase III, randomized, open-label, multicentre, multinational study to evaluate the efficacy and safety of vutrisiran over 18 months in patients with hATTR-PN. The study had 2 groups: a vutrisiran treatment group and a patisiran treatment group. HELIOS-A used an external placebo control group from the APOLLO study to compare the efficacy of vutrisiran with placebo. Adult patients with hATTR (N = 164) were randomized in a 3:1 ratio to receive vutrisiran 25 mg SC 3 times a month or patisiran 0.3 mg/kg IV infusion 3 times a week for 18 months. There were 2 HELIOS-A sites in Canada, each with 1 patient (1 patient received vutrisiran and the other received patisiran). APOLLO was a multinational, multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of patisiran over 18 months in patients with hATTR-PN. Adult patients with hATTR (N = 225) were randomized in a 2:1 ratio to receive patisiran (n = 148; 0.3 mg/kg every 3 weeks by IV infusion for 18 months) or placebo (normal saline; n = 77). Both the HELIOS-A and APOLLO trials had similar inclusion and exclusion criteria and outcome definitions. All patients were diagnosed with hATTR-PN. Patients were excluded if they had advanced disease (Neuropathy Impairment Score + 7 [NIS+7] > 130) or moderate cardiac involvement (New York Heart Association Functional Classification [NYHA] > 2).

In the HELIOS-A trial, the primary outcome measured the change in modified NIS+7 (mNIS+7) in the vutrisiran and placebo groups at 9 months, per protocol, and used that metric for submissions to the US, Japan, and Brazil. The primary outcome for the European Union and other regions was mNIS+7 at 18 months. Secondary efficacy outcomes were planned, with a hierarchical testing approach, subsequent to the primary outcome of mNIS+7 at 9 months; these were mNIS+7 at 18 months, Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) score at 18 months,10-metre walk test (10MWT) gait speed at 18 months, modified body mass index (mBMI) at 18 months, Rasch-built Overall Disability Scale (R-ODS) at 18 months, and the noninferiority of vutrisiran versus patisiran for TTR percent reduction at 18 months.

In the HELIOS-A and APOLLO trials, 189 and 323 patients, respectively, were considered for randomization. The HELIOS-A trial allocated 122 patients to vutrisiran and 42 to patisiran, while the APOLLO trial allocated 77 patients to a placebo and 148 to patisiran.

The median age in both trials was around 60 years; and the majority were male and white. Similarly, most patients were diagnosed within 2 years of first symptom in both trials. Both trials had an almost equal

allocation of patients with V30M *TTR* genotype. There were more patients with a polyneuropathy disability (PND) score of IIIA or IIIB in the APOLLO trial than in the HELIOS-A trial. In the APOLLO trial, there were more patients in both study groups with NYHA class I (48.9% of patients) and class II (50.2% of patients) heart failure than in the HELIOS-A trial, where more than half the patient population (54.3% of patients) had no signs of heart failure, and 9.8% and 36.0% of patients had NYHA class I and class II heart failure, respectively. The sponsor noted that, in the APOLLO study, NYHA class was classified as I through IV, without the option to categorize patients as having "no heart failure"; thus, patients classified as having NYHA class I heart failure in the APOLLO trial included both those without heart failure and those with heart failure who had no symptoms during ordinary physical activity.

Efficacy Results

The PND score provides a measure of ambulatory function and polyneuropathy-related disability. Lower scores indicate greater ambulatory function and reduced disability. The change in PND score from baseline to month 18 was an exploratory outcome in both the HELIOS-A and APOLLO trials, with no formal statistical testing. Overall, in the HELIOS-A trial, among the vutrisiran group (n = 122), [redacted]% ([redacted]) of patients showed improvement [redacted] of patients exhibited no change. In the same trial, for the within-study patisiran group (n = 42), [redacted]% ([redacted]) of patients improved, and [redacted]% ([redacted]) of patients had no change. Among the placebo group (n = 77) in the APOLLO trial, [redacted] and [redacted]% ([redacted]) of patients had no change.

The primary outcome in both the HELIOS-A and APOLLO trials was change from baseline in the mNIS+7 score. mNIS+7 assesses the progression of the motor and the sensory aspects of polyneuropathy. A negative change from a patient's own baseline score represents neurologic improvement. In the HELIOS-A trial, among patients who contributed to the analysis at month 18, the vutrisiran group (n = 112) started with a mean baseline of 60.57 (standard deviation [SD] = 35.99) and exhibited a mean change of −0.46 (standard error of the mean [SEM] = 1.60). The within-study patisiran group (n = 36) had a mean baseline of 57.68 (SD = 33.71), with a mean change of 1.53 (SEM = 2.59). In the APOLLO trial, the baseline mean mNIS+7 score for the placebo group (n = 51) was 74.61 (SD = 37.04), with a change of 28.09 (SEM = 2.28). The treatment difference in change from baseline for vutrisiran versus placebo (APOLLO trial) was −28.55 (95% confidence interval [CI], −34.00 to −23.10) in favour of vutrisiran.

The R-ODS is a 24-item scale used to assess the ability to perform everyday activities, with a lower score indicating worsening disability. In the HELIOS-A trial, the change from baseline for the vutrisiran group was −1.5 (SEM = 0.6); for the within-study patisiran group, it was −1.3 (SEM = 0.9). In the APOLLO trial, the placebo group showed a change of −9.9 (SEM = 0.8). The treatment difference of vutrisiran versus placebo (APOLLO trial) was 8.4 (95% CI, 6.5 to 10.4) in favour of vutrisiran. The R-ODS was a secondary outcome and was the fifth end point to be tested in the testing hierarchy. All previous end points achieved statistical significance. Similarly, the results for R-ODS of vutrisiran compared with placebo were statistically significant.

The Norfolk QoL-DN score assesses 35 measures of symptoms and functional impairment related to nerve function, with higher scores indicating worse health-related quality of life. The 5 domains of the Norfolk QoL-

DN are activities of daily living, physical function/large-fibre neuropathy, small-fibre neuropathy, symptoms, and autonomic neuropathy. In the HELIOS-A trial, the change in the vutrisiran group was −1.2 (SEM = 1.8) and the change in the within-study patisiran group was −0.8 (SEM = 3.0). In the APOLLO trial, the change in the placebo group was 19.8 (SEM = 2.6). The treatment differences of vutrisiran versus placebo (APOLLO trial) was −21.0 (95% CI, −27.1 to −14.9) in favour of vutrisiran. Norfolk QoL-DN was a secondary outcome and was the second end point to be tested after the primary outcome. The presented results achieved statistical significance compared with placebo.

TTR is a tetrameric protein composed of 4 monomers. In the case of hATTR (in addition to wild-type transthyretin-mediated amyloidosis [wtATTR]), the tetrameric protein destabilizes into unstable monomers and TTR fragments that can misfold and form amyloid fibril deposits in multiple organs, including the peripheral nervous system, heart, and gastrointestinal tract, leading to cellular injury and organ dysfunction, with corresponding clinical manifestations. Serum TTR is considered a biomarker for vutrisiran's biological activity; however, no validated correlation with efficacy outcomes is available. The vutrisiran group exhibited an average reduction of [redacted]% (SD = [redacted]) from a baseline of [redacted] (SD = [redacted]). The within-study patisiran group showed an average reduction of [redacted]% (SD = [redacted]) from a baseline of [redacted] (SD = [redacted]). The vutrisiran group exhibited a median reduction of [redacted] (range, [redacted]) from a median baseline of [redacted] (range, [redacted]). The within-study patisiran group showed a median reduction of [redacted] (range, [redacted]) from a median baseline of [redacted] (range, [redacted] to [redacted]). The median treatment group difference between vutrisiran and within-study patisiran was 5.28 (95% CI, 1.17 to 9.25). This outcome was the last end point in the testing hierarchy for the HELIOS-A trial. All previous end points achieved statistical significance. Vutrisiran met the prespecified 10% margin noninferiority criteria versus patisiran.

Post hoc analyses from the HELIOS-A trial were conducted for the primary and selected secondary efficacy outcomes comparing vutrisiran against within-study patisiran. For the mNIS+7 outcome, the post hoc least squares [LS] mean difference between vutrisiran and within-study patisiran at 18 months was −1.46 (95% CI, −7.36 to 4.43); for the Norfolk QoL-DN outcome, the post hoc LS mean difference was −1.6 (95% CI, −8.6 to 5.4); and for the R-ODS outcome, the LS mean difference was 0.1 (95% CI, −2.0 to 2.2).

Harms Results

In the HELIOS-A and APOLLO trials, a majority of participants experienced at least 1 adverse event (AE) after treatment with vutrisiran, patisiran, or placebo. In the HELIOS-A trial, 98% of patients treated with vutrisiran experienced AEs such as falls, pain in an extremity, and diarrhea; similar rates were seen for patients treated with patisiran. In the APOLLO trial, both the patients treated with patisiran (97%) and the placebo group (97%) reported AEs, including diarrhea, peripheral edema, and urinary tract infection (UTI). Serious adverse events (SAEs) varied between trials, with 26% of patients treated with vutrisiran in the HELIOS-A trial experiencing at least 1 SAE versus 43% of patients treated with patisiran (HELIOS-A). In the APOLLO trial, 36% of patients treated with patisiran and 40% of the placebo group reported at least 1 SAE. Treatment discontinuations due to AEs were noted in both trials, with death being a primary reason. Of all enrolled patients in the HELIOS-A

trial, the percentage that died in each treatment group was 2.0% for those treated with vutrisiran and 7% for those treated with patisiran. In the APOLLO trial, 5.0% of patients treated with patisiran and 8.0% of the placebo group died. Notable harms included cardiac arrhythmias: 24.6% of patients treated with vutrisiran and 7.1% of patients treated with patisiran in the HELIOS-A trial, 19.0% of patients treated with patisiran in the APOLLO trial, and 29.0% of the placebo group in APOLLO experienced such arrhythmias.

Critical Appraisal

The HELIOS-A trial used an external control; specifically, the placebo arm from the APOLLO trial. To infer whether the magnitude of the effect is attributable to treatment when using an external control, the trials are typically required to have a similar design and participant characteristics. In this setting, the HELIOS-A and APOLLO trials were aligned in terms of participant inclusion and exclusion criteria and outcome measures. Additionally, to help compare responses between the 2 trials, a patisiran group was included in the HELIOS-A trial. However, comparison of patient baseline characteristics indicated that patients in the APOLLO trial were at more advanced disease stages than those in the HELIOS-A trial. According to the clinical experts consulted by CADTH, this imbalance could have had an impact on treatment responses and on the natural progression of the disease in the 2 trials. Overall, the extent and direction of the potential bias caused by imbalances in disease characteristic cannot be determined. To address potential imbalances in important clinical baseline variables, the sponsor conducted a propensity score sensitivity analysis. Although the results from the propensity score sensitivity analysis were supportive of the main finding, not all of the differences between the 2 studies could be addressed, including unmeasured or unrecognized factors. There were design differences between the HELIOS-A and APOLLO trials; the HELIOS-A trial had an open-label design, whereas the APOLLO trial used a double-blind approach. To mitigate biases from this difference, several data integrity strategies were employed in the HELIOS-A trial, such as restricting access to certain previous patient data or knowledge of treatment assignments by specific personnel. Despite these precautions, the potential for biases remained; the extent and direction of this potential bias cannot be determined.

Part of the HELIOS-A secondary end points was to test for the noninferiority of vutrisiran against patisiran in the percent reduction in serum TTR protein levels. The sponsor established a noninferiority margin of 10%, but no clear justification was available about why 10% would be an acceptable noninferiority margin. However, considering that the 95% CI of the result of the end point was over the null and not close to the lower noninferiority margin, this limitation in clinical justification of the noninferiority margin is unlikely to affect the validity of the result.

The sponsor provided a number of post hoc analyses at the request of the European Medicines Agency (EMA), which compared the efficacy of vutrisiran to within-study patisiran in the HELIOS-A group. Although useful when considered in the context of the larger body of evidence, post hoc analyses have a number of limitations. These include the lack of sufficient power to detect a difference, an inflated and uncontrolled type I error, and lack of an established noninferiority margin to test noninferiority. The post hoc analysis should be considered as supportive evidence.

The mNIS+7 is limited in its application to clinical practice in Canada. The clinical expert consulted for this review provided feedback that the mNIS+7 instrument is not routinely used in Canadian clinical practice; instead, the Composite Autonomic Symptom Score (COMPASS) is more frequently used in clinical settings. Although the COMPASS score was an outcome assessed in the APOLLO trial, it was not assessed in the HELIOS-A trial. The sponsor noted that mNIS+7 is not used in routine clinical assessment due to its complexity but provides a more comprehensive assessment of neuropathy, including manifestations of both peripheral and autonomic neuropathy. mNIS+7 is a standard outcome used in clinical trials in the present therapeutic setting.[9] The PND score is an applicable clinical measure. However, the finding of the PND score in the HELIOS-A and APOLLO trials is limited due to the exploratory nature of the outcome and the lack of formal comparative statistical testing. Mortality (death) was reported as part of the safety assessment of vutrisiran. However, the duration of the trial (18 months) is likely insufficient to adequately capture the full impact of treatment on patient mortality. Hospitalizations, an additional clinically relevant outcome, was lacking in the available evidence.

The available evidence, from the HELIOS-A trial and an external placebo control group from the APOLLO trial, provides evidence of the efficacy of vutrisiran in patients with polyneuropathy. Both the HELIOS-A and APOLLO trials excluded patients in advanced disease stages. None of the studies included patients previously treated with TTR-lowering medications.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For the pivotal studies (HELIOS-A and APOLLO) identified in the sponsor's systematic review, Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined, as outlined by the GRADE Working Group.[10,11] Following the GRADE approach, evidence from the pivotal study started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: mortality, hospitalization, PND score, mNIS+7, the 31-question Composite Autonomic Symptom Score (COMPASS 31), R-ODS, Norfolk QoL-DN, and TTR levels. No data were available for hospitalization or COMPASS 31.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for Norfolk QoL-DN and R-ODS, based on a threshold

identified in the literature and/or informed by the clinical experts consulted by CADTH for this review. The target of the certainty of evidence assessment was the presence or absence of any (nonnull) effect for mNIS+7, PND, serum TTR, and mortality.

Long-Term Extension Studies

No relevant long-term extension studies were available.

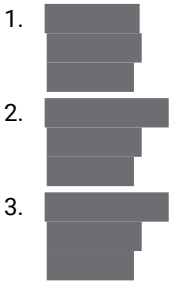
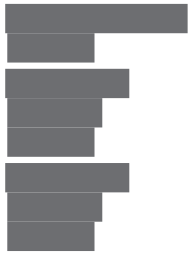
Indirect Comparisons

Description of Studies

One sponsor-submitted indirect treatment comparison (ITC) informed the efficacy of vutrisiran versus placebo, patisiran, and inotersen in patients with hATTR-PN. The ITC estimated relative effects using a Bayesian network meta-analysis with noninformative priors and a fixed-effects model. The measures chosen by the sponsor to inform on this comparison were the PND score (improvement or no change at month 18), mNIS+7 (change from baseline at month 18), and Norfolk QoL-DN (change from baseline at month 18). The sponsor identified evidence through a literature review of phase III randomized controlled trials (RCTs) for inotersen, patisiran, and vutrisiran. One reviewer conducted screening and data extraction. No quality assessment of included studies was conducted.

Three trials — HELIOS-A, APOLLO, and NEURO-TTR — were incorporated into the ITC to examine the effects of vutrisiran, patisiran, and inotersen on hATTR-PN. HELIOS-A, an 18-month, phase III, open-label trial, compared vutrisiran and patisiran in 164 participants randomized to 1 of the 2 treatments in a 3:1 ratio and used the placebo arm of the APOLLO trial as an external control group. APOLLO, an 18-month, international, double-blind, placebo-controlled trial, assessed the effects of patisiran in 225 patients randomized to either patisiran or placebo in a 2:1 ratio. NEURO-TTR, a phase II/III, double-blind trial, compared the efficacy of inotersen with placebo in 173 patients with early-stage hATTR-PN randomized in a 2:1 ratio. Notable distinctions between these studies include the assessment time frame (15 months for NEURO-TTR versus 18 months for APOLLO and HELIOS-A) and the study design (double-blind for NEURO-TTR and APOLLO versus open-label for HELIOS-A). Each trial sought patients in the early disease stage without prior TTR therapy. Available data suggest differences in disease duration and stage across trials, with APOLLO participants seemingly at a more advanced disease stage. Information on participants in the NEURO-TTR trial was, however, limited and may not allow proper assessment of clinical heterogeneity.

Table 2: Summary of Findings for Vutrisiran Versus Placebo (APOLLO Trial) for Patients With hATTR in the HELIOS-A Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo (APOLLO)	Vutrisiran (HELIOS-A)	Difference		
Neurologic impairment							
Percentage of patients with PND score: 1. Improvement 2. No change 3. Worsened Follow-up: 18 months	199 (1 single arm with external control group)	NR				Low[a,c,f,g,j]	Vutrisiran may result in more patients with a PND score of "improvement" and "no change" and fewer patients with "worsened" when compared with placebo. There is some uncertainty about the clinical importance of the estimates.
mNIS+7: LS mean (SE) change from baseline (range, 0 [best] to 304 [worst]) Follow-up: 18 months	163 (1 single arm with external control group)	NR	28.09	−0.46 (1.60)	−28.55 (−34.00 to −23.10)	Low[a,c,f]	Vutrisiran may result in a decrease (improvement) in mNIS+7 scores compared to placebo.
COMPASS 31: change from baseline Follow-up: 18 months	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of vutrisiran on neurologic impairment (as measured by COMPASS 31) compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo (APOLLO)	Vutrisiran (HELIOS-A)	Difference		
Functional impairment							
R-ODS: LS mean (SE) change from baseline (range, 48 [best] to 0 [worst]) Follow-up: 18 months	167 (1 single arm with external control group)	NR	−9.9	−1.5 (SE = 0.6)	8.4 (6.5 to 10.4)	Low[a,b,f]	Vutrisiran may result in a clinically important increase (improvement) in functional impairment measured by R-ODS compared to placebo.
HRQoL							
Norfolk QoL-DN: mean (SE) change from baseline (range, −4 [best] to 136 [worst]) Follow-up: 18 months	165 (1 single arm with external control group)	NR	19.8	−1.2 (SE = 1.8)	−21.0 (−27.1 to −14.9)	Low[a,d,f]	Vutrisiran may result in a clinically important decrease (improvement) in HRQoL measured with Norfolk QoL-DN compared to placebo.
Serum TTR							
Serum TTR: percent change from baseline, median	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of vutrisiran on serum TTR compared to placebo.
Harms							
Mortality Follow-up: 18 months	199 (1 single arm with external control group)	NR	[redacted]	[redacted]	[redacted]	Very low[e,f,g,h]	The evidence is very uncertain about the effects of vutrisiran on mortality vs. placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo (APOLLO)	Vutrisiran (HELIOS-A)	Difference		
Hospitalization Follow-up: 18 months	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of vutrisiran on hospitalizations compared to placebo.

CI = confidence interval; COMPASS 31 = Composite Autonomic Symptom Score-31; HRQoL = health-related quality of life; LS = least squares; mNIS+7 = modified Neuropathy Impairment Score + 7; NA = not applicable; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NR = not reported; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Score; SD = standard deviation; SE = standard error; TTR = transthyretin

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]There was a risk of bias due to the open-label study design and the subjective nature of the outcome. The open-label study design may have biased measurement scores due to knowledge of assigned treatment, although the direction of potential bias is unclear. The HELIOS-A trial implemented integrity strategies for the mNIS+7 and Norfolk QoL-DN measures to mitigate any potential bias. The CADTH review team did not rate down for risk of bias because, in the CADTH review team's judgment, the potential risk of bias arising from the open-label study design did not warrant rating down the evidence to very low certainty.

[b]Imprecision was not rated down. No known threshold was identified but, according to the clinical experts consulted by CADTH for the review, a 4-point difference between groups in the R-ODS score could be considered clinically meaningful. The CADTH review team judged that the effect estimate, as well as both lower and upper bounds of the 95% CI of the between-group difference, exceeded the threshold and suggested a benefit. Despite the small sample size, the clinical experts consulted by CADTH judged the observed benefit of vutrisiran against placebo to be plausible and in line with what is observed with the comparator patisiran, which shares a mechanism of action with vutrisiran.

[c]Imprecision was not rated down. There is no known threshold, and the clinical experts consulted by CADTH could not provide a threshold of important difference, so the null was used as the threshold. The CADTH team judged that the point estimate and both the lower and upper bounds of the 95% CI of the between-group comparison suggested a possibility of benefit. Treatment effect estimates observed in a small study sample may not be replicable in a larger study sample. However, the clinical experts consulted by CADTH judged the observed benefit with vutrisiran against placebo to be plausible and in line with what is observed with comparator patisiran, which shares a mechanism of action with vutrisiran.

[d]Imprecision was not rated down. A threshold of 8.8 was identified in the literature. The CADTH review team judged that the effect estimate, as well as both lower and upper bounds of the 95% CI of the between-group difference, exceeded the threshold and suggested a benefit. Despite the small sample size, the clinical experts consulted by CADTH judged the observed benefit with vutrisiran against placebo to be plausible and in line with what is observed with comparator patisiran, which shares a mechanism of action with vutrisiran.

[e]Rated down 1 level for serious imprecision. There is no known threshold and the clinical experts consulted by CADTH could not provide a threshold of important difference. In the absence of a known threshold, the null was used. The CADTH review team judged that the point estimate for the between-group difference was unlikely to include an important effect; however, the lower bound of the 95% CI for the difference between groups suggested a possibility of little to no difference.

[f]The HELIOS-A study used an external control (placebo group in the APOLLO trial) for comparison with the vutrisiran group. This observational comparison introduced potential for bias, resulting from confounding and selection bias, and the certainty of evidence was started at low.

[g]This analysis was not part of the sponsor's statistical analysis plan and was requested by CADTH to facilitate the certainty of evidence appraisal.

[h]Rated down 1 level for serious indirectness due to an insufficient duration of follow-up for the outcome, according to clinical expert input.

Table 3: Summary of Findings for Vutrisiran Versus Patisiran for Patients With hATTR in the HELIOS-A Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Patisiran (within-study HELIOS-A)	Vutrisiran (HELIOS-A)	Difference		
Neurologic impairment							
Percentage of patients with PND score 1. Improvement 2. No change 3. Worsened Follow-up: 18 months	164 (1 RCT)	NR	1. [redacted]	1. [redacted] 2. [redacted] 3. [redacted]	1. [redacted] 2. [redacted] 3. [redacted]	1. Low[d,f,h,i] 2. Very low[e,f,h,i] 3. Very low[e,f,h,i]	Vutrisiran may result in more patients with a PND score of improvement compared to patisiran. The evidence is very uncertain about the effects of vutrisiran on a PND score of no change or worsened compared to patisiran. There is some uncertainty about the clinical importance of the estimates.
mNIS+7: LS mean (SE) change from baseline (range, 0 [best] to 304 [worst]) Follow-up: 18 months	148 (1 RCT)	NR	1.53	0.06 (SE = 1.48)	−1.46 (−7.36 to 4.43)	Moderate[a,f,i]	Vutrisiran likely results in little to no difference in mNIS+7 scores compared to patisiran. There is some uncertainty about the clinical importance of the estimates.
Functional Impairment							
R-ODS: LS mean (SE) change from baseline (range, 48 [best] to 0	151 (1 RCT)	NR	−1.3	−1.2 (SE = 0.5)	0.1 (−2.0 to 2.2)	Moderate[b,f,i]	Vutrisiran likely results in little to no difference

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Patisiran (within-study HELIOS-A)	Vutrisiran (HELIOS-A)	Difference		
[worst]) Follow-up: 18 months							in R-ODS scores compared to patisiran.
HRQoL							
Norfolk QoL-DN: mean (SE) change from baseline (range, −4 [best] to 136 [worst]) Follow-up: 18 months	149 (1 RCT)	NR	−0.8	−2.5 (SE = 1.8)	−1.6 (−8.6 to 5.4)	Moderate[c,f,i]	Vutrisiran likely results in little to no difference in Norfolk QoL-DN score when compared to patisiran.
Serum TTR							
Serum transthyretin: percent change from baseline, median Follow-up: 12 months (month 6 to month 18)	160 (1 RCT)	NR	[redacted]	[redacted]	5.28 (1.17 to 9.25)	High[g]	Vutrisiran results in little to no clinically important difference (i.e., a noninferior effect) for serum TTR compared to patisiran.
Harms							
Mortality Follow-up: 18 months	164 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Very low[d,f,h,j]	The evidence is very uncertain about the effects of vutrisiran on mortality compared to patisiran.

CI = confidence interval; hATTR = hereditary transthyretin-mediated amyloidosis; HRQoL = health-related quality of life; LS = least squares; mNIS+7 = modified Neuropathy Impairment Score + 7; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NR = not reported; PND = polyneuropathy disability; RCT = randomized controlled trial; R-ODS = Rasch-built Overall Disability Score; SD = standard deviation; SE = standard error; TTR = transthyretin.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Imprecision was not rated down. The was no known minimally important difference), and the clinical experts consulted by CADTH could not estimate the threshold of a clinically important difference. The CADTH team judged the point estimate and entire CI to suggest little to no difference.

[b]Imprecision was not rated down. No known threshold was identified but, according to the clinical experts consulted by CADTH for the review, a 4-point difference between groups in the R-ODS score could be considered clinically meaningful. The between-group difference and lower and upper bounds of the 95% CI did not meet the threshold, suggesting little to no difference.

[c]Imprecision was not rated down. A threshold of 8.8 was identified in the literature. The between-group difference and lower and upper bounds of the 95% CI did not meet the threshold, suggesting little to no difference.

[d]Rated down 1 level for serious imprecision. There is no known threshold, and clinical experts consulted by CADTH could not provide a threshold of important difference, so the null was used as the threshold. The CADTH team judged that the point estimate for the between-group difference, as well as the upper bound of the 95% CI, was likely to include an important benefit, whereas the lower bound of the 95% CI suggested little to no difference.

[e]Rated down 2 levels for very serious imprecision. There is no established minimally important difference, and clinical experts consulted by CADTH could not provide a threshold of important difference. In the absence of a known threshold, the null was used. The CADTH review team judged that the point estimate for the between-group difference was unlikely to include an important effect; however, the upper and lower bounds of the 95% CI for difference between groups suggested a possibility of both benefit and harm.

[f]Rate down 1 level for serious risk of bias due to analyses being post hoc and not part of the protocol, and may have been chosen from many potential analyses of the data.

[g]Imprecision was not rated down. The clinical experts consulted by CADTH could not provide a threshold of important difference. The noninferiority margin set out in the HERLIOS-A trial was used as threshold. The CADTH review team judged that the point estimate and both the lower and upper bounds of the 95% CI of the between-group comparison suggested little to no difference; the 95% CI excluded the noninferiority margin (10%).

[h]This analysis was not part of the sponsor's statistical analysis plan and was requested by CADTH to facilitate certainty of evidence appraisal.

[i]There was a risk of bias due to the open-label study design and the subjective nature of the outcome. The open-label study design may have biased measurement scores due to knowledge of assigned treatment, although the direction of potential bias is unclear. The HELIOS-A trial implemented integrity strategies for the mNIS+7 and Norfolk QoL-DN measures to mitigate any potential bias. The CADTH review team did not rate down for risk of bias, as it was believed that rating down 1 time due to the post hoc nature of the analyses was adequate to account for risk of bias concerns.

[j]Rated down 1 level for serious indirectness due to the insufficient duration of follow-up for the outcome, according to clinical expert input.

Efficacy Results

For the PND score of improvement or no change at 18 months, the median estimated posterior odds ratio (OR) for vutrisiran compared to placebo was [redacted], with a 95% credible interval (CrI) of [redacted] to [redacted], [redacted] of vutrisiran. Against patisiran, the median estimated posterior OR was [redacted], with a 95% CrI of [redacted] to [redacted]. When vutrisiran was compared to inotersen, the median estimated posterior OR was [redacted], and the 95% CrI ranged from [redacted] to [redacted], [redacted] of vutrisiran. When using observed data, the results are [redacted]. In terms of mNIS+7 change from baseline to 18 months, vutrisiran compared to placebo showed a median estimated posterior mean change from baseline of [redacted], with a 95% CrI of [redacted] to [redacted] of vutrisiran. Compared to patisiran, the median estimated posterior mean change from baseline was [redacted], with a 95% CrI of [redacted] to [redacted]. Against inotersen, the median estimated posterior mean change was [redacted], with a 95% CrI of [redacted] to [redacted] of vutrisiran. For the Norfolk QoL-DN change from baseline to 18 months, the median estimated posterior mean change for vutrisiran relative to placebo was [redacted], with a 95% CrI of [redacted] to [redacted]. Compared to patisiran, the median estimated posterior mean change was [redacted], with a 95% CrI of [redacted] to [redacted]. Against inotersen, the median estimated posterior mean change was [redacted], and the 95% CrI ranged from [redacted] to [redacted] of vutrisiran.

Harms Results

None reported.

Critical Appraisal

Limitations in the ITC are the lack of a systematic review approach, lack of clear inclusion and exclusion criteria, single reviewer screening and data extraction, lack of quality assessment of included studies, various heterogeneity in the included studies, lack of comprehensive data to assess clinical heterogeneity, the use of a fixed-effects model, and wide CrIs of vutrisiran versus inotersen results. Considering the wide CrIs in the results of vutrisiran against inotersen in light of all the previous limitations, the certainty of the comparison of vutrisiran against inotersen is not sufficiently high to inform decision-making. Indirect results for vutrisiran compared to placebo should be used to support the results of the HELIOS-A trial. Indirect results for vutrisiran against patisiran should be viewed in totality with the noninferiority TTR result in the HELIOS-A trial, as well as with the post hoc analysis of HELIOS-A outcomes for vutrisiran compared to patisiran.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies were available to address gaps in the systematic review evidence.

Conclusions

The efficacy and safety of vutrisiran compared to placebo was assessed in the phase III, open-label HELIOS-A trial and an external placebo control group from the APOLLO trial. Both the HELIOS-A and APOLLO trials enrolled patients with hATTR-PN in familial amyloid polyneuropathy (FAP) stage I and stage II. GRADE assessment of clinically relevant outcomes indicated that, compared to placebo, vutrisiran may result

in clinically important disease improvements in PND, mNIS+7, R-ODS, and Norfolk QoL-DN scores. The evidence was very uncertain about the effects of vutrisiran on mortality compared to placebo.

The noninferiority comparison of vutrisiran against within-study patisiran was assessed using a biomarker, serum TTR, suggesting that vutrisiran results in little to no difference compared to patisiran.

A post hoc analysis suggested that, compared to patisiran, vutrisiran likely results in little to no difference in mNIS+7, R-ODS, or Norfolk QoL-DN scores, and may result in PND improvement. The lack of power to detect differences between vutrisiran and patisiran in the HELIOS-A trial, the lack of a predefined noninferiority margin, and the exploratory nature of post hoc analyses limit the validity of the results. Post hoc analyses are considered to be supportive evidence.

Given the limited evidence available to inform the comparative efficacy of vutrisiran versus the current standards of care (patisiran and inotersen), the sponsor submitted an ITC. A number of limitations (e.g., heterogeneity across study designs, outcome assessments, and patient populations, as well as missing baseline data) prevented firm conclusions to be made on the comparative efficacy of vutrisiran versus inotersen. Despite limitations (e.g., heterogeneity across study design and patient populations) leading to uncertainty in the comparative efficacy estimates of vutrisiran versus patisiran, there was consistency in the direction of effects of the ITC, the post hoc analysis results, and the noninferiority TTR result in the HELIOS-A trial, which suggested similar efficacy between vutrisiran and patisiran.

The totality of these results, along with the identical mechanism of action of vutrisiran and patisiran, suggests that vutrisiran's efficacy is likely similar to that of patisiran in the treatment of patients with hATTR and stage 1 or stage 2 polyneuropathy.

Over 18 months of treatment, most participants reported at least 1 AE. The proportion of patients experiencing SAEs was numerically higher in the patisiran group of the HELIOS-A trial than in the vutrisiran group. A relatively small proportion of patients in both groups discontinued treatment due to AEs. Cardiac arrhythmias were recorded in one-quarter of patients treated with vutrisiran, which is similar to the proportion in placebo group (APOLLO trial) but higher than that in patisiran group (HELIOS-A). However, due to the small sample size, the deteriorating nature of the disease, and the progressive cardiac involvement, additional data are needed to draw firm conclusions on safety. The clinical experts consulted by CADTH anticipated that the safety profile of vutrisiran would be similar to that of patisiran.

Currently, there is no evidence to support the efficacy or safety of vutrisiran in patients with hATTR cardiomyopathy or in patients with advanced-stage hATTR-PN. However, the current indication and request for imbursement for vutrisiran is for adult patients with stage 1 or stage 2 polyneuropathy; as such, patients with hATTR cardiomyopathy and patients with stage 1 or stage 2 polyneuropathy are outside the scope of this review. No appropriate evidence exists to inform the efficacy of vutrisiran in patients who switch from patisiran.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of vutrisiran, 25 mg, administered as an SC injection once every 3 months in the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis.

Disease Background

The contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the CADTH review team.

TTR amyloidosis is a systemic, rare, life-threatening disease resulting from deposition of amyloid in multiple tissues. This disease has 2 main forms: hATTR) and wtATTR. Both conditions are characterized by the abnormal deposition of TTR protein in various organs, leading to organ dysfunction. The primary difference lies in their origins. hATTR is a genetic condition caused by mutations in the *TTR* gene, which leads to the production of unstable TTR proteins that are more prone to misfolding and amyloid deposition. In contrast, wtATTR occurs in the absence of *TTR* gene mutations.[9,12]

This review focuses on hATTR, a rare genetic condition characterized by its debilitating progression and wide-ranging clinical implications. This autosomal dominant disease is passed from generation to generation, potentially affecting multiple family members. The disease arises from a mutation in the *TTR* gene, which encodes a protein primarily produced by the liver. Normally, the TTR protein exists as a tetramer, a complex of 4 monomers; however, in hATTR, a gene mutation destabilizes the tetrameric protein structure, causing it to break down into unstable monomers and TTR fragments. These misfolded fragments subsequently aggregate, forming amyloid fibrils. Over time, these fibrils accumulate into deposits in a range of body organs, a hallmark of the disease. Importantly, the peripheral nervous system and the cardiac system are heavily affected, leading to 2 of the primary manifestations of the disease: polyneuropathy and cardiomyopathy.[2,3,13]

Clinically, hATTR often progresses rapidly and leads to worsening sensorimotor neuropathy, a condition that damages the patient's sensory and motor nerves and leads to escalating disability over time. Beyond sensorimotor neuropathy, the disease can also instigate a progressive autonomic neuropathy. This condition affects the nerves controlling the body's automatic functions, such as digestion, leading to gastrointestinal impairment, weight loss, and cashexia.[2] The life expectancy of patients with hATTR-PN ranges from 10 to 15 years following the time of symptoms developing.[3] The median survival of patients with hATTR-PN from the time of diagnosis is 4.7 years.[4]

In the clinical setting, hATTR-PN is assessed and classified using 2 key staging systems: the PND score, and the FAP staging system.[2] Both systems classify disease progression on a categorical scale, ranging from symptom-free (PND 0 or FAP stage 0) to a complete lack of ambulation, where patients may require a wheelchair or be bedridden (PND IV or FAP stage III).

hATTR-PN is classified as an ultra-rare disease, affecting approximately 10,000 individuals worldwide.[2,3] hATTR-PN has specific geographical endemic areas where prevalence is noticeably high; for example, in

Europe, the highest prevalence has been observed in northern Portugal and northern Sweden (as high as 50 per 100,000 inhabitants).[3,5]

According to the 2019 consensus recommendation, the list of tests and investigations for the follow-up of *TTR* mutation carriers are clinical evaluation, neurophysiology assessment, biomarkers measurement, and cardiac evaluation. Also, the minimum criteria to establish the diagnosis of symptomatic hATTR include "at least one quantified or objective symptom or sign definitively related to the onset of symptomatic hATTR; or at least one probably related symptom plus one abnormal definitive or confirmed test result; or 2 abnormal definitive or confirmed test results in the absence of clinical symptoms."[14]

The diagnosis of hATTR-PN should include gene sequencing to identify *TTR* variants and amyloid detection with tissue biopsy or bone scintigraphy scans.[15] In some patients, hATTR manifests in the form of cardiomyopathy, which is characterized by the infiltration of TTR amyloid fibrils in the myocardium, leading to cardiomyopathy and heart failure. Cardiac involvement manifestations include diastolic and, later in the disease course, systolic dysfunction, heart failure, palpitations, syncope, arrhythmia, heart block, and angina or infarction.[16] Autonomic dysfunction and peripheral neuropathy are the main determinants of quality of life, but cardiac involvement is the most important determinant of prognosis, with a median survival of 4 to 5 years when cardiac amyloidosis is present.[17]

Standards of Therapy

The contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the CADTH review team.

The current treatment landscape for patients with hATTR in Canada is guided by accurate diagnosis and distinction of the disease manifestation — whether the symptomatic presentation is neuropathy, cardiac disease, or a combination of both.

There are 2 primary treatments authorized for market use in Canada for managing hATTR-PN: patisiran and inotersen. Both these therapies have received a positive CADTH recommendation.[6,7] Additionally, tafamidis (Vyndaqel), a TTR tetramer stabilizer, has been indicated for use in patients with ATTR who present primarily with cardiomyopathy.[8]

Historically, orthotopic liver transplant was employed as a therapeutic option, especially for a selective cohort of patients in the early stages of hATTR-PN. This procedure was essential, as it eliminated variant TTR from circulating in the liver by substituting the native liver (responsible for the genetic defect that leads to variant TTR production) with a liver free from the defect.[18] However, due to the complications and the need for immunosuppression regimens as a result of organ transplant, combined with the evolution of therapies like patisiran and inotersen, there has been a marked decline in liver transplant over the past 2 decades, making orthotopic liver transplant increasingly obsolete.[19]

The 2022 Canadian guidelines highlight the use of both patisiran and inotersen as first-line treatments for managing hATTR-PN.[19] The guidelines further emphasize a shift away from liver transplant as a

primary intervention, citing potential perioperative complications and the ensuing need for continuous immunosuppression.[19]

For patients diagnosed with neuropathy, small interfering (si)RNA or oligonucleoside therapies emerge as potent disease-modifying strategies. These treatments stabilize the otherwise persistent disease progression once neuropathy commences. Furthermore, symptomatic treatments are commonly prescribed, including cardiac medications, interventions for neuropathic pain, surgical solutions like those for severe symptomatic compressive neuropathy (e.g., carpal tunnel syndrome), and management techniques for autonomic dysfunction, which often prominently manifests in patients with hATTR.

Drug Under Review

Vutrisiran is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR. The recommended dose of vutrisiran is 25 mg administered via SC injection once every 3 months. Vutrisiran has not been previously reviewed by CADTH.

Vutrisiran is a chemically modified double-stranded siRNA that specifically targets variant and wild-type TTR messenger RNA (mRNA). Through a natural process called RNA interference, vutrisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in a reduction in serum TTR protein and a consequent reduction in amyloid deposits in tissues.

Vutrisiran employs the same mechanism of action as patisiran (targeting TTR mRNA, which leads to decreased TTR protein production). Patisiran and vutrisiran have the same sponsor. Vutrisiran has a novel delivery mechanism (enabled by the enhanced stabilization chemistry GalNAc platform). The high metabolic stability of the medicinal substance due to its use of enhanced stabilization chemistry, in combination with the use of GalNAc ligands to target the medicinal substance to the liver, allows for infrequent (administered every 3 months) SC injections ([redacted]). Patisiran involves IV administration (every 3 weeks), which last [redacted] each. Patisiran uses a weight-based dosing, whereas vutrisiran is administered as a fixed dose.

The Health Canada indication for vutrisiran is for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR. The Notice of Compliance for vutrisiran was granted on October 18, 2023. The sponsor's reimbursement request is per the indication.

The FDA has approved vutrisiran for the treatment of the polyneuropathy of hATTR in adults. It should only be administered subcutaneously and by a health care professional.

The EMA has approved vutrisiran for the treatment of hATTR in adult patients with stage 1 or stage 2 polyneuropathy.

The key characteristics of vutrisiran are summarized in Table 4 with other treatments available for adults with hATTR.

Table 4: Key Characteristics of Vutrisiran, Patisiran, Inotersen, and Tafamidis

Characteristic	Vutrisiran	Patisiran	Inotersen	Tafamidis
Mechanism of action	siRNA-mediated degradation of TTR mRNA in the liver	siRNA-mediated degradation of TTR mRNA in the liver	Selective binding of inotersen to TTR mRNA causes the degradation of both mutant and wild-type TTR mRNA	Stabilizer of TTR
Indication[a]	For the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR	Treatment of polyneuropathy in adult patients with hATTR	Treatment of stage1 or 2 polyneuropathy in adult patients with hATTR	Treatment of cardiomyopathy due to transthyretin-mediated amyloidosis (wild-type or hereditary); reduces cardiovascular mortality and cardiovascular-related hospitalization
Route of administration	Subcutaneous	Intravenous	Subcutaneous	Oral
Recommended dose	25 mg every 3 months	0.3 mg/kg to a maximum dose of 30 mg once every 3 weeks	284 mg inotersen (300 mg inotersen sodium once weekly)	80 mg once a day
Serious adverse effects or safety issues	Reduced vitamin A levels Contraindication: severe hypersensitivity to the product	Infusion-related reactions, reduced vitamin A levels Contraindication: severe hypersensitivity to the product	Thrombocytopenia, glomerulonephritis, reduced vitamin A levels Contraindicated in patients with hypersensitivity to the product, a platelet count < 100×10^9/L, a urine protein to creatinine ratio ≥ 113 mg/mmoL, an estimated glomerular filtration rate < 45 mL/min/1.73 m^2, and severe liver impairment	Contraindication: severe hypersensitivity to the product
Other	Must be administered by a health care professional. Vitamin A supplementation is recommended.	Must be administered by a health care professional in a supervised setting. Premedications are required to minimize the risk of infusion-related reactions (oral acetaminophen, IV corticosteroid, IV H_1 blocker, and IV H_2 blocker).	Monitoring of platelet count is required every 2 weeks for platelet levels > 100×10^9/L (increased monitoring and dose adjustments are required for levels < 100×10^9/L, and drug discontinuation is required for levels < 25×10^9/L). Vitamin A	None

Characteristic	Vutrisiran	Patisiran	Inotersen	Tafamidis
		Vitamin A supplementation is recommended.	supplementation is recommended.	

H_1 blocker = histamine-1 receptor antagonist; H_2 blocker = histamine-2 receptor antagonist; hATTR = hereditary transthyretin-mediated amyloidosis, mRNA = messenger RNA, siRNA = small interfering RNA, TTR = transthyretin.

[a]Health Canada–approved indication.

Sources: Vutrisiran product monograph,[20] patisiran product monograph,[21] inotersen product monograph,[22] tafamidis product monograph.[23]

Stakeholder Perspectives

Patient Group Input

This section was prepared by the CADTH review team based on the input provided by patient groups. The full original patient input received by CADTH have been included in the Stakeholder section of this report.

CADTH received 1 patient group submission from TAC. TAC is a not-for-profit organization dedicated to educating and supporting patients living with all forms of transthyretin amyloidosis. TAC primarily represents patients, caregivers, families, and some volunteer health workers in Canada, but also has members in the US, UK, and other European countries.

TAC provided input based on qualitative interviews conducted with patients who had experience with both vutrisiran and patisiran. The interviewees mentioned that vutrisiran is more convenient than patisiran, as the administration is less frequent (every 3 months versus every 3 weeks), less time consuming (3 hours for patisiran injection procedure, plus travel time), and the root of administration is SC rather than IV. Patients stated that they were able to learn to administer a SC injection, which freed them from having to rely on an infusion network, need preinjection therapy and clinic visits and a caregiver for clinic visits, and miss a workday.

Furthermore, the interviewees found that vutrisiran may decrease the pharmacoeconomic burden of illness related to hATTR; avoiding the need for IV administration and being able to keep patients out of hospital centres may benefit overburdened health systems and protect frail immunocompromised patients. Patients also believed that the risk of falls may be lessened, which would lead to fewer hospital visits and a better maintenance of quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of

the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of hATTR.

Unmet Needs

According to the clinical experts consulted by CADTH, the current treatment landscape for hATTR primarily focuses on slowing disease progression; there are no therapies available to reverse neuropathy. Existing treatments, including therapies like inotersen and procedures like liver transplant, come with notable risks, such as thrombocytopenia, glomerulonephritis, and complications from immunosuppression. Additionally, treatment administration varies, with some requiring specialized IV access, and there is a noticeable inconsistency in clinical outcomes between cardiac and neurologic responses. Critically, comprehensive data on functional outcomes and overall patient quality of life remain scant, underscoring the unmet needs in this therapeutic domain.

Place in Therapy

According to the clinical experts consulted by CADTH, vutrisiran would likely be offered as first-line treatment to most patients with hATTR-PN. There exists a subset of patients who might have undergone liver transplant or taken other genetic therapies (like inotersen), tetramer stabilizers (such as tafamidis), or a comparable genetic therapy (like patisiran). For these individuals, initiating vutrisiran may be a viable option, although there is little evidence supporting its use in patients who have undergone liver transplant or received other forms of genetic or tetramer stabilizer therapy. There is a theoretical inclination toward combining therapies to evaluate the synergistic benefits of both reducing TTR protein production and stabilizing TTR tetramers, but there is little evidence to support treatment combinations. Vutrisiran is unlikely to change the treatment paradigm, but it may provide improved convenience and additional efficacy and safety data in the same class of therapy.

Patient Population

According to the clinical experts consulted by CADTH, the optimal patients would mimic the conditions of patients in the relevant clinical trial, which included adults with confirmed neuropathy through a reliable assessment and without other contributions to neuropathy. Ideally, this would occur through an objective test, such as nerve conduction studies or small-fibre assessments, to ensure the presence of neuropathy. Improving access to these kinds of assessments done in a reliable and accurate way would help prevent underdiagnosis and overdiagnosis. Access to genetic testing may be limited for patients and for at-risk family members. There has been improved access to testing through free testing supported by pharmaceutical companies and provincial labs and now includes testing with saliva or cheek swabs in addition to blood testing. Although all patients with neuropathy may benefit from treatment with vutrisiran, patients with rapidly advancing neuropathy may experience the most obvious treatment effects when disease progression has been arrested.

Assessing the Response Treatment

According to the clinical experts consulted by CADTH, specific metrics are used to evaluate treatment efficacy in patients with hATTR. A reduction in mortality is a critical outcome, particularly for those with

advanced amyloidosis. Another key outcome for this patient group is the rate of serious complications leading to hospitalization.

For a detailed understanding of disease progression, especially from the neuromuscular perspective, it is common to monitor changes in neuropathy outcomes and autonomic symptoms. Objective measures include nerve conduction studies and small-fibre tests, such as laser Doppler imaging and quantitative sensory thresholds, which measure large-fibre and small-fibre function, respectively.

Various neuropathy questionnaires and scales are employed to gauge patient experiences. These include the COMPASS scale for autonomic function, the Toronto Clinical Neuropathy Scale, the Overall Neuropathy Limitation Scale, and the R-ODS for neuropathies. A clinical examination, which includes assessment of the patient's gait, provides a tangible indicator of neuropathic progression.

A patient's overall functioning, quality of life, and ability to perform daily activities are determined from their comprehensive clinical history. Continuous clinical assessments using this approach ensure accurate monitoring of the patient's response to treatment. In addition, it is common to monitor TTR levels in patients as part of the monitoring of response to treatment.

The timing of assessments depends on the severity of the disease. If a patient is asymptomatic or minimally symptomatic, yearly assessment is acceptable; in more active patients, assessment every 3 or 6 months is appropriate.

Discontinuing Treatment

The decision to discontinue therapy arises when AEs, such as extremity pain and/or arthralgia, cardiac effects, or vision disturbances due to vitamin A depletion, outweigh the benefits of ongoing treatment. The decision to discontinue treatment takes into account patient tolerance, willingness to continue treatment, and potential for therapeutic efficacy. Furthermore, discontinuation might be contemplated if neuropathy progression aligns with the expected course of hATTR-PN, which could involve transitioning to an alternative treatment approach in specific instances. Although the specific outcomes of significance vary for each patient with neuropathy, they encompass factors like lower extremity function, mobility, and upper extremity dexterity, and function. These aspects can be effectively measured with neuropathy-specific scales. Additionally, improvements in autonomic symptoms, like dizziness, bladder and bowel dysfunction, and sweating abnormalities, are important indicators of treatment effectiveness. Overall, the primary expectation is to continue therapy unless there is a major issue with AEs, patient preference and/or inconvenience, lack of efficacy, and disease progression despite a significant trial of therapy.

Prescribing Considerations

According to the clinical experts consulted by CADTH, the most effective approach involves designating a clinician as the principal caregiver for patients with this condition who has experience overseeing patients with neuropathy, which encompasses conditions with progressive large-fibre, small-fibre, and autonomic neuropathies. This provision of care can take place in either a hospital or clinic environment, provided it is equipped with the capacity and resources to comprehensively address all facets of advanced neuropathy, including cardiac and autonomic symptoms.

Clinician Group Input

This section was prepared by the CADTH review team based on the input provided by clinician groups. The full original clinician group input received by CADTH have been included in the Stakeholder section of this report.

One clinician from the Amyloidosis Program of Calgary submitted input to CADTH in the form of a letter. The clinician expressed that the dosing and regimen of vutrisiran are improvements over the currently approved patisiran therapy, in that treatment is only administered every 3 months, rather than every 3 weeks. In addition, the clinician noted that vutrisiran has the potential to improve patients' quality of life while attenuating disease progression.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 5.

The drug plan's input focuses on the selection of relevant comparators, notably vutrisiran and patisiran, for patients with hATTR-PN. The input seeks expert perspectives on various aspects, as outlined in Table 5.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
One submitted trial (HELIOS-A) and an NMA support the comparable efficacy of vutrisiran and patisiran in patients with hATTR-PN. Alnylam is the market authorization holder for both Amvuttra (vutrisiran) and Onpattro (patisiran). They advise that vutrisiran (SC q.3.m.) is expected to replace patisiran (IV q.3.w.) as the standard of care for hATTR-PN in Canada. Tegsedi (Inotersen) is also a relevant comparator, indicated by Health Canada for the treatment of hATTR-PN; the CADTH reimbursement criteria (December 2019) are identical to those of patisiran (July 2019).	This is a comment from the drug plans to inform CDEC deliberations.
Patisiran and inotersen are both reimbursed in the majority of, but not all, federal, provincial, and territorial jurisdictions.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
The key inclusion and exclusion criteria for the HELIOS-A (vutrisiran) and APOLLO (patisiran) trials are the same. The CADTH reimbursement criteria for patisiran and inotersen are also same. Consider alignment with the initiation criteria for patisiran and inotersen, if appropriate.	Eligibility for vutrisiran should ideally follow the same eligibility as patisiran. There is no a priori reason to suggest the need for additional patient characteristics.

Drug program implementation questions	Clinical expert response
• Are there any additional patient characteristics beyond disease diagnosis, scoring, or staging that should be considered for eligibility criteria for vutrisiran?	
The pre-NOC indication and reimbursement request for vutrisiran is for the treatment of hATTR in adults. The submitted trial (HELIOS-A) only evaluated vutrisiran for hATTR-PN. Given the heterogeneous nature of the disease, there is potential for vutrisiran to be used more broadly, including for patients with cardiomyopathy. Special subtypes to consider separately would include: • Are there other patient subtypes that should be assessed for eligibility for vutrisiran, such as patients with: ◦ hATTR cardiomyopathy ◦ a confirmed genetic mutation but presymptomatic (patients in the HELIOS-A trial were in FAP stage I or stage II at baseline) ◦ advanced polyneuropathy (the HELIOS-A trial did not include any patients in FAP stage III at baseline), or ◦ previous liver transplant	The clinical experts suggested that evidence of the efficacy of vutrisiran may have limited generalizability to the following patient populations: • patients with cardiomyopathies • patients with advanced stage of polyneuropathies • post liver transplant patients • patients with confirmed genetic mutation but are presymptomatic. Note: NOC was issued on October 18, 2023, with the following indication: Amvuttra (vutrisiran injection) is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. The sponsor updated their request for reimbursement to be per indication.
Considerations for continuation or renewal of therapy	
The primary end point in the HELIOS-A trial was the mNIS+7. In 2019, the clinical experts consulted for the CADTH reviews of patisiran and inotersen advised that mNIS+7 is not used in clinical practice to monitor patients and that some components (i.e., quantitative sensory testing) are not available in all centres. There are no clearly defined renewal criteria for patisiran or inotersen. • What objective measures can be employed to assess the efficacy of vutrisiran over time, ensuring ongoing reimbursement?	The clinical experts suggested that similar approaches as the ones already in place should be implemented for patients on patisiran.
Considerations for discontinuation of therapy	
The discontinuation criteria for patisiran and inotersen include being permanently bedridden and dependent on assistance for basic activities of daily living, and receiving end-of-life care. Consider alignment with the discontinuation criteria for patisiran and inotersen, if appropriate. • Are there additional parameters that can be used to define loss of response, absence of clinical benefit, or disease progression specific to vutrisiran?	The clinical experts noted that no additional parameters are needed beyond what is already in place for patients on patisiran.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
The product monograph notes that vutrisiran should be administered by a health care professional. There may be limited access to specialists with experience in the diagnosis and management of hATTR in some jurisdictions. • Is there evidence supporting the combination use of vutrisiran with other RNA-targeted treatments (like inotersen), TTR stabilizers (such as tafamidis for ATTR cardiomyopathy), or diflunisal (off-label)? • Should patients who are already on another RNA-targeted treatment or TTR stabilizer be eligible for treatment with vutrisiran?	The clinical experts noted that no current evidence exists to support the combination use of vutrisiran with other RNA-targeted treatments or TTR stabilizers. Therefore, the clinical experts felt that it would be unlikely that such a combination of treatments would be used.
Generalizability	
There is the potential for patients currently receiving patisiran (possibly inotersen) to be switched to vutrisiran. • Is it appropriate for patients currently receiving patisiran (or possibly inotersen) to switch to vutrisiran?	The clinical experts did not anticipate any issues with switching patients receiving patisiran (or possibly inotersen) to vutrisiran.
Care provision issues	
The product monograph notes that vutrisiran should be administered by a health care professional. The sponsor has indicated that vutrisiran will be imported, distributed, and administered through Innomar Strategies. Vutrisiran reduces serum vitamin A levels, so vitamin A supplementation is advised. Genetic testing is required to confirm a diagnosis of hATTR and differentiate it from other causes of amyloidosis. • Beyond administration by health care professionals, are there any additional concerns regarding the preparation, storage, administration, or dispensing of vutrisiran?	The clinical experts noted that although some patients may have a preference for infusions by health care professionals, most patients will likely be able to self-administer vutrisiran.
Regarding vitamin A supplementation due to reduced serum vitamin A levels caused by vutrisiran, are there specific recommendations or considerations for its administration?	There is no specific recommendation for vutrisiran beyond what is already implemented with patisiran.
System and economic issues	
Vutrisiran costs $143,041 per prefilled syringe. The sponsor's BIA indicates that vutrisiran is anticipated to be associated with a cost of $173 million over the 3-year forecast horizon; a net budget increase of $24 million over 3 years vs. the current scenario (patisiran and inotersen only).	This is a comment from the drug plans to inform CDEC deliberations.
Patisiran and inotersen have successfully completed price negotiations for hATTR-PN. Alnylam is the market authorization holder for patisiran and is aware of its negotiated price.	This is a comment from the drug plans to inform CDEC deliberations.

ATTR = transthyretin-mediated amyloidosis; BIA = budget impact analysis; CDEC = Canadian Drug Expert Committee; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin-mediated amyloidosis and polyneuropathy; mNIS+7 = modified Neuropathy Impairment Score + 7; NMA = network meta-analysis; NOC = Notice of Compliance; q.3.m. = every 3 months; q.3.w. = every 3 weeks; SC = subcutaneous; TTR = transthyretin.

Clinical Evidence

The objective of the Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of vutrisiran, 25 mg, administered as an SC injection once every 3 months for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR. The focus will be placed on comparing vutrisiran to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of vutrisiran is presented in 2 sections, with CADTH's critical appraisal of the evidence included at the end of each section. The first section, the Systematic Review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. CADTH's assessment of the certainty of the evidence in this first section using the GRADE approach follows the critical appraisal of the evidence. The second section includes indirect evidence from the sponsor.

Included Studies

Clinical evidence from the following are included in the CADTH review and appraised in this document:

- 1 pivotal phase III trial and 1 phase III trial identified in the systematic review
- 1 ITC.

Systematic Review

The contents within this section have been informed by materials submitted by the sponsor. The following have been summarized and validated by the CADTH review team.

Description of Studies

Characteristics of the included studies are summarized in Table 6.

HELIOS-A was a phase III, randomized, open-label, multicentre trial that evaluated the efficacy and safety of vutrisiran over 18 months in patients with hATTR-PN.[27] The study had 2 study groups: a vutrisiran treatment group and a patisiran treatment group.[1,25] Adult patients with hATTR (N = 164) from 57 sites in 22 countries (Table 6) were randomized in a 3:1 ratio to receive vutrisiran 25 mg SC every 3 months or patisiran 0.3 mg/kg IV infusion every 3 weeks for 18 months.[28] There were 2 HELIOS-A sites in Canada, each with 1 patient (1 patient received vutrisiran and the other received patisiran). Randomization of treatment assignment was stratified by *TTR* genotype and baseline NIS. Assessment of inclusion and exclusion criteria was performed during a 42-day screening period. The APOLLO placebo group served as an external comparator for the primary end point and all secondary end points, except for the percent reduction in serum TTR, for which a prespecified within-trial noninferiority test of vutrisiran versus patisiran was conducted. The sponsor reported that the patisiran group in the HELIOS-A trial was to validate the use of the external control group from the APOLLO trial, to establish a similar reduction in serum TTR, and to allow assessment of tolerance between the 2 treatments.

For most inferentially evaluated efficacy end points, the null hypothesis was that there is no difference between vutrisiran and placebo (APOLLO trial). For the TTR percent reduction end point, the null hypothesis was that vutrisiran is inferior to patisiran (i.e., the difference in median TTR reduction [vutrisiran – patisiran] was ≤ –10%). The primary outcome was the change from baseline in mNIS+7 for vutrisiran versus placebo (APOLLO trial). The time point of this primary outcome was 9 months for the purpose of regulatory submission to the US, Japan, and Brazil, but was 18 months for the purpose of regulatory submission to the European Union and other regions. Based on input from clinical experts and other stakeholders, efficacy end points at month 18 are presented in this report. The study cut-off date for month 18 analyses was August 26, 2021.

The sponsor followed a hierarchical approach to control for type I error of multiple comparisons for the primary and secondary end points; subsequent hypotheses were only tested if the previous null hypothesis was rejected. Results for the primary end point, mNIS+7 change from baseline at month 18, had to be statistically significant to declare a positive trial.[29] The order of the hierarchical approach is as follows:

1. mNIS+7 change from baseline at month 18
2. Norfolk QoL-DN total score change from baseline at month 18
3. 10MWT gait speed change from baseline at month 18
4. mBMI (BMI [kg/m^2] multiplied by serum albumin level [g/L]) change from baseline at month 18
5. R-ODS change from baseline at month 18
6. TTR percent reduction through month 18.

Table 6: Details of Studies Included in the Systematic Review

Detail	HELIOS-A (pivotal)	APOLLO
Designs and populations		
Study design	Phase III, multinational, randomized, open-label, 18-month study to evaluate the efficacy and safety of vutrisiran in patients with hATTR. Patients were randomized 3:1 to receive vutrisiran or patisiran. **The placebo group of the APOLLO study was used as an external comparator for vutrisiran in analyses of the primary and secondary efficacy end points, excluding serum TTR reduction, in the HELIOS-A study.**	Phase III, global, randomized, double-blind, placebo-controlled, 18-month study to evaluate the efficacy and safety of patisiran in patients with hATTR. Patients were randomized 2:1 to receive patisiran or placebo.
Locations	The HELIOS-A trial was conducted at 57 sites in 22 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada [2 sites], Cyprus, France, Germany, Greece, Italy, Japan, Republic of Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, the UK, and the US).	The APOLLO trial was conducted at 52 sites in 21 countries (Argentina, Australia, Brazil, Bulgaria, Canada [1 site], Cyprus, France, Germany, Italy, Japan, Republic of Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, Turkey, the UK, and the US).
Patient enrolment dates	**Start date:** February 2019 **End date:** November 2020	**Start date:** November 2013 **End date:** August 2017

Detail	HELIOS-A (pivotal)	APOLLO
Randomized (N)	**N** = 164 **Vutrisiran**: n = 122 **Patisiran**: n = 42	**N** = 225 **Placebo**: n = 77 **Patisiran** n = 148
Inclusion criteria	Key criteria for inclusion in both studies (HELIOS-A and APOLLO): • male or female aged 18 to 85 years • diagnosis of hATTR with documented *TTR* variant (for the APOLLO trial, diagnosis of FAP[a] with documented *TTR* variant) • NIS of 5 to 130 • KPS ≥ 60% • a PND score of ≤ 3b (this criterion must be met at screening visit 2)	
Exclusion criteria	Key criteria for exclusion in both studies (HELIOS-A and APOLLO): • prior liver transplant or planning to undergo liver transplant during the study period • other known causes of sensorimotor and/or autonomic neuropathy (i.e., other than hATTR) or other known forms of non-hATTR • NYHA heart failure classification > II • current or future participation in another investigational device or drug study scheduled to occur during this study or receipt of an investigational drug or device in the 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to dosing (day 1) • receipt of prior TTR-lowering treatment or previous participation in a gene therapy trial for hATTR • currently taking tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these drugs, must have completed a 14-day washout prior to dosing (day 1) • currently taking diflunisal; if previously on this drug, must have at least a 3-day washout prior to dosing (day 1)	
Drugs		
Intervention	**Vutrisiran**: 25 mg SC q.3.m.	**Patisiran**: 0.3 mg/kg IV q.3.w.
Comparator	**Patisiran**: 0.3 mg/kg IV q.3.w.	**Placebo**: IV q.3.w.
Study duration		
Screening phase	42 days	42 days
Treatment phase	18 months	18 months
Extension phase	18-month RTE period to evaluate continued administration of vutrisiran q.3.m. (25 mg) or administration of vutrisiran q.6.m. (50 mg SC). This follow-up phase is ongoing.	Patients from the APOLLO trial are eligible to enrol in the global OLE trial of patisiran (NCT02510261) to evaluate long-term dosing of patisiran q.3.m.[24] Primary completion of the trial occurred on November 23, 2022.
Outcomes		
Primary, secondary, and exploratory end points	Primary (vs. external placebo arm from the APOLLO trial): • mNIS+7 (month 9 and month 18[b]) Secondary (vs. external placebo group from the APOLLO trial): • Norfolk QoL-DN (key secondary outcome; month 9 and month 18)	For the primary and secondary outcome measures, patisiran was compared to the within-trial placebo group from the APOLLO trial at month 18. Primary: • mNIS+7 Secondary:

Detail	HELIOS-A (pivotal)	APOLLO
	• 10MWT (Month 9 and Month 18) • mBMI (month 18) • R-ODS (month 18) Secondary (vs. within-trial patisiran group from the HELIOS-A trial): • serum TTR levels (noninferiority analysis; month 18) Select exploratory analyses: • PND score change (month 18)	• Norfolk QoL-DN (key secondary outcome) • NIS-W • 10MWT • mBMI • R-ODS • COMPASS 31 Select exploratory analyses: • PND score • serum TTR levels
Publication status		
Publications	**Clinicaltrials.gov:** NCT03759379 **Primary publication:** Adams et al. (2023)[25]	**Clinicaltrials.gov:** NCT01960348 **Primary publication:** Adams et al. (2018)[26]

10MWT = 10-metre walk test; COMPASS 31 = 31-question Composite Autonomic Symptom Score; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin-mediated amyloidosis; KPS = Karnofsky Performance Scale; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score + 7; NIS = Neuropathy Impairment Score; NIS-W = Neurological Impairment Score-Weakness; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; q.3.m. = every 3 months; q.3.w. = every 3 weeks; q.6.m. = every 6 months; R-ODS = Rasch-built Overall Disability Score; RTE = randomized treatment extension; SC, subcutaneous; TTR, transthyretin.

[a]The term FAP has historically been used to describe hATTR-PN. Thus, the patient populations in the APOLLO and HELIOS-A trials had the identical hereditary condition, namely hATTR-PN.

[b]Month 9 assessment of mNIS+7 served as the primary end point for the FDA and select other regulatory bodies; the month 18 assessment served as primary end point for the EMA, but Health Canada retained months 9 and 18 as end points for analyses.

Source: Sponsor's Summary of Clinical Evidence.[1]

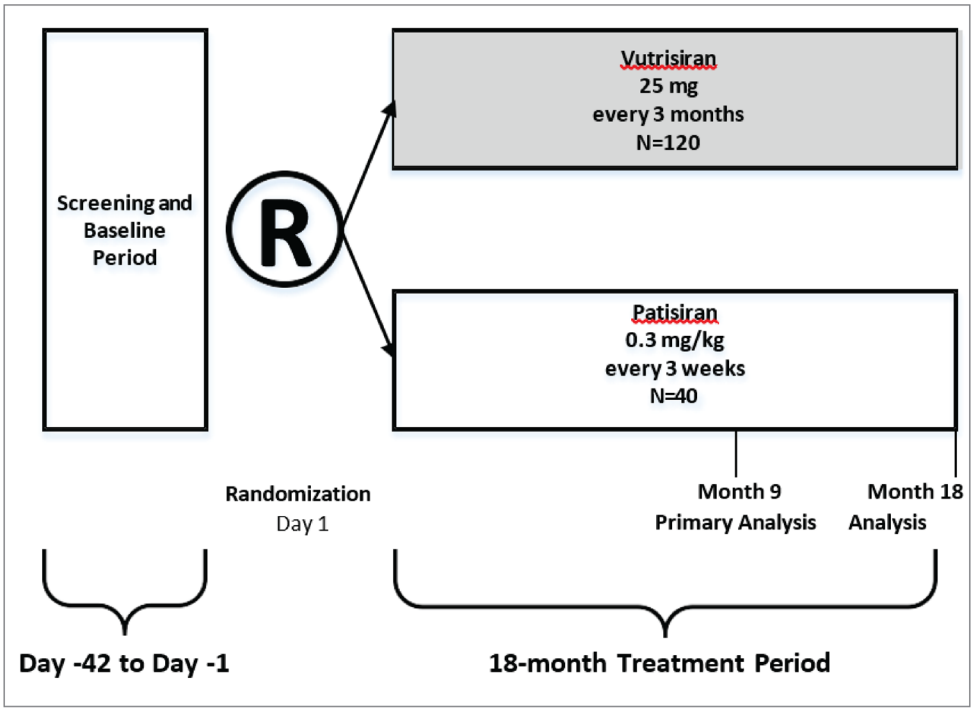
Subsequent to study completion and submission to the EMA, the sponsor, at the request of the EMA, conducted a post hoc analysis comparing the efficacy (including primary and secondary outcomes) of vutrisiran to that of patisiran in the HELIOS-A trial. Considering the relevance of these comparative efficacy estimates, they have been included in this report.[1] A flow diagram of HELIOS-A study design is presented in Figure 1.

The sponsor conducted a treatment extension period after the completion of the 18-month treatment period, in which patients were randomized in a 1:1 ratio to receive vutrisiran 25 mg every 3 months or vutrisiran 50 mg every 6 months over a period of 18 months. Due to the nature of the design and the treatment dose, which does not align with the Health Canada recommended dose, available information from the extension study is not reported in this report.

APOLLO was a phase III, international, multicentre, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of patisiran over 18 months in patients with hATTR-PN.[26] Adult patients with hATTR (N = 225) were recruited from 52 sites in 21 countries (Table 6). There was 1 APOLLO site in Canada, with a total of 5 patients (4 received patisiran and 1 received placebo). Patients were randomized in a 2:1 ratio to receive patisiran (n = 148; 0.3 mg/kg every 3 weeks by IV infusion for 18 months) or placebo (normal saline; n = 77).[26] Randomization was stratified by level of baseline neuropathy (NIS, 5 to 49 versus 50 to 130), TTR genotype (early onset V30M and < 50 years of age at onset versus all other mutations [including late-onset V30M]), and previous tetramer stabilizer use (tafamidis or diflunisal) versus no previous tetramer

stabilizer use. Assessment of inclusion and exclusion criteria was performed during a 42-day screening period. The study cut-off date for month 18 analyses was August 17, 2017.[26]

Figure 1: HELIOS-A Study Design Flow Diagram



R = randomization.

Sources: HELIOS-A Clinical Study Report;[27] sponsor's Summary of Clinical Evidence.[1]

Populations

Inclusion and Exclusion Criteria

The key eligibility criteria for the HELIOS-A and APOLLO trials are provided in Table 6. Because the design of the HELIOS-A trial included the use of an external placebo control group, reusing the control group from the APOLLO trial, the sponsor aimed to align the inclusion and exclusion criteria of the HELIOS-A trial with those used in the APOLLO trial. The eligibility criteria for these studies were highly similar, including identical key inclusion and exclusion criteria. There are no notable differences to highlight. Specifically, patients were aged 18 to 85 years, diagnosed with hATTR-PN (the APOLLO trial used the term FAP, as historically this was the diagnosis of hATTR-PN), and had confirmed *TTR* mutation. Inclusion required an NIS ranging from 5 to 130, along with a PND score of less than or equal to 3b, indicating no impediment to walking with the assistance of 2 sticks or crutches. Exclusions were applicable to individuals with prior liver transplant, an NYHA heart failure classification of III or IV (indicating symptoms during less than regular physical activity or even at rest), a history of uncontrolled cardiac arrhythmia or unstable angina, acute coronary syndrome in the previous 3 months, type I diabetes, type II diabetes mellitus for at least 5 years, or other known causes of polyneuropathy.

In the APOLLO trial, patients who had previously participated in a clinical trial involving antisense oligonucleotides were required to undergo a 3-month washout period before starting the study drug administration; in the HELIOS-A trial, patients required a washout period of 30 days or 5 half-lives for any investigational drug. In the HELIOS-A trial, individuals who had been taking tafamidis, doxycycline, or tauroursodeoxycholic acid before enrolling had to complete a 14-day washout period; for those on diflunisal, a washout period of at least 3 days was necessary before randomization. Finally, patients were excluded from the HELIOS-A trial if they had received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR.

Interventions

In the HELIOS-A trial, vutrisiran was administered via SC injection by study personnel. Two presentations of vutrisiran were administered in the HELIOS-A trial; 1 was a vial for SC injection and the other was a prefilled syringe with a passive needle safety system, which was implemented in Amendment 1.[27] For both formats, administration involved a total injection volume of 0.5 mL containing 25 mg of vutrisiran.[27] Patisiran was administered in the HELIOS-A trial in the same manner as described subsequently for the APOLLO trial. No dose modification was allowed. Patients and investigators were allowed to stop the study drug at any point. Furthermore, dosing was stopped if sustained elevation of liver function tests was observed.

In the APOLLO trial, both patisiran or normal saline (placebo) were administered by study personnel as an IV infusion over 80 minutes (1 mL/min for the first 15 minutes and 3 mL/min thereafter).[26,30] All patients received the following premedications or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen or paracetamol; a histamine-1 receptor (H_1) blocker (e.g., ranitidine or famotidine); and an H_2 blocker.

HELIOS-A was an open-label trial, whereas APOLLO was a double-blind trial. In the APOLLO trial, all site personnel were blinded to the study treatment, except the pharmacist and designated site personnel who set up, dispensed, and prepared the infusion. Patisiran has a slightly opalescent colour relative to the clear saline (placebo); therefore, all infusion bags and lines were covered with amber bags and line covers by the unblinded personnel to prevent visualization by the blinded study personnel and patient. All patients were blinded to study drug assignment and received an IV infusion every 3 weeks, with identical volumes for patisiran and placebo. Blinded personnel administered the study drug and monitored the patient during and after the infusion.[30]

Concomitant Therapy

Prohibited medications during the study included inotersen, tafamidis, diflunisal, and taurodeoxycholic acid. Use of patisiran outside of the protocol-specified administration was also prohibited. Any investigational drug other than the assigned ones were not permitted during the study. A similar approach was used in both trials.

Protocol Amendments

The original protocol was finalized on October 11, 2018. Since then, there have been 4 global protocol amendments plus a number of country-specific protocol amendments. Relevant amendments include the

removal of all-cause hospitalization and death as a secondary end point, and a number of changes related to the impact of COVID-19, including removing the Norfolk QoL-DN total score as a coprimary end point and instead including it as a key secondary end point.

Outcomes

A list of efficacy end points assessed in this Clinical Review Report is provided in Table 7 and is followed by descriptions of the outcome measures. Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence, as well as any outcomes identified as important to this review, according to the clinical experts consulted by CADTH and stakeholder input from patient and clinician groups and public drug plans. Using the same considerations, the CADTH review team selected end points that were considered to be most relevant to inform CADTH's expert committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points were assessed using GRADE. Select notable harms outcomes considered important for informing CADTH's expert committee deliberations were also assessed using GRADE.

Table 7: Outcomes Summarized From the Studies Included in the Systematic Review

Outcome measure	Time point	HELIOS-A end point (comparison vs. external placebo group from APOLLO)	APOLLO end point (comparison vs. placebo)
PND score – change from baseline	Month 18	Exploratory	Exploratory
mNIS+7 – change from baseline	Month 18	Primary[a]	Primary[a]
R-ODS	Month 18	Secondary[a]	Secondary[a]
Norfolk QoL-DN – change from baseline	Month 18	Secondary[a]	Secondary[a]
TTR proteins levels – change from baseline	Month 18	Secondary[a]	Exploratory
Mortality	Month 18	Safety	Safety
Overall survival[b]	Month 18	NR	NR
Hospitalization[b]	Month 18	NR	NR
COMPASS 31[b]	Month 18	NR	Secondary

COMPASS 31 = 31-question Composite Autonomic Symptom Score; mNIS+7 = modified Neuropathy Impairment Score + 7; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NR = not reported; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Score; TTR = transthyretin.

[a]Statistical testing for these end points was adjusted for hierarchical testing. Note that the month 9 assessment of mNIS+7 served as the primary end point for the FDA and select other regulatory bodies; Health Canada retained month 9 and month 18 as primary end points for analyses.

[b]Outcomes determined as clinically relevant by stakeholders consulted on this review, including the clinical experts, were not part of the HELIOS-A trial.

Sources: HELIOS-A Clinical Study Report 2,[27] APOLLO Clinical Study Report,[30] sponsor's Summary of Clinical Evidence.[1]

PND Score

The PND score provides a measurable indication of ambulatory function and the level of disability associated with polyneuropathy. No minimal clinically important difference (MCID) for change in PND score has been established. PND score categories are defined in such a way that a change in category represents a change in ambulatory status (reflecting a milestone in the progression of disability). Lower scores indicate greater

ambulatory function. A finding of no change (i.e., maintenance) in PND score over time reflects preservation of ambulatory function and therefore a halting of advancing disease impairment. There are 5 scores for PND, as follows:

- PND score I: sensory disturbances, preserved walking capability
- PND score II: impaired walking capability but able to walk without supportive devices (e.g., crutches)
- PND score IIIA: only able to walk with the help of 1 stick or crutch
- PND score IIIB: only able to walk with the help of 2 sticks or crutches
- PND score IV: confined to a wheelchair or bedridden.

PND score was identified as a relevant and important clinical outcome by the clinical experts consulted by CADTH and patient input groups on this review. PND directly informs on the extent of the ability of patients to ambulate, and loss of ambulation is clinically meaningful as a sign of disease progression. In addition, this outcome is a key source of input for the sponsor-submitted health economic model.

Modified Neuropathy Impairment Score + 7

The mNIS+7 assesses the progression of the motor and sensory aspects of polyneuropathy, as well as some autonomic manifestations, such as postural hypotension, and correlates with both FAP and PND scores.[31] The mNIS+7 assessment scale ranges from 0 to 304 points. A score of zero equates to absence of polyneuropathy, and the upper bound represents a maximally affected individual. Therefore, a negative change versus a patient's own baseline score represents neurologic improvement.[32-34]

A consensus report of the international Peripheral Nerve Society defined a 2-point change as the MCID for scores on the original NIS assessment (from which the mNIS+7 assessment is derived).[35] The rationale provided for this threshold was that it represented the degree of change that was twice (to account for the 2 sides of the body) the least degree of change in unilateral neurologic impairment that can be recognized on physical exam by an examining physician. At present, an MCID has not been defined for the mNIS+7 assessment used in the APOLLO and HELIOS-A trials.

The clinical experts consulted by CADTH indicated the mNIS+7 is a relevant outcome that is able to capture various aspects of the disease accurately, although it was noted that this measure is not routinely used in clinical practice due to the level of expertise and resources needed.

Rasch-Built Overall Disability Score

The R-ODS is a 24-item scale used to assess the ability to perform everyday activities, with a lower score indicating worsening disability.[34] The MCID of the R-ODS has not yet been reported in the literature. However, according to opinion provided by the clinical experts consulted by CADTH, a clinical threshold of 4 points could be considered meaningful. Patient group input indicated the importance of outcome measures that reflect daily activities.

Norfolk Quality of Life-Diabetic Neuropathy

The Norfolk QoL-DN score assesses 35 measures of symptoms and functional impairment related to nerve function, with higher scores indicating worse health-related quality of life.[34] The 5 domains of the

Norfolk QoL-DN are activities of daily living, physical function/large-fibre neuropathy, small-fibre neuropathy, symptoms, and autonomic neuropathy.[34] An MCID of 8.8 points has recently been reported in the literature for Norfolk QoL-DN.[34] The clinical expert and patient group indicated the importance of quality-of-life measurements.

Serum TTR

TTR is a tetrameric protein composed of 4 monomers.[36] In the case of hATTR, the tetrameric protein destabilizes into unstable monomers and TTR fragments that can misfold and form amyloid fibril deposits in multiple organs, including the peripheral nervous system, heart, and gastrointestinal tract, leading to cellular injury and organ dysfunction with corresponding clinical manifestations.[2,3,13,36,37] Although no MCID exists for serum TTR reduction, the clinical experts who provided feedback on the UK National Institute for Health and Care Excellence (NICE) highly specialized technology guidance for patisiran noted that "Reducing neuropathy in hATTR amyloidosis is dependent on a reduction in TTR levels and that an 80% reduction of TTR levels would be clinically meaningful for most patients."[38] Because vutrisiran and patisiran share the same mechanism of action, an assessment of vutrisiran's ability to achieve sustained reduction in serum TTR levels compared to patisiran was considered relevant. Sustained serum TTR reduction appears to be indicative of the drug's sustained biological activity, but no formal assessment of the correlation between the rate of TTR reduction and efficacy outcomes in patients with hATTR who receive vutrisiran was available at the time of this CADTH review.

Hospitalization

Clinical experts identified hospitalization as a relevant clinical outcome to inform on overall response and as a measure of potential deterioration. No data on hospitalization were available in the HELIOS-A trial.

31-Question Composite Autonomic Symptom Score

COMPASS 31 is a patient-reported measure that assesses changes in autonomic symptoms. It consists of 31 questions that evaluate 6 domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor. Scores range from 0 to 100, with higher scores indicating more severe symptoms.[31] This outcome was considered clinically relevant by the clinical experts consulted by CADTH and, according to the experts, is commonly used in clinical settings in Canada. No data for COMPASS 31 were available in the HELIOS-A trial.

Survival and Mortality

The life expectancy of patients with hATTR-PN ranges from 10 to 15 years after symptoms develop.[3] The clinical experts noted that a finding of improved survival would be highly relevant. They also noted that any difference in mortality that would ensure the exclusion of a chance finding would be clinical meaningful. No MCID exists in the literature. In the included trial, information regarding patients who died was captured as part of the safety outcomes. Overall survival probabilities using Kaplan-Meier estimates were not available from the HELIOS-A trial.

Overall, outcomes assessed in the HELIOS-A and APOLLO trials were very similar, as the 2 trials had the same primary outcome, mNIS+7, and multiple secondary outcomes in common (Norfolk QoL-DN score,

10MWT, R-ODS, and mBMI). Both studies also evaluated the pharmacodynamic outcome of serum TTR lowering (a secondary end point in the HELIOS-A trial and an exploratory end point in the APOLLO trial) and the exploratory outcome of change from baseline (improvement, maintenance, or worsening) in PND score.

Table 8: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID
mNIS+7	mNIS+7 is a score developed specifically for polyneuropathy in patients with hATTR, and quantifies decreased muscle weakness, muscle stretch reflexes, sensory loss, and autonomic impairment.[9] The mNIS+7$_{Ionis}$ differs from the mNIS+7 in that it includes NIS-Sensation and assesses autonomic dysfunction related to heart rate decrease with deep breathing rather than postural blood pressure. The mNIS+7 assessment scale ranges from 0 to 304 points. A score of 0 equates to an absence of polyneuropathy and the upper bound represents a maximally affected individual.[9]	The clinometric performance of the mNIS+7$_{Ionis}$, was evaluated by Dyck et al. (2017).[39] Baseline assessments of neuropathy signs (NIS, NIS+7, mNIS+7$_{Ionis}$, PND score, Norfolk QoL-DN, Dyck-Rankin score, NSC score, and the SF-36v2) were evaluated in the first 100 patients with FAP enrolled in the NEURO-TTR trial (inotersen vs. placebo). **Validity:** The mNIS+7$_{Ionis}$ was correlated with the Norfolk QoL-DN, PND stage, the Dyck-Rankin score, and the NSC score (Spearman rank correlation $r \geq 0.5$ or $r \leq -0.5$).[39] The correlation between mNIS+7$_{Ionis}$ and SF-36v2 was also evaluated with Spearman rank correlation of $r \geq 0.5$ or $r \leq -0.5$ or ($r \geq 0.25$ to $r < 0.5$ or $r \leq -0.25$ to $r > -0.5$)[39] **Reliability:** Test-retest reproducibility of the NIS, sigma 5 NCS and heart rate with deep breathing was high (Krippendorff alpha = 0.97, alpha = 0.98, and alpha = 0.93, respectively). Test-retest reproducibility for QST was lower (Krippendorff alpha = 0.57; alpha = 0.44 for touch pressure, and alpha = 0.65 for heat pain).[39] 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.[39]	For the NIS in patients with diabetic polyneuropathy, the Peripheral Nerve Society proposed that a mean difference between groups of 2 points was meaningful, as a change of 2 points represents a 50% change in sensation or muscle stretch reflexes and a 25% change in muscle strength.[35] A responder definition threshold of 12.2 points has recently been reported for mNIS+7 in patients with hATTR-PN.[40]
Norfolk QoL-DN	The Norfolk QoL-DN score assesses 35 measures of symptoms and functional impairment related to nerve function in patients with diabetic neuropathy, with higher scores indicating worse QoL. The 5 domains of the Norfolk QoL-DN are activities of daily living, physical functioning and large-fibre neuropathy, small--	The Norfolk QoL-DN was validated in 61 patients with hATTR and the V30M mutation and FAP stage I to III disease; and in 16 healthy volunteers from a single study centre in Portugal. The questionnaire was translated into Portuguese and validated linguistically.[41] **Validity:** The Norfolk QoL-DN was correlated with objective measures of neurologic function, which included the modified form of the NIS, NIS-Lower Limbs, and QST.[41] **Reliability**: The instrument was	A responder definition threshold of 8.8 points has recently been reported for Norfolk QoL-DN in patients with hATTR-PN.[40]

Outcome measure	Type	Conclusions about measurement properties	MCID
	fibre neuropathy, symptoms, and autonomic neuropathy.[41]	demonstrated to have test-retest reliability, as there were no statistically significant differences between the baseline and week 4 assessments in patients with FAP stage II or III disease. Aside from small-fibre neuropathy in patients with stage 2 disease, there were no statistically significant differences in the individual domains between baseline and week 4.[41]	
R-ODS	The R-ODS is a 24-item scale used to assess the ability to perform everyday activities and social participation in patients with Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. A lower score indicates worsening disability.[42]	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.[42] **Validity:** The intraclass correlation of the R-ODS with the Overall Disability Sum Score was evaluated. The intraclass correlation coefficient was 0.85, which demonstrated good external construct validity.[42] **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.[42] No studies were identified that examined the validity, reliability, or MCID of the R-ODS in patients with hATTR.	No MCID reported
PND score	The PND score provides a measure for the impact of neuropathy on ambulation. PND is not sensitive to small changes. During monitoring, a change in score indicates increased functional impairment.[12]	The validity, reliability, and responsiveness to change have not been investigated in patients with hATTR.	No MCID reported

FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; MCID = minimum clinically important difference; mNIS+7 = modified Neuropathy Impairment Score + 7; NIS = Neurological Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NSC = neuropathy symptoms and change; PND = polyneuropathy disability; QoL = quality of life; QST = quantitative sensory testing; R-ODS = Rasch-built Overall Disability Score; SF-36v2 = 36-item Short Form Health Survey version 2; V30M = valine to methionine substitution at amino acid position 30.

Sources: Dyck et al. (2019),[9] Report of the Peripheral Nerve Society,[35] Dyck et al. (2017),[39] Yarlas et al. (2022),[40] Vinik et al. (2014),[41] van Nes et al. (2011),[42] Ando et al. (2022).[12]

Statistical Analysis

A summary of the statistical analysis methods used for the primary and secondary end points in the HELIOS-A and APOLLO trials is provided in Table 9.

Sample Size and Power Calculation

HELIOS-A Trial

Enrolment of approximately 160 patients was planned for the HELIOS-A study.[29] The sample size was chosen to enable an adequate characterization of the long-term safety profile, as well as the efficacy of vutrisiran in this patient population. Additionally, this sample size was chosen to achieve sufficient power for the primary hypotheses using data from the APOLLO trial. Specifically, for mNIS+7 change from baseline at 9 months, the observed mean was 15 (SD = 17) points for the placebo group from the APOLLO study. Under an assumed alternative hypothesis of zero-point change from baseline in the vutrisiran group, a 2-sided t test would have greater than 90% power to establish superiority over placebo at the target sample size, using a significance level of 0.05. For the Norfolk QoL-DN total score change from baseline at 9 months, the observed mean was 11.5 (SD = 19.2) points for the placebo group from the APOLLO study. By assuming a mean change of −4 points for the vutrisiran group, it was determined that the target sample size resulted in greater than 90% power to establish superiority over placebo using a 2-sided t test with a significance level of 0.05. Noninferiority of vutrisiran against patisiran in reduction of serum TTR was determined if the lower limit of the 95% CI for the treatment difference was greater than −10%. Information regarding the rationale for the 10% margin or the power of the sample size to detect this difference was not available.

APOLLO Trial

For the estimation of sample size, a mean mNIS+7 progression rate in the placebo group of 24 (SD = 16) points over 18 months was estimated using natural history data.[30] A sample of 154 individuals provided 90% power for a 2-sided t test with an assumed alternative 8.95-point (37.5%) mean difference between treatment arms in terms of mNIS+7 change from baseline at a 2-sided alpha of 0.05. Assuming a 25% random premature discontinuation rate, the required sample size to achieve this level of statistical power was approximately 200 patients.[30]

Statistical Testing

In both the HELIOS-A and APOLLO trials, analyses of the primary and secondary end points (excluding serum TTR lowering in the HELIOS-A trial) used a mixed model for repeated measures (MMRM), adjusted for baseline covariates. The covariates included in the MMRM were the baseline efficacy outcome measurement of interest, the treatment group assignment, study visit (9 or 18 months), *TTR* genotype (V30M or not V30M), age at onset, and (for analysis of outcomes other than mNIS+7) baseline NIS. Additional factors included in the APOLLO MMRM were region and previous tetramer stabilizer use. Secondary outcomes in both the HELIOS-A and APOLLO trials were similarly evaluated using the MMRM, adjusted for key covariates.

In the HELIOS-A trial, for the secondary end point analysis of TTR percent reduction through month 18, a time-averaged trough TTR percent reduction through month 18 was used to capture the steady state for both vutrisiran and patisiran between month 6 and month 18. The Hodges-Lehmann method, with stratification by previous TTR stabilizer use (yes versus no), was used to estimate the 95% CI for the median difference in this measure between the vutrisiran and patisiran groups. Noninferiority of vutrisiran (versus patisiran) was declared if the lower limit of the 95% CI for the median treatment difference in TTR percent reduction (vutrisiran − patisiran) in this study was greater than −10%.

Table 9: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
HELIOS-A				
Change from baseline to month 18 in mNIS+7, Norfolk QoL-DN, 10MWT, R-ODS, and mBMI	MMRM	**Continuous covariate:** • baseline value of measure of interest **Categorical factors:** • treatment • visit • *TTR* genotype • age at symptom onset • baseline NIS[a] **Interaction:** • Treatment by visit	The use of MMRM implies that missing outcomes were missing at random. All efficacy data collected during the study for a given end point were included in the analyses, with the exception of mNIS+7 and Norfolk QoL-DN data collected from patients who initiated local BSC due to rapid disease progression, and all outcome data collected after the onset of a serious COVID-19 AEs. For missing subcomponents within efficacy measures, imputation was performed when possible. If imputation was not possible, the efficacy data were treated as missing completely.	Sensitivity analyses included: • MMRM without censoring data collected from patients after initiation of local BSC due to disease progression, or on or after the onset of a serious COVID-19 AEs • Analysis in which the propensity score for belonging to the vutrisiran treatment group (based on baseline patient characteristics) was an analysis covariate • PMM analysis under structured MNAR assumptions.
Percent reduction in serum TTR (noninferiority analysis vs. within-trial patisiran)	Hodges-Lehmann test	Previous TTR stabilizer use	Patients were excluded from the analysis if they were missing a TTR assessment at baseline or if they did not have ≥ 1 trough TTR assessment between months 6 and 18. Additional requirements for inclusion in the data analysis were: • assessments performed before administration of the study drug (assessments performed after initiation of local standard treatment for hATTR were excluded from the analysis) • planned and complete administration of the study drug at the treatment visit (approximately 12 weeks before the TTR	Comparison of vutrisiran in the HELIOS-A trial vs. pooled patisiran in the APOLLO and HELIOS-A trials.

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
			assessment for vutrisiran and approximately 3 weeks before the TTR assessment for patisiran) • planned and complete administration of vutrisiran at 2 consecutive treatment visits at any time before the TTR assessment visit to ensure steady state.	
APOLLO				
Change from baseline to month 18 in mNIS+7, Norfolk QoL-DN, 10MWT, R-ODS, and mBMI	MMRM	**Continuous covariate:** • Baseline value of measure of interest **Categorical factors:** • treatment • visit • *TTR* genotype • age at symptom onset • baseline NIS[a] • region • previous tetramer stabilizer use **Interaction:** • treatment by visit	As in the HELIOS-A trial, except that serious COVID-19–related AEs were not a reason for censoring.	Sensitivity analyses included: • MI ANCOVA method: missing data were multiply imputed separately for each treatment group using a regression procedure. • PMM analysis under structured MNAR assumptions. Note that results from sensitivity analyses are not presented here.

10-MWT = 10-metre walk test; AE = adverse event; ANCOVA = analysis of covariance; BSC = best supportive care; mBMI = modified body mass index; MI = multiple imputation; MMRM = mixed models for repeated measures; MNAR = missing-not-at-random; mNIS+7 = modified Neuropathy Impairment Score + 7; NIS = Neuropathy Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PMM = pattern-mixture model; R-ODS, Rasch-built Overall Disability Score.

[a]Baseline NIS was not a covariate for mNIS+7.

Sources: HELIOS-A Clinical Study Report 2,[27] APOLLO Clinical Study Report,[30] HELIOS-A statistical analysis plan,[29] APOLLO statistical analysis plan,[43] sponsor's Summary of Clinical Evidence.[1]

Harms were assessed by identifying treatment-emergent adverse events (TEAEs), defined as any AE that occurred during or after the administration of the study drug up to 28 days after the last dose of patisiran or 84 days after the last dose of vutrisiran. Additionally, any event that was considered drug-related was also considered treatment-emergent, irrespective of timing. No formal hypothesis testing for AE incidence rates was performed.

Results of efficacy and harms were reported at month 9 and month 18.

Data Imputation Methods

For each primary and secondary outcome in the HELIOS-A and APOLLO trials, the MMRM was used to estimate treatment differences; missing outcomes were not imputed. In both the HELIOS-A and APOLLO trials, efficacy outcomes were censored after patients experienced disease progression or received a liver

transplant, TTR-stabilizing drugs, or TTR-targeting antisense oligonucleotides. In addition, the HELIOS-A trial had censoring requirements for patients who received patisiran while in the vutrisiran group and for patients who experienced severe COVID-19-related AEs.

Multiple Testing Procedure

In both trials, type I error control for secondary end points was maintained with a hierarchical ordering procedure. If 1 end point was found significant at a 2-sided 0.05 level, the subsequent end point was then evaluated. However, if any end point was not significant, the subsequent hypotheses would not be tested for significant differences, but nominal P values would still be reported.

The HELIOS-A trial adhered to the following testing hierarchy for secondary end points: Norfolk QoL-DN total score change from baseline at month 18 (vutrisiran versus placebo [APOLLO trial]), 10MWT gait speed change from baseline at month 18 (vutrisiran versus placebo [APOLLO]), mBMI change from baseline at month 18 (vutrisiran versus placebo [APOLLO trial]), R-ODS change from baseline at month 18 (vutrisiran versus placebo [APOLLO trial]), then percent reduction in serum TTR levels at month 18 (vutrisiran versus patisiran [HELIOS-A]). The testing hierarchy for secondary outcomes in the APOLLO trial was as follows: Norfolk QoL-DN questionnaire, NIS-Weakness score, R-ODS, 10MWT speed, mBMI, and COMPASS 31 total score.

No information was provided regarding possible type I error control for the primary outcome as a consequence of testing the primary outcome at both month 9 and at month 18.

Subgroup Analyses

Subgroup analyses in the HELIOS-A and APOLLO trials were defined by:

- age (≥ 65 or < 65 years)
- sex (male or female)
- region (North America or Western Europe or rest of the world)
- previous tetramer stabilizer use (yes or no)
- genotype (V30M or non-V30M)
- NIS (< 50 or ≥ 50)
- FAP stage (I or II/III)
- cardiac subpopulation (yes or no to evidence of preexisting cardiac amyloid involvement, defined as a baseline left ventricular wall thickness of at least 1.3 cm and no aortic valve disease or hypertension in a patient's medical history).

Sensitivity Analyses

Three sensitivity analyses were conducted on HELIOS-A primary and secondary outcomes: inclusion of data previously censored due to SAEs related to COVID-19 or the initiation of standard of care due to disease progression; propensity score analysis; and pattern-mixture model analysis.

The propensity score sensitivity analysis aimed to address possible imbalances in baseline and disease characteristics between the APOLLO and HELIOS-A populations. To that extent, the following variables were included in the logistic regression model of the propensity score: N-terminal pro b-type natriuretic peptide (NT-proBNP) (log-transformed); mNIS+7; Norfolk QoL-DN total score; previous tetramer stabilizer use (tafamidis or diflunisal) (yes or no); Karnofsky Performance Status score (60, 70 to 80, or 90 to 100); cardiac subpopulation (yes or no); PND score (I, II, IIIA, of IIIB/IV); age at hATTR symptom onset (< 50 or ≥ 50 years); NIS (< 50 or ≥ 50); genotype (V30M or non-V30M); and FAP stage [I or II/III].

To assess the validity of the primary analysis results that operate under a missing-at-random assumption, a sensitivity analysis using a pattern-mixture model was performed. This sensitivity analysis considered 3 different scenarios of missing data: data missing due to COVID-19 was imputed based on a hypothetical situation in which the pandemic did not occur; for non–COVID-related missing data, imputation methods differ, depending on whether patients are taking placebo or vutrisiran and whether they were on treatment or had stopped their study treatment; if patients with missing data died (not due to COVID-19) before month 9 (or month 18), their data were imputed using samples from the worst-performing 10% at those time points. After this multiple imputation step, 100 datasets were created and analyzed using an analysis of covariance (ANCOVA), consistent with the primary analysis.

Post Hoc Analysis

The EMA requested a post hoc analysis from the sponsor comparing vutrisiran with patisiran in the HELIOS-A trial for the outcomes of mNIS+7, Norfolk QoL-DN, 10MWT, R-ODS, and mBMI.[5] The comparison of vutrisiran with patisiran at 18 months was conducted as a post hoc analysis using the MMRM method. Considering the clinical relevance of comparative end points against patisiran, applicable post hoc analyses have been included in this Clinical Review Report. The post hoc analysis estimated the LS mean change from the MMRM, controlling for categorical factors (treatment, visit), continuous covariate (baseline value), and interaction (treatment by visit).

Analysis Populations

Analysis populations from the HELIOS-A and APOLLO populations are described in Table 10.

Table 10: Analysis Populations of the HELIOS-A and APOLLO Trials

Study	Population	Definition	Application
HELIOS-A	mITT	All randomized patients who received any amount of the study drug.	Primary population for all efficacy analyses from baseline to month 18 between vutrisiran and external placebo.
	TTR PP	All mITT population patients with a nonmissing TTR assessment at baseline and ≥ 1 trough TTR assessment between month 6 and month 18.	Noninferiority analysis of the percent reduction in serum TTR between vutrisiran and within-trial patisiran.
	Month 18 efficacy PP population	All mITT population patients treated with vutrisiran or placebo are considered if they had their month 18 efficacy visit within 3 months of the planned date, had no severe	Primary end point sensitivity analysis.

Study	Population	Definition	Application
		COVID-19 effects by that time, and, for those on vutrisiran, received all doses up to week 72 with a delay of no more than 28 days. These patients will be analyzed based on their randomized treatment.	
	Safety population	All patients who received any amount of the study drug.	Safety analyses.
APOLLO	mITT	All patients who were randomized and received at least 1 dose of patisiran or placebo.	Primary population for all efficacy analyses from baseline to month 18 between patisiran and placebo.
	PP	All randomized patients who received at least 1 dose of patisiran LNP or placebo, completed baseline and either the 9-month or 18-month mNIS+7 and Norfolk QoL-DN assessments, and did not experience any major protocol deviations that may impact the efficacy results.	Primary end point sensitivity analysis.
	Safety population	All patients who received at least 1 dose of patisiran or placebo.	Safety analyses.

LNP = lipid nanoparticles; mITT = modified intention to treat; PP = per-protocol; TTR = transthyretin.

Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report,[30] sponsor's Summary of Clinical Evidence.[1]

Results

Patient Disposition

In the HELIOS-A and APOLLO trials, 189 and 323 patients were screened for randomization, respectively. In the HELIOS-A trial, 122 participants were randomized to receive vutrisiran and 42 to receive patisiran; in the APOLLO trial, 77 participants were randomized to receive a placebo and 148 to receive patisiran. Notably, a discrepancy appeared in the discontinuation of treatment rates (37.7% for the placebo group in the APOLLO trial, which is notably higher than other groups). The main reason for patient discontinuation from the placebo group was patient request (15.6%) and AEs (9.1%). In terms of withdrawal from the trial, the placebo group in the APOLLO trial had a 28.6% withdrawal rate, driven primarily by patient request (14.3%) and AEs (7.8%). Patient disposition from the HELIOS-A and APOLLO trials is summarized in Table 11.

Table 11: Summary of Patient Disposition From Studies Included in the Systematic Review

Patient disposition	HELIOS-A		APOLLO	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
Screened, N	189		323	
Reason for screening failure, n (%)	NR	NR	NR	NR
Randomized, N (%)	122	42	77	148
Discontinuation of treatment, n (%)	5 (4.1)	4 (9.5)	29 (37.7)	11 (7.4)
Reason for discontinuation, n (%)				
Adverse events	1 (0.8)	1 (2.4)	7 (9.1)	3 (2.0)
Death	2 (1.6)	3 (7.1)	4 (5.2)	5 (3.4)
Progressive disease	0	0	4 (5.2)	1 (0.7)
Physician decision	1 (0.8)	0	2 (2.6)	0
Protocol deviation	0	0	0	1 (0.7)
Patient request	1 (0.8)	0	12 (15.6)	1 (0.7)
Withdrawn from trial, n (%)	5 (4.1)	5 (11.9)	22 (28.6)	10 (6.8)
Reason for withdrawal, n (%)				
Adverse events	0	1 (2.4)	6 (7.8)	2 (1.4)
Death	3 (2.5)	3 (7.1)	4 (5.2)	6 (4.1)
Physician decision	0	1 (2.4)	1 (1.3)	0
Protocol deviation	0	0	0	1 (0.7)
Patient request	1 (0.8)	0	11 (14.3)	1 (0.7)
Lost to follow-up	1 (0.8)	0	0	0
mITT, N	122	42	77	148
TTR PP population	120	40	NA	NA
HELIOS-A PP efficacy population	96	NA	58	NA
APOLLO PP population	NA	NA	64	139
Safety, N	122	42	77	148

mITT = modified intention to treat; NA = not applicable; NR = not reported; PP = per protocol; TTR = transthyretin.

Note: HELIOS-A data cut-off date was August 26, 2021. APOLLO data cut-off date was August 17, 2017.

Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report,[30] sponsor's Summary of Clinical Evidence.[1]

Baseline Characteristics

A summary of the baseline characteristics of patients in the HELIOS-A and APOLLO trials is presented in Table 12. In the HELIOS-A and APOLLO trials, 164 and 225 patients were assessed, respectively.

In the HELIOS-A trial, median age at screening was 60 years for patients treated with vutrisiran and patisiran, and the majority of participants in the vutrisiran and patisiran groups were male (65% for vutrisiran and 64% for patisiran) and white (71% for vutrisiran and 69% for patisiran). For regional distribution in the vutrisiran group of the HELIOS-A trial, 22% of participants were in North America, 35% were in Western Europe, and 43% were in the rest of the world. The median number of years since diagnosis was 1.9 years for the vutrisiran group and 2.4 years for the patisiran group. The *TTR* genotype was evenly split between V30M and non-V30M in both groups. Previous tetramer stabilizer use was observed in 62% of the vutrisiran group and 79% of the patisiran group. In terms of FAP stage and PND score, both groups showed a similar pattern, with the majority being in stage 1 of FAP and PND scores of I or II. Finally, more participants in the vutrisiran group were not in heart failure according to NYHA classification (56%) compared to the patisiran group (50%).

In the APOLLO trial, median age in the placebo group was 63 years, 75% of participants were male, and the majority were white (65%). In the patisiran group, median age was 62 years, 74% of participants were male, and 76% were white. Regionally, Western Europe accounted for the largest proportion of both the placebo (47%) and patisiran (42%) groups. The median number of years since diagnosis was 1.4 years for the placebo group and 1.3 years for the patisiran group. The number of participants with a non-V30M *TTR* genotype was higher in the patisiran group than in the placebo group (62% versus 48%), whereas it was evenly split in the placebo group. Previous tetramer stabilizer use was observed in 53% of patients in both groups. The distribution of PND scores and FAP stage was similar in the 2 groups, with approximately half of the patients with early-stage disease.

Table 12: Summary of Baseline Characteristics From Studies Included in the Systematic Review

Characteristic	HELIOS-A (N = 164)		APOLLO (N = 225)	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
Age at screening, years, median (range)	60 (26 to 85)	60 (31 to 81)	63 (34 to 80)	62 (24 to 83)
Sex				
Male, n (%)	79 (65)	27 (64)	58 (75)	109 (74)
Female, n (%)	43 (35)	15 (36)	19 (25)	39 (26)
Race, n (%)				
Asian	21 (17)	8 (19)	25 (33)	27 (18)
Black	4 (3)	4 (10)	1 (1)	4 (3)
White	86 (71)	29 (69)	50 (65)	113 (76)
Other	10 (8)	1 (2)	0	1 (1)
More than 1 race	1 (1)	0	0	2 (1)
Unknown	0	0	1 (1)	1 (1)
Region,[a] n (%)				

Characteristic	HELIOS-A (N = 164)		APOLLO (N = 225)	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
North America	27 (22)	8 (19)	10 (13)	37 (25)
Western Europe	43 (35)	20 (48)	36 (47)	62 (42)
Rest of world	52 (43)	14 (33)	31 (40)	49 (33)
Years since diagnosis, median (range)	1.9 (0.0 to 15.3)	2.4 (0.1 to 12.5)	1.4 (0.0 to 16.5)	1.3 (0.0 to 21.0)
***TTR* genotype, n (%)**				
V30M	54 (44)	20 (48)	40 (52)	56 (38)
non-V30M	68 (56)	22 (52)	37 (48)	92 (62)
Previous tetramer stabilizer use, n (%)	75 (62)	33 (79)	41 (53)	78 (53)
FAP stage, n (%)				
I	85 (70)	31 (74)	37 (48)	67 (45)
II	37 (30)	11 (26)	39 (51)	81 (55)
III	0	0	1 (1)	0
PND score, n (%)				
I	44 (36)	15 (36)	20 (26)	36 (24)
II	50 (41)	17 (41)	23 (30)	43 (29)
IIIA	16 (13)	7 (17)	22 (29)	41 (28)
IIIB	12 (10)	3 (7)	11 (14)	28 (19)
IV	0	0	1 (1)	0
NYHA class,[b] n (%)				
No heart failure	68 (56)	21 (50)	–	–
Class I	11 (9)	5 (12)	40 (52[b])	70 (47[b])
Class II	43 (35)	16 (38)	36 (47)	77 (52)
Missing data	0	0	1 (1)	1 (1)

hATTR = hereditary transthyretin-mediated amyloidosis; FAP = familial amyloid polyneuropathy; NYHA = New York Heart Association; PND = polyneuropathy disability; TTR = transthyretin; V30M = valine to methionine substitution at amino acid position 30.

Note: HELIOS-A data cut-off date was August 26, 2021. APOLLO data cut-off date was August 17, 2017.

[a]North America includes Canada and the US; Western Europe includes Belgium, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden, and the UK; and the rest of the world includes Argentina, Australia, Brazil, Bulgaria, Cyprus, Japan, Korea, Malaysia, Mexico, Taiwan, and Turkey.

[b]In the APOLLO study, NYHA class was classified as I through IV, with no option to categorize patients as having no heart failure; thus, patients with NYHA class I heart failure in the APOLLO trial included both those without heart failure and those with heart failure who had no symptoms during ordinary physical activity.

Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report,[30] sponsor's Summary of Clinical Evidence,[1] Adams et al. (2018),[26] Adams et al. (2023).[25]

When comparing baseline characteristics between the HELIOS-A and APOLLO trials, there were differences in the demographic and clinical characteristics of the participant populations. Patients enrolled in the APOLLO trial were at a more advanced stage of the disease than patients enrolled in the HELIOS-A trial. This can be seen in the higher proportion of patients in FAP stage II in the APOLLO trial (51% in the placebo group)

than in the HELIOS-A trial (30% in the vutrisiran group). Similarly, 50.2% of patients in the APOLLO trial had NYHA class II heart failure, as did 36.0% of patients in the HELIOS-A trial.

Exposure to Study Treatments

Study drug exposure over 18 months in the HELIOS-A and APOLLO trials is summarized in Table 13. Median treatment duration was around [redacted] in the HELIOS-A trial in both arms, and around [redacted] in both the APOLLO study groups.

In the HELIOS-A trial, [redacted] who received vutrisiran or patisiran received at least 1 concomitant medication. Similarly, in the APOLLO trial, [redacted] who received patisiran or placebo all received at least 1 concomitant medication. Concomitant medications taken by at least 20% of patients in the HELIOS-A and APOLLO trials are summarized in Table 14. All patients who received patisiran in both trials and patients who received placebo in the APOLLO trial received the required premedication (IV corticosteroid [dexamethasone 10 mg or equivalent], H_1 blocker [diphenhydramine 50 mg or equivalent], H_2 blocker [famotidine 50 mg or equivalent], and oral acetaminophen [500 mg]).

[redacted].

Table 13: Summary of Patient Exposure From Studies Included in the Systematic Review

Exposure	HELIOS-A		APOLLO	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
Total, patient-years	[redacted]	[redacted]	[redacted]	[redacted]
Duration (months), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Duration (months), median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Adherence, percentage of total doses missed (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.

Note: HELIOS-A data cut-off date was August 26, 2021. APOLLO data cut-off date was August 17, 2017.

[a]These data are not readily available; however, in the HELIOS-A trial, it is understood that 0.1% of total vutrisiran doses and 0.3% of total patisiran doses were missed due to COVID-19.

Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report Report,[30] Sponsor's Summary of Clinical Evidence,[1] Adams et al. (2023),[25] Adams et al. (2018),[26] CADTH Pharmacoeconomic Review Report (patisiran).[6]

Table 14: Summary of Concomitant Medications Used in the HELIOS-A and APOLLO Trials

Study group	HELIOS-A		APOLLO	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
Concomitant medication	• [redacted]	• Required premedications for patisiran infusion (100%) [redacted]	• Required premedications for patisiran infusion (100%) [redacted]	• Required premedications for patisiran infusion (100%) [redacted]

Study group	HELIOS-A		APOLLO	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
				

Notes: Concomitant medications are classified by anatomical therapeutic chemical level subgroup and/or preferred term.
HELIOS-A data cut-off date was August 26, 2021. APOLLO data cut-off date was August 17, 2017.
Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report,[30] Adams et al. (2018),[26] sponsor's Summary of Clinical Evidence.[1]

Efficacy

Key efficacy results are presented in Table 15. Results of the relevant post hoc analysis are presented in Table 16.

The HELIOS-A trial was a positive trial that met its primary and all secondary end points measured at 18 months.

Change in PND Score From Baseline to Month 18

In the HELIOS-A trial, in the vutrisiran group (n = 122), [redacted]% ([redacted] patients) of patients showed improvement, [redacted]% ([redacted] patients) of patients exhibited no change, [redacted]% ([redacted] patients) of patients worsened, and [redacted]% ([redacted] patients) of patients had missing data. In the same trial, in the patisiran group (n = 42), [redacted]% ([redacted] patient) of patients improved, [redacted]% ([redacted] patients) had no change, [redacted]% ([redacted] patients) worsened, and [redacted]% ([redacted] patients) had missing data.

In the placebo group (n = 77) of the APOLLO trial, [redacted], [redacted]% ([redacted] patients) of patients had no change, [redacted]% ([redacted] patients) worsened, and [redacted]% ([redacted] patients) had missing data. In the APOLLO trial, in the patisiran group (n = 148), [redacted]% ([redacted] patients) of patients

improved, [redacted]% ([redacted] patients) saw no change, [redacted]% ([redacted] patients) worsened, and [redacted]% ([redacted] patients) had missing data.

Change in PND score was an exploratory outcome in both trials and no formal statistical hypothesis was tested.

mNIS+7 Change From Baseline to Month 18

In the HELIOS-A trial, among patients that contributed to the analysis at month 18, the vutrisiran group (n = 112) started with a nMIS + 7 baseline score of 60.57 (SD = 35.99) and the mean change was −0.46 (SEM = 1.60). For the within-study patisiran group (n = 36), the mean baseline score was 57.68 (SD = 33.71), with a change of 1.53 (SEM = 2.59).

In the APOLLO trial, the placebo group (n = 51),had a baseline mNIS+7 score of 74.61 (SD = 37.04), with a change of 28.09 (SEM = 2.28). In the patisiran group (n = 137), the mean baseline score was 80.93 (SD = 41.51), with a change of −6.03 (SEM = 1.74).

In the HELIOS-A trial, the treatment difference in change from baseline for vutrisiran versus placebo (APOLLO trial) was −28.55 (95% CI, −34.00 to −23.10) in favour of the vutrisiran group. For patisiran versus placebo in the APOLLO trial, it was −33.99 (95% CI, −39.86 to −28.13) in favour of patisiran.

The mNIS+7 was the primary outcome in both trials and was inferentially tested; the mean difference compared to placebo was statistically significant in both trials.

R-ODS Change From Baseline to Month 18

In the HELIOS-A trial, the change from baseline for vutrisiran was −1.5 (SEM = 0.6) and for within-study patisiran was −1.3 (SEM = 0.9).

In the APOLLO trial, the placebo group showed a change of −9.9 (SEM = 0.8), whereas the patisiran group showed no change.

In the HELIOS-A trial, the treatment difference for vutrisiran versus placebo (APOLLO) was 8.4 (95% CI, 6.5 to 10.4) in favour of vutrisiran. For patisiran versus placebo in the APOLLO trial, it was 9.0 (95% CI, 7.0 to 10.9) in favour of patisiran.

R-ODS was a secondary outcome in both trials and was the fifth end point to be tested in the testing hierarchy. All previous end points achieved statistical significance. Similarly, the results of R-ODS compared to placebo were statistically significant.

Norfolk QoL-DN Change From Baseline to Month 18

In the HELIOS-A trial, the change in the vutrisiran group was −1.2 (SEM = 1.8), and −0.8 (SEM = 3.0) for the within-study patisiran group.

In the APOLLO trial, the placebo group had a change of 19.8 (SEM = 2.6), whereas the patisiran group showed a decrease of −6.7 (SEM = 1.8).

The treatment differences for vutrisiran versus placebo (APOLLO) was −21.0 (95% CI, −27.1 to −14.9) in favour of vutrisiran. For patisiran versus placebo in the APOLLO trial, it was −21.1 (95% CI, −27.2 to −15.0) in favour of patisiran.

Norfolk QoL-DN was a secondary outcome in both trials and was the second end point to be tested after the primary outcome. The presented results achieved statistical significance versus placebo.

Serum TTR Percent Reduction From Baseline Through Month 18

In the HELIOS-A trial, the vutrisiran group exhibited an average reduction of [redacted]% (SD = [redacted]) from a baseline of [redacted] (SD = [redacted]). The within-study patisiran group showed an average reduction of [redacted]% (SD = [redacted]) from a baseline of [redacted] (SD = [redacted]).

The vutrisiran group exhibited a median reduction of [redacted] (range, [redacted]) from a median baseline of [redacted] (range, [redacted]). The within-study patisiran group showed a median reduction of [redacted] (range, [redacted]) from a median baseline of [redacted] (range, [redacted]). The median treatment group difference between vutrisiran and patisiran was 5.28% (95% CI, 1.17 to 9.25).

This outcome was the last end point in the testing hierarchy in the HELIOS-A trial. All previous end points achieved statistical significance. Vutrisiran met the prespecified 10% margin noninferiority criteria versus patisiran.

Post Hoc Analysis: Efficacy From Baseline to Month 18

Post hoc results from the HELIOS-A trial, including key efficacy outcomes comparing vutrisiran to within-study patisiran, are presented in Table 16. For the mNIS+7 outcome, the post hoc LS mean difference between vutrisiran and within-study patisiran at 18 months was −1.46 (95% CI, −7.36 to 4.43); for the Norfolk QoL-DN outcome, the post hoc LS mean difference was −1.6 (95% CI, −8.6 to 5.4); and for the R-ODS outcome, the LS mean difference was 0.1 (95% CI, −2.0 to 2.2).

Table 15: Summary of Key Efficacy Results From Studies Included in the Systematic Review

Variable	HELIOS-A		APOLLO	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
Change in PND score for vutrisiran and patisiran in the HELIOS-A and APOLLO trials from baseline to month 18				
Improved, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
No change, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Worsened, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Variable	HELIOS-A		APOLLO	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
mNIS+7,[a] change from baseline to month 18				
Number of patients contributing to the analysis at month 18, n	112	36	51	137
Baseline, LS mean (SD)	60.57 (35.99)	57.68 (33.71)	74.61 (37.04)	80.93 (41.51)
Change from baseline, mean (SEM)	−0.46 (1.60)	1.53 (2.59)	28.09 (2.28)	−6.03 (1.74)
Treatment group difference vs. placebo from the APOLLO trial, mean difference in change from baseline (95% CI) (study drug minus placebo)	−28.55 (−34.00 to −23.10)	NR	Reference	−33.99 (−39.86 to −28.13)
P value	< 0.001	NR	Reference	< 0.001
R-ODS,[b] change from baseline to month 18				
Number of patients contributing to the analysis at month 18, n	113	38	54	138
Baseline, mean (SD)	34.1 (11.0)	34.0 (10.4)	29.8 (10.8)	29.7 (11.5)
Change from baseline, LS mean (SEM)	−1.5 (0.6)	−1.3 (0.9)	−8.9 (0.9)	0.0 (0.6)
Treatment group difference vs. placebo from the APOLLO trial, mean difference in change from baseline (95% CI) (study drug minus placebo)	8.4 (6.5 to 10.4)	NR	Reference	9.0 (7.0 to 10.9)
P value	< 0.001	NR	Reference	< 0.001
Norfolk QoL-DN,[a] change from baseline to month 18				
Number of patients contributing to the analysis at month 18, n	111	38	49	136
Baseline, mean (SD)	47.1 (26.3)	47.3 (29.9)	55.5 (24.3)	59.6 (28.2)
Change from baseline, LS mean (SEM)	−1.2 (1.8)	−0.8 (3.0)	19.8 (2.6)	−6.7 (1.8)
Treatment group difference vs. placebo from the APOLLO trial, mean difference in change from baseline (95% CI) (study drug minus placebo)	−21.0 (−27.1 to −14.9)	NR	Reference	−21.1 (−27.2 to −15.0)
P value	< 0.001	NR	Reference	< 0.001
Serum TTR, percent reduction from baseline through month 18				
Number of patients contributing to the analysis, n	120	40	NA	NA
Baseline, mean (SD)	[redacted]	[redacted]	NA	NA
% change from baseline, mean (SD)	[redacted]	[redacted]	NA	NA
Baseline, median	[redacted]	[redacted]	NA	NA
% change from baseline, median	[redacted]	[redacted]	NA	NA

Variable	HELIOS-A		APOLLO	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)
Treatment group difference, median difference (95% CI) (vutrisiran minus patisiran)	5.28 (1.17 to 9.25)	Reference	NA	NA
Noninferiority (95% lower CI > −10%)	Yes	Reference	NA	NA

10MWT = 10-metre walk test; CI = confidence interval; LS = least squares; mBMI = modified body mass index; MMRM = mixed models for repeated measures; mNIS+7 = modified Neuropathy Impairment Score + 7; NA = not applicable; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NR = not reported; R-ODS = Rasch-built Overall Disability Score; SD = standard deviation; SEM = standard error of the mean; TTR = transthyretin.

Notes: LS estimates derived from MMRM; separate MMRM analyses were implemented in the APOLLO and HELIOS-A trials.

The APOLLO placebo group, which served as the comparator for these analyses, included 77 patients.

HELIOS-A data cut-off date was August 26, 2021. APOLLO data cut-off date was August 17, 2017.

[a]A lower score indicates less impairment/fewer symptoms.

[b]A higher score indicates less disability/less impairment.

Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report,[30] Adams et al. (2018),[26] Adams et al. (2023),[25] sponsor's Summary of Clinical Evidence.[1]

Table 16: Post Hoc Within-Study Comparison of Key Clinical Efficacy Outcomes Between Vutrisiran and Patisiran in the HELIOS-A Trial at Month 18

Outcome	Vutrisiran (n = 122)	Patisiran (n = 42)
mNIS+7,[a] change from baseline to month 18		
Number of patients contributing to the analysis at month 18, n	112	36
Baseline, mean (SD)	60.57 (35.99)	57.68 (33.71)
Change from baseline, mean (SEM)	0.06 (1.48)	1.53 (2.59)
Post hoc treatment group difference vs. patisiran, mean difference in change from baseline (95% CI)	−1.46 (−7.36 to 4.43)	Reference
Norfolk QoL-DN,[a] change from baseline to month 18		
Number of patients contributing to the analysis at month 18, n	111	38
Baseline, mean (SD)	47.1 (26.3)	47.3 (29.9)
Change from baseline, mean (SEM)	−2.5 (1.8)	−0.8 (3.0)
Post hoc treatment group difference vs. patisiran, mean difference in change from baseline (95% CI)	−1.6 (−8.6 to 5.4)	Reference
R-ODS,[b] change from baseline to month 18		
Number of patients contributing to the analysis at month 18, n	113	38
Baseline, mean (SD)	34.1 (11.0)	34.0 (10.4)
Change from baseline, mean (SEM)	−1.2 (0.5)	−1.3 (0.9)

Outcome	Vutrisiran (n = 122)	Patisiran (n = 42)
Post hoc treatment group difference vs. patisiran, mean difference in change from baseline (95% CI)	0.1 (−2.0 to 2.2)	Reference

CI = confidence interval; mNIS+7 = modified Neuropathy Impairment Score + 7; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; R-ODS = Rasch-built Overall Disability Score; SD = standard deviation; SEM = standard error of the mean.

Note: HELIOS-A data cut-off date was August 26, 2021. APOLLO data cut-off date was August 17, 2017.

[a]Estimates were derived from MMRM, controlling for categorical factors (treatment, visit), continuous covariate (baseline value), and interaction (treatment by visit). A lower score indicates less impairment and/or fewer symptoms.

[b]A higher value indicates less disability and/or less impairment.

Sources: EMA CHMP Assessment Report,[5] sponsor's Summary of Clinical Evidence.[1]

Harms

Table 17 presents the AEs, SAEs, and notable AEs based on the safety population from the HELIOS-A and APOLLO trials.

Adverse Events

In the HELIOS-A trial for patients treated with vutrisiran (n = 122), 98% experienced at least 1 AE, with falls being most commonly reported in 18% of participants. Other commonly reported TEAEs in the vutrisiran group were pain in extremity and diarrhea, occurring in 14.8% and 13.9% of patients, respectively. Peripheral edema and UTI both were observed in 13.1% of the participants. Other common TEAEs in the vutrisiran group included arthralgia and dizziness, each at 10.7%, followed by nausea and syncope, each at 9.8%. Headaches were reported by 9% of participants, cough and vomiting by 7.4% each, and muscular weakness by 4.9%. Among the 42 patients treated with patisiran in the HELIOS-A trial, 98% experienced at least 1 AE. Falls were reported in 14.3% of patients in this group, and pain in extremity in 7.1% of patients. Diarrhea was reported by 16.7% of patients, and peripheral edema, UTI, arthralgia, and nausea were each reported by 9.5% of patients. Dizziness was absent in this group, and 11.9% of participants reported having a headache. Cough and vomiting were seen in 2.4% and 9.5% of patients, respectively.

In the APOLLO trial, among the 148 patients treated with patisiran, 97% of patients reported at least 1 AE. Falls and pain in extremity were reported by 17% and 7% of patients, respectively. Diarrhea was reported in 37% of patients, with 30% experiencing peripheral edema. UTIs and dizziness were each reported by 13% of patients, with nausea reported by 15%, syncope by 2%, headache by 11%, cough by 10%, and vomiting by 10%. Among the placebo group of 77 patients, 97% reported at least 1 AE. Falls were more prevalent in this group, at 28.6%, pain in extremity was at 10.4%, and diarrhea and peripheral edema were at 37.7% and 22.1%, respectively. UTIs affected 18.2% of patients, dizziness affected 14.3%, nausea affected 20.8%, syncope affected 10.4%, headache affected 11.7%, cough affected 11.7%, and vomiting affected 10.4%.

Serious Adverse Events

In the HELIOS-A trial, among the patients treated with vutrisiran (n = 122), 26% experienced at least 1 SAE. Acute kidney injury and pneumonia were each reported in 3% of patients. COVID-19 pneumonia, falls, hypokalemia, pyelonephritis, sepsis, ventricular tachycardia, and syncope each affected 2% of patients. In

contrast, among the 42 patients treated with patisiran in the HELIOS-A trial, a larger proportion, 43%, reported at least 1 SAE. There is a lack of information on the specifics of these SAEs.

In the APOLLO trial, among the patients treated with patisiran (n = 148), 36% of patients experienced at least 1 SAE. In this group, diarrhea was the most frequently reported SAE, affecting 5% of patients. Pneumonia and cardiac-related issues, specifically complete atrioventricular block and cardiac failure (both standard and congestive), were observed in 2% of patients each. Dehydration and vomiting each impacted 1% of patients. In the placebo group of the APOLLO trial (n = 77), 40% of patients reported at least 1 SAE. Acute kidney injury was observed in 5% of participants, whereas other events, like pneumonia, cardiac failure, congestive cardiac failure, hereditary neuropathic amyloidosis, constipation, vomiting, UTI, dehydration, hyponatremia, pneumonia aspiration, and orthostatic hypotension, each affected around 2% to 3% of patients in the placebo group.

Withdrawals Due to Adverse Events

Six discontinuations of the study treatment in the HELIOS-A trial were recorded, 3 in patients taking vutrisiran and 3 in patients taking patisiran. Five of these discontinuations were due to death and 1 was due to acute cardiac failure in the vutrisiran group. AEs that led to treatment discontinuation and study withdrawal in the APOLLO trial in 2 or more patients included cardiac failure (2 patients) in the patisiran group and acute kidney injury (2 patients) in the placebo group.

Mortality

In the HELIOS-A trial, 2% (n = 2) of patients treated with vutrisiran died. One death was attributed to COVID-19 pneumonia, and the other to iliac artery occlusion. In the patisiran group 7% (3) of patients died. Among these deaths, 1 was due to COVID-19 pneumonia, 1 was due to arrhythmia, and 1 was associated with coronary artery disease.

In the APOLLO trial, 5% (n = 7) of patients treated with patisiran died. All 7 deaths in this group were attributed to cardiac arrest or sudden cardiac death. In the placebo group, 8% (n = 6) of patients died. The causes of these deaths varied, with 1 death each from subarachnoid hemorrhage, sepsis, gastrointestinal hemorrhage, acute kidney failure, metastatic colorectal cancer, and ischemic stroke.

Notable Harms

Cardiac arrhythmias were reported using the high-level group term (HLGT) classification. In the HELIOS-A trial, among patients treated with vutrisiran, 24.6% (n = 30) of patients experienced cardiac arrhythmias. In contrast, 7.1% (n = 3) of patients treated with patisiran experienced arrhythmias.

In the APOLLO trial, of the 148 patients treated with patisiran, 19% (n = 28) experienced cardiac arrhythmias. Of the 77 patients in the placebo group, 29% (n = 22) experienced cardiac arrhythmias.

Table 17: Summary of Harms Results From Studies Included in the Systematic Review

Adverse events	HELIOS-A		APOLLO	
	Vutrisiran (N = 122)	Patisiran (N = 42)	Placebo (N = 77)	Patisiran (N = 148)
Most common adverse events, n (%)				
≥ 1 adverse event	119 (98)	41 (98)	75 (97)	143 (97)
Fall	22 (18.0)	6 (14.3)	22 (28.6)	25 (17)
Pain in extremity	18 (14.8)	3 (7.1)	8 (10.4)	10 (7)
Diarrhea	17 (13.9)	7 (16.7)	29 (37.7)	55 (37)
Peripheral edema	16 (13.1)	4 (9.5)	17 (22.1)	44 (30)
Urinary tract infection	16 (13.1)	8 (19.0)	14 (18.2)	19 (13)
Arthralgia	13 (10.7)	4 (9.5)	0	11 (7)
Dizziness	13 (10.7)	0	11 (14.3)	19 (13)
Nausea	12 (9.8)	4 (9.5)	16 (20.8)	22 (15)
Syncope	12 (9.8)	1 (2.4)	8 (10.4)	3 (2)
Headache	11 (9.0)	5 (11.9)	9 (11.7)	16 (11)
Cough	9 (7.4)	1 (2.4)	9 (11.7)	15 (10)
Vomiting	9 (7.4)	4 (9.5)	8 (10.4)	15 (10)
Muscular weakness	6 (4.9)	0	11 (14.3)	5 (3)
Asthenia	5 (4.1)	0	9 (11.7)	14 (10)
Constipation	5 (4.1)	5 (11.9)	13 (16.9)	22 (15)
Fatigue	5 (4.1)	1 (2.4)	8 (10.4)	18 (12)
Anemia	1 (0.8)	2 (4.8)	8 (10.4)	3 (2)
Infusion-related reaction	0	10 (23.8)	7 (9.1)	28 (19)
Serious adverse events, n (%)				
Patients with ≥ 1 SAE	32 (26)	18 (43)	31 (40)	54 (36)
Acute kidney injury	3 (3)	0	4 (5)	1 (1)
Pneumonia	3 (3)	0	3 (4)	3 (2)
COVID-19 pneumonia	2 (2)	1 (2)	0	0
Fall	2 (2)	0	0	0
Hypokalemia	2 (2)	0	0	0
Pyelonephritis	2 (2)	0	0	0
Sepsis	2 (2)	0	0	0
Syncope	2 (2)	0	0	0
Ventricular tachycardia	1 (2)	0	0	0
Complete atrioventricular block	NR	NR	0	3 (2)

Adverse events	HELIOS-A		APOLLO	
	Vutrisiran (N = 122)	Patisiran (N = 42)	Placebo (N = 77)	Patisiran (N = 148)
Cardiac failure	NR	NR	2 (3)	3 (2)
Congestive cardiac failure	NR	NR	2 (3)	3 (2)
Hereditary neuropathic amyloidosis	NR	NR	2 (3)	0
Constipation	NR	NR	2 (3)	0
Diarrhea	NR	NR	1 (1)	8 (5)
Vomiting	NR	NR	3 (4)	1 (1)
Urinary tract infection	NR	NR	3 (5)	0
Dehydration	NR	NR	3 (4)	1 (1)
Hyponatremia	NR	NR	2 (3)	0
Pneumonia aspiration	NR	NR	2 (3)	0
Orthostatic hypotension	0	0	1 (1)	3 (2)
Patients who stopped treatment due to adverse events, n (%)				
Treatment discontinuations due to adverse events	3 (3)	3 (7)	11 (14)	7 (5)
Deaths, n (%)				
Patients who died	2 (2)	3 (7)	6 (8)	7 (5)
COVID-19 pneumonia	1	1	0	0
Iliac artery occlusion	1	0	0	0
Arrhythmia	0	1	0	0
Coronary artery disease	0	1	0	0
Cardiac arrest or sudden cardiac death	0	0	0	7
Subarachnoid hemorrhage	0	0	1	0
Sepsis	0	0	1	0
Gastrointestinal hemorrhage	0	0	1	0
Acute kidney failure	0	0	1	0
Metastatic colorectal cancer	0	0	1	0
Ischemic stroke	0	0	1	0
Adverse events of special interest, n (%)				
Cardiac arrhythmias (HLGT)	30 (24.6)	3 (7.1)	22 (29)	28 (19)

HLGT = high-level group term; NR = not reported; SAE = serious adverse event.

Note: HELIOS-A data cut-off date was August 26, 2021. APOLLO data cut-off date was August 17, 2017.

Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report,[30] Adams et al. (2018),[26] Adams et al. (2023),[25] sponsor's Summary of Clinical Evidence.[1]

Critical Appraisal

Internal Validity

HELIOS-A utilized an external control, the placebo group from the APOLLO trial. To infer whether the magnitude of the effect is attributable to the treatment when using an external control, careful attention must be exercised in assessing the homogeneity of study design and patient population between the HELIOS-A and APOLLO trials. To that end, the inclusion and exclusion criteria of the HELIOS-A trial were largely similar to those in the APOLLO trial. In addition, the outcome measures were similar in the 2 studies. Furthermore, the HELIOS-A trial included a patisiran group to help gauge similarities in responses between the APOLLO and HELIOS-A trials.

However, comparing the baseline characteristics of patients in the APOLLO and HELIOS-A trials suggests that patients enrolled in the APOLLO trial were more advanced in their disease course than patients enrolled in the HELIOS-A trial. The proportion of patients with NYHA class II heart failure and the proportion with a PND score of IIIA or IIIB was higher in the APOLLO trial than in the HELIOS-A trial. This imbalance in baseline characteristics between the 2 trials suggests that patients may exhibit variations in their response to treatment and natural disease course, which could potentially bias results. For example, it appears that patients in the APOLLO trial exhibited a numerically better response to patisiran than in the HELIOS-A trial. The clinical experts consulted by CADTH suggested that clinical changes in the disease in response to treatment can be more pronounced and easier to detect in patients at more advanced stages of the disease (i.e., APOLLO) than at earlier stages of the disease. The clinical experts suggested that this could be explained by the accelerating rate of deterioration as the disease advances, as well as by the mechanism of action of vutrisiran and patisiran, which aims to halt disease progression. However, the clinical experts consulted by CADTH cautioned that, at the same time, patients with advanced disease may be more resistant to treatment, which may reduce the effect of therapy. Overall, the extent and direction of the potential bias caused by imbalances in disease characteristics cannot be determined.

To address potential imbalances in important clinical baseline variables, the sponsor conducted a propensity score sensitivity analysis. The propensity score was defined as the probability of being treated with vutrisiran under a logistic regression model for treatment assignment (vutrisiran or placebo [APOLLO]). The logistic regression included the following baseline variables: N-terminal pro b-type natriuretic peptide (NT-proBNP), mNIS+7, Norfolk QoL-DN total score, previous tetramer stabilizer use, Karnofsky Performance Status, cardiac subpopulation, PND score (I, II, IIIA, or IIIB/IV), age at hATTR symptom onset, NIS, genotype (V30M or non-V30M), and FAP stage. The results from the propensity score sensitivity analysis were in line with and supportive of the main finding. However, the propensity score would not have been able to address all of the differences between the 2 studies, including unmeasured or unrecognized factors.

One divergent aspect in the 2 studies is design: the HELIOS-A trial is an open-label study, and the APOLLO trial is a double-blind study. The sponsor aimed to minimize the potential bias that may arise from an open-label approach (i.e., assessors' knowledge of assigned treatment) by implementing a number of data integrity strategies. These included lack of access of site personnel performing the mNIS+7 assessment to previous mNIS+7 values, having patients complete the Norfolk questionnaire with no assistance to minimize

potential influence interpretation and response to questionnaire items, lack of knowledge of treatment assignment by the central lab personnel evaluating the mNIS+7 scores, lack of sponsor's access to data before the primary analysis at month 9. Although these measures help mitigate and minimize biases arising from the open-label design and the divergence in design between the 2 studies, it does not eliminate the potential for bias in the efficacy and safety results. The extent and direction of this potential bias cannot be determined.

The HELIOS-A trial used different time points for its efficacy analysis to target different regulatory agencies. Specifically, month 9 was the primary analysis time point used in the regulatory submissions to the FDA, Brazil, and Japan, whereas month 18 was the primary analysis time point used for filings in the European Union and other regions.[29] The sponsor communicated that Health Canada is maintaining both time points, month 9 and month 18, as primary end points. However, the HELIOS-A trial contained no adjustments for multiple testing to address the fact that all analyses were conducted twice, at 9 and 18 months.

Among the secondary end points in the HELIOS-A trial was a test for the noninferiority of vutrisiran against patisiran in percent reduction in serum TTR protein levels. The sponsor established a noninferiority margin of 10%, but no clear justification was available as to why 10% would be an acceptable noninferiority margin. However, considering that the 95% CI of the result of the end point was over the null and not close to the lower noninferiority margin, this limitation in clinical justification of the noninferiority margin is unlikely to affect the validity of the result.

To address the need for additional comparative clinical results, the sponsor provided a post hoc analysis at the request of the EMA. Although useful when considered in the context of the larger body of evidence, post hoc analyses have a number of limitations. These include the lack of sufficient power to detect a difference, an inflated and uncontrolled type I error, and the lack of an established noninferiority margin to test noninferiority. The post hoc analysis results should not be used on their own; instead, these should be considered as supportive evidence.

External Validity

Vutrisiran received an indication for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR. The available evidence, from the HELIOS-A trial with an external placebo control group from the APOLLO trial, provides evidence of the efficacy of vutrisiran in this indicated patient population. This is evident by the exclusion of patients with a NYHA heart failure classification of III or IV or with advanced-stage polyneuropathy.

Patients who received prior treatment with TTR-lowering treatment were excluded from the HELIOS-A trial. As such, the current available evidence is insufficient to inform the efficacy of vutrisiran in patients who previously received patisiran. An extension study is ongoing, in which patients who completed the HELIOS-A trial are randomized to their current vutrisiran regimen of 25 mg every 3 months or to 50 mg every 6 months. Although the extension study may offer the potential for exploratory and preliminary findings regarding the efficacy of vutrisiran in patients who switch from patisiran, such information is not yet available.

Another external validity concern is the limited evidence available on the comparative efficacy of vutrisiran versus the current standards of care (patisiran and inotersen). Although patients in the HELIOS-A trial were randomized to either vutrisiran or patisiran, the study was neither designed nor powered to detect differences in clinical outcomes between vutrisiran and patisiran. To address this evidence gap, and upon the request of the EMA, the sponsor conducted a post hoc analysis of key HELIOS-A end points of vutrisiran versus patisiran. The HELIOS-A trial does provide evidence of the noninferiority of vutrisiran versus patisiran in the percent reduction of TTR protein levels. The percent reduction in TTR protein levels is a biomarker that has not been identified as a validated surrogate outcome for efficacy end points in patients with hATTR-PN who receive vutrisiran. However, the clinical experts consulted by CADTH indicated that serum TTR levels are commonly used to assess the effect of the treatment. Considering the identical mechanism of action of vutrisiran and patisiran, noninferiority on TTR would help confirm the similarity of the drugs in terms of biological activity.

The mNIS+7 is limited in its application to clinical practice in Canada. The clinical experts consulted for this review provided feedback that the mNIS+7 instrument is not routinely used in Canadian clinical practice; instead, the COMPASS is more frequently used in clinical settings. Although COMPASS score was an outcome assessed in the APOLLO trial, it was not assessed in the HELIOS-A trial. The sponsor noted that mNIS+7 is not used in routine clinical assessment due to its complexity but that it provides a more comprehensive assessment of neuropathy than COMPASS, including manifestations of both peripheral and autonomic neuropathy. mNIS+7 is a standard outcome used in clinical trials in the present therapeutic setting.[9]

The PND score is an applicable clinical measure. However, the use of PND scores in the HELIOS-A and APOLLO trials is limited due to the exploratory nature of the outcome and the lack of formal comparative statistical testing. Mortality (death) was reported as part of the safety assessment of vutrisiran. However, the duration of the trial (18 months) is likely insufficient to adequately capture the full impact of treatment on patients' mortality. Hospitalizations, an additional clinically relevant outcome, was lacking in the available evidence.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For the pivotal studies (HELIOS-A and APOLLO) identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to CADTH's expert committee deliberations, and a final certainty rating was determined, as outlined by the GRADE Working Group.[10,11] Following the GRADE approach, evidence from the pivotal study started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias. Degrees of certainty are defined as follows:

- **High certainty** — We are very confident that the true effect lies close to that of the estimate of the effect.

- **Moderate certainty** — We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word "likely" for evidence of moderate certainty (e.g., "X intervention likely results in Y outcome").
- **Low certainty** — Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. We use the word "may" for evidence of low certainty (e.g., "X intervention may result in Y outcome").
- **Very low certainty** — We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as "very uncertain."

Studies using external control arm in comparison to single within-study arm: For this observational comparison, The CADTH review team assessed evidence for a single arm with an external control arm for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Due to the potential for bias resulting from confounding and selection bias, the certainty of evidence was started at low.

For RCTs: Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for mNIS+7, Norfolk QoL-DN, and R-ODS, based on a threshold identified in the literature and/or informed by the clinical experts consulted by CADTH for this review. The target of the certainty of evidence assessment was the presence or absence of any (nonnull) effect for PND, serum TTR, and mortality.

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for vutrisiran and placebo for the treatment of patients with hATTR and stage 1 or stage 2 polyneuropathy. Table 3 presents the GRADE summary of findings for vutrisiran and patisiran in patients with hATTR-PN.

Long-Term Extension Studies

No relevant long-term extension studies were available.

Indirect Evidence

The contents within this section have been informed by materials submitted by the sponsor. The following have been summarized and validated by the CADTH review team.

Objectives for the Summary of Indirect Evidence

The sponsor submitted 1 ITC. Due to the lack of direct evidence comparing vutrisiran with other treatments for patients with hATTR, an evidence gap exists that may be informed by an ITC. In addition, the sponsor used the results from the ITC to inform their pharmacoeconomic model. The aim of this section is to review and appraise the sponsor-submitted ITC.

Description of Indirect Comparisons

The sponsor-submitted ITC used a Bayesian network meta-analysis approach, under a fixed-effects model, to compare vutrisiran with patisiran and inotersen in patients with hATTR-PN. The measures chosen by the sponsor to inform this comparison were PND, mNIS+7, and Norfolk QoL-DN scores. The sponsor identified evidence through a literature review of phase III RCTs for inotersen, patisiran, and vutrisiran. One reviewer conducted screening and data extraction.

Table 18: Study Selection Criteria and Methods for ITCs Submitted by the Sponsor

Characteristics	Indirect comparison
Population	hATTR amyloidosis with polyneuropathy
Intervention	Vutrisiran
Comparator	Patisiran, inotersen, placebo
Outcome	List outcomes, including time points
Study designs	Phase III clinical trials
Publication characteristics	Published studies
Exclusion criteria	NR
Databases searched	NR
Selection process	One reviewer
Data extraction process	One reviewer and another person who conducted quality checks
Quality assessment	No quality assessment was conducted

hATTR-PN = hereditary transthyretin-mediated amyloidosis with polyneuropathy; ITC = indirect treatment comparison; NR = not reported.
Source: Sponsor's ITC.[44]

ITC Design

Objectives

The sponsor-submitted ITC aimed to inform the Health Technology Assessment submission for vutrisiran. Specifically, the ITC aimed to inform on the comparative efficacy of vutrisiran versus patisiran and inotersen in patients with hATTR-PN in the measures of PND score, mNIS+7, and Norfolk QoL-DN.

Study Selection Methods

A literature review was conducted to identify relevant studies. No description was provided on the search strategy or the bibliographic databases used. No explicit inclusion and exclusion criteria were provided. However, based on the CADTH reviewer reading, the sponsor ITC aimed to include a population of patients

with hATTR-PN who had received vutrisiran, patisiran, inotersen, or placebo and who had available PND, mNIS+7, or Norfolk QoL-DN scores, as informed by phase III clinical trials. It was reported in the sponsor's submitted ITC report that 1 reviewer conducted the screening and data extraction, and another reviewer conducted a quality check of the extracted data. No quality assessment tool was used to assess the quality of the included studies. Analyzed outcomes were improvement or no change in PND at month 18, change from baseline in mNIS+7 score category at month 18, and change from baseline in Norfolk QoL-DN score at month 18.

ITC Analysis Methods

The sponsor ITC used a Bayesian network meta-analysis approach, implemented using a Markov chain Monte Carlo method. The sponsor ITC only implemented a fixed-effects model due to network sparsity. The specified Bayesian implementation used a noninformative prior, and convergence was assessed through trace and Gelman-Rubin plots. The models were run with 3 chains and 50,000 iterations per chain (with 5,000 adaptation and 50,000 burn-in iterations). Five thousand posterior samples per chain were generated using a thinning factor of 10 and used to estimate posterior statistics. Improvement or no change in PND score was modelled as a binary outcome, with probabilities estimated using logit link. The mean changes from baseline in mNIS+7 and Norfolk QoL-DN scores were modelled as continuous variables. For the binary outcome of improvement or no change in PND score, compared with worsening, treatment effects were estimated as the risk ratio and OR of achieving improvement or no change with a given treatment, relative to placebo. For mNIS+7 and Norfolk QoL-DN scores, treatment effects were estimated as differences between a given treatment and placebo in terms of mean change from baseline to study end points. As applicable, median risk ratios, ORs, and treatment differences, compared with placebo (drawn from posterior distributions), and the corresponding 95% CrIs were reported.

Missing data for PND scores were handled using 2 approaches. In 1 approach, missing PND scores at the main analysis time point were imputed using nonresponder imputation, which assumes that patients with a missing value had a worse PND score than at baseline. In the other approach, patients with missing PND scores at the main analysis time point were excluded from the network meta-analysis.

The ITC aimed to use observed mean change values from baseline in mNIS+7 and Norfolk QoL-DN scores when available; otherwise, the publication-reported change from baseline was used. Missing mNIS+7 scores at baseline or month 18 were excluded from the analysis, as the calculation of change from baseline was not possible for these patients. The empirical mean change and the model-based, covariate-adjusted marginal estimated mean change in mNIS+7 and Norfolk QoL-DN scores for the placebo arms were included in the network to inform estimates of change from baseline within placebo arms.

Table 19: ITC Analysis Methods

Methods	Description
Analysis methods	Bayesian network meta-analysis under a fixed-effects model
Priors	Noninformative
Assessment of model fit	NR
Assessment of consistency	A feasibility assessment was conducted to inform on the similarities and differences of included studies
Assessment of convergence	Trace and Gelman-Rubin plots
Outcomes	Improvement or no change in PND at month 18 Change from baseline in mNIS+7 score category at month 18 Change from baseline in Norfolk QoL-DN score at month 18
Follow-up time points	18 months
Construction of nodes	NR
Sensitivity analyses	Different missing-data-imputation approach for the outcome of improvement or no change in PND at month 18
Subgroup analysis	None conducted
Methods for pairwise meta-analysis	NA

ITC = indirect treatment comparison; mNIS+7 = modified Neuropathy Impairment Score + 7; NA = not applicable; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NR = not reported; PND = polyneuropathy disability.

Source: Sponsor's ITC.[44]

Results of the Sponsor-Submitted ITC

Summary of Included Studies

Three trials were included in the ITC: HELIOS-A, APOLLO, and NEURO-TTR. HELIOS-A was a phase III, randomized, open-label, multicentre, global study to evaluate the efficacy and safety of vutrisiran over 18 months in patients with hATTR-PN.[25] The study had 2 arms: a vutrisiran treatment group and a patisiran treatment group (reference group).[25] Adult patients with hATTR (N = 164) from 57 sites in 22 countries were randomized in a 3:1 ratio to receive vutrisiran 25 mg SC every 3 months or patisiran 0.3 mg/kg IV infusion every 3 weeks for 18 months.[28] The APOLLO placebo group served as an external comparator for the primary end point and all for secondary end points except the percent reduction in serum TTR, for which a prespecified within-trial noninferiority test of vutrisiran versus patisiran was conducted. The sponsor reported that the aim of the patisiran group in the HELIOS-A trial was to validate the use of the external control group from the APOLLO trial to establish a similar reduction in serum TTR and to allow an assessment of tolerance between the 2 treatments. Outcomes from the HELIOS-A trial were assessed at 18 months.

APOLLO was an international, multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of patisiran over 18 months in patients with hATTR-PN.[26] Adult patients with hATTR (N = 225) were recruited from 52 sites in 21 countries. Patients were randomized in a 2:1 ratio to receive patisiran

(n = 148; 0.3 mg/kg every 3 weeks by IV infusion for 18 months) or placebo (normal saline; n = 77).[26] Outcomes from the APOLLO trial were assessed at 18 months.

NEURO-TTR was a phase II/III, double-blind, RCT that compared the efficacy and safety of inotersen 300 mg SC injection weekly to placebo in patients with hATTR and stage I or II polyneuropathy. Of the 278 patients screened, 173 (62.2%) were randomized in a 2:1 ratio to inotersen (n = 112) or placebo (n = 60). Outcomes in the NEURO-TTR trial were assessed at 15 months.[45]

The main differences in study design between the 3 included trials is the time point at which outcomes were measured (15 months in the NEURO-TTR trial versus 18 months in the APOLLO and HELIOS-A trials), as well as the double-blind design of the NEURO-TTR and APOLLO trials compared to the open-label design of the HELIOS-A trial.

The inclusion and exclusion criteria of the 3 trials were similar in their aim to include patients with a relatively early stage of disease and patients who had not received prior TTR-lowering therapy. Assessment of the baseline characteristics of the enrolled patients is limited by the publicly available information from the NEURO-TTR trial but suggests that patients enrolled in the NEURO-TTR trial had been diagnosed with the disease longer than their counterparts in the HELIOS-A and APOLLO trials. However, FAP stage suggest that patients in the APOLLO trial were at a more advanced stage of disease than those in the other 2 trials. Due to the lack of sufficient information from the NEURO-TTR trial (e.g., lack of PND score, NYHA class), it is not possible to make a decision regarding the potential clinical homogeneity of the included population.

Table 20: Summary of Baseline Characteristics in the Included Studies

	HELIOS-A (N = 164)		APOLLO (N = 225)		NEURO-TTR (N = 172)	
Characteristic	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)	Placebo (n = 60)	Inotersen (n = 112)
Age at screening (years)	Median = 60 (range, 26 to 85)	Median = 60 (range, 31 to 81)	Median = 63 (range, 34 to 80)	Median = 62 (range, 24 to 83)	Mean = 59.5 (SD = 14.0)	Mean = 59.0 (SD = 12.5)
Male, n (%)	79 (65)	27 (64)	58 (75)	109 (74)	41 (68.3)	77 (68.8)
Race, n (%)						
Asian	21 (17)	8 (19)	25 (33)	27 (18)	3 (5.0)	1 (0.9)
Black	4 (3)	4 (10)	1 (1)	4 (3)	1 (1.7)	3 (2.7)
White	86 (71)	29 (69)	50 (65)	113 (76)	53 (88.3)	105 (93.8)
Other	10 (8)	1 (2)	0	1 (1)	3 (5.0)	3 (2.7)
More than 1 race	1 (1)	0	0	2 (1)	NR	1 (1)
Unknown	0	0	1 (1)	1 (1)	NR	0
Region,[a] n (%)						
North America	27 (22)	8 (19)	10 (13)	37 (25)	NR	NR
Western Europe	43 (35)	20 (48)	36 (47)	62 (42)	NR	NR

Characteristic	HELIOS-A (N = 164)		APOLLO (N = 225)		NEURO-TTR (N = 172)	
	Vutrisiran (n = 122)	Patisiran (n = 42)	Placebo (n = 77)	Patisiran (n = 148)	Placebo (n = 60)	Inotersen (n = 112)
Rest of world	52 (43)	14 (33)	31 (40)	49 (33)	NR	NR
Years since diagnosis, median (range)	1.9 (0.0 to 15.3)	2.4 (0.1 to 12.5)	1.4 (0.0 to 16.5)	1.3 (0.0 to 21.0)	3.3 (0.08 to 13.3)	3.5 (0.17 to 24.8)
***TTR* genotype, n (%)**						
V30M	54 (44)	20 (48)	40 (52)	56 (38)	33 (55.0)	56 (50)
non-V30M	68 (56)	22 (52)	37 (48)	92 (62)	27 (45.0)	56 (50)
Previous tetramer stabilizer use, n (%)	75 (62)	33 (79)	41 (53)	78 (53)	NR	NR
FAP stage, n (%)						
I	85 (70)	31 (74)	37 (48)	67 (45)	42 (70)	74 (66.1)
II	37 (30)	11 (26)	39 (51)	81 (55)	18 (30)	38 (33.9)
III	0	0	1 (1)	0	0	0
PND score, n (%)						
I	44 (36)	15 (36)	20 (26)	36 (24)	NR	NR
II	50 (41)	17 (41)	23 (30)	43 (29)	NR	NR
IIIA	16 (13)	7 (17)	22 (29)	41 (28)	NR	NR
IIIB	12 (10)	3 (7)	11 (14)	28 (19)	NR	NR
IV	0	0	1 (1)	0	NR	NR
NYHA class,[b] n (%)						
No heart failure	68 (56)	21 (50)	–	–	NR	NR
Class I	11 (9)	5 (12)	40 (52[b])	70 (47[b])	NR	NR
Class II	43 (35)	16 (38)	36 (47)	77 (52)	NR	NR
Missing data	0	0	1 (1)	1 (1)	NR	NR

FAP = familial amyloid polyneuropathy; NR = not reported; NYHA = New York Heart Association; PND = polyneuropathy disability; TTR = transthyretin; V30M = valine to methionine substitution at amino acid position 30.

[a]North America includes Canada and the US; Western Europe includes Belgium, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden, and the UK; the rest of the world includes Argentina, Australia, Brazil, Bulgaria, Cyprus, Japan, Korea, Malaysia, Mexico, Taiwan, and Turkey.

[b]In the APOLLO study, NYHA class was classified as I through IV, with no option to categorize patients as having no heart failure; thus, patients classified as NYHA class I in the APOLLO trial included both patients without heart failure and those with heart failure who had no symptoms during ordinary physical activity.

Sources: HELIOS-A Clinical Study Report,[27] APOLLO Clinical Study Report,[30] Adams et al. (2018),[26] Adams et al. (2023).[25]

Table 21: Assessment of Homogeneity for the Sponsor-Submitted ITC

Characteristic	Description and handling of potential effect modifiers
Disease severity	Unclear; longer time since disease diagnosis in the NEURO-TTR trial, but higher proportion of patients in FAP stage II in the APOLLO trial
Treatment history	Similar between APOLLO and HELIOS-A; unclear in the NEURO-TTR trial
Trial eligibility criteria	Similar in all 3 trials
Dosing of comparators	Placebo dosing varied in the APOLLO and NEURO-TTR trials; patisiran recommended dosing was identical in the APOLLO and HELIOS-A trials
Placebo response	Similar between the NEURO-TTR and APOLLO trials in the outcome of mNIS+7, worst in the APOLLO trial in the outcome of Norfolk QoL-DN, unclear in the outcome of PND score change
Definitions of end points	Similar
Timing of end point evaluation	Different; 15 months in the NEURO-TTR trial vs. 18 months in the APOLLO and HELIOS-A trials
Withdrawal frequency	Higher proportion of patients who discontinued treatment in the placebo group of APOLLO compared to NEURO-TTR; no information in the NEURO-TTR trial on withdrawals
Clinical trial setting	Similar
Study design	The HELIOS-A trial had an open-label, external control, design

FAP = familial amyloid polyneuropathy; ITC = indirect treatment comparison; mNIS+7 = modified Neuropathy Impairment Score + 7; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PND = polyneuropathy disability.

Source: Sponsor's ITC.[44]

Results

Table 22 lists the results comparing vutrisiran against patisiran, inotersen, and placebo in the outcomes of improvement or no change in PND score at 18 months, the mNIS+7 difference in change from baseline at 18 months, and the Norfolk QoL-DN difference in change from baseline at 18 months.

For the PND score of improvement or no change at 18 months, the median estimated posterior OR for vutrisiran compared to placebo was [redacted], with a 95% CrI of [redacted] to [redacted] in favour of vutrisiran. Against patisiran, the median estimated posterior OR was [redacted], with a 95% CrI of [redacted] to [redacted]. When vutrisiran was compared to inotersen, the median estimated posterior OR was [redacted], and the 95% CrI ranged from [redacted] to [redacted] in favour of vutrisiran. For observed data, the results are similar in direction.

In terms of mNIS+7 change from baseline to 18 months, vutrisiran, compared to placebo, showed a median estimated posterior mean change from baseline of [redacted], with a 95% CrI of [redacted] to [redacted] in favour of vutrisiran. Compared to patisiran, the median estimated posterior mean change from baseline was [redacted], with a 95% CrI of [redacted] to [redacted]. Against inotersen, the median estimated posterior mean change was [redacted], with a 95% CrI of [redacted] to [redacted] in favour of inotersen.

For the Norfolk QoL-DN change from baseline to 18 months, the median estimated posterior mean change for vutrisiran relative to placebo was [redacted], with a 95% CrI of [redacted] to [redacted] in favour of vutrisiran. Compared to patisiran, the median estimated posterior mean change was [redacted], with a

95% CrI of [redacted] to [redacted]. Against inotersen, the median estimated posterior mean change was [redacted], and the 95% CrI ranged from [redacted] to [redacted] in favour of vutrisiran.

All 3 studies employed a fixed-effects model for their analysis. No model diagnostics that assessed data fit to the model were provided. No further vutrisiran-relevant data are available. An evidence network diagram that is applicable to all 3 outcomes is presented in Figure 2.

Table 22: ITC Results

Detail	PND score (improvement or no change) at 18 months, median OR	mNIS+7 change from baseline to 18 months, median posterior estimated mean difference	Norfolk QoL-DN change from baseline to 18 months, median posterior estimated mean difference
Number of studies (patients)	3 studies (561)	3 studies (561)	3 studies (561)
Model	Fixed-effects model	Fixed-effects model	Fixed-effects model
Vutrisiran vs. comparator, measure (95% CrI)			
Placebo	[redacted]	[redacted]	[redacted]
Patisiran	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]

CrI = credible interval; ITC = indirect treatment comparison; mNIS+7 = modified Neuropathy Impairment Score + 7; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; OR = odds ratio; PND = polyneuropathy disability.

[a]Favours vutrisiran.

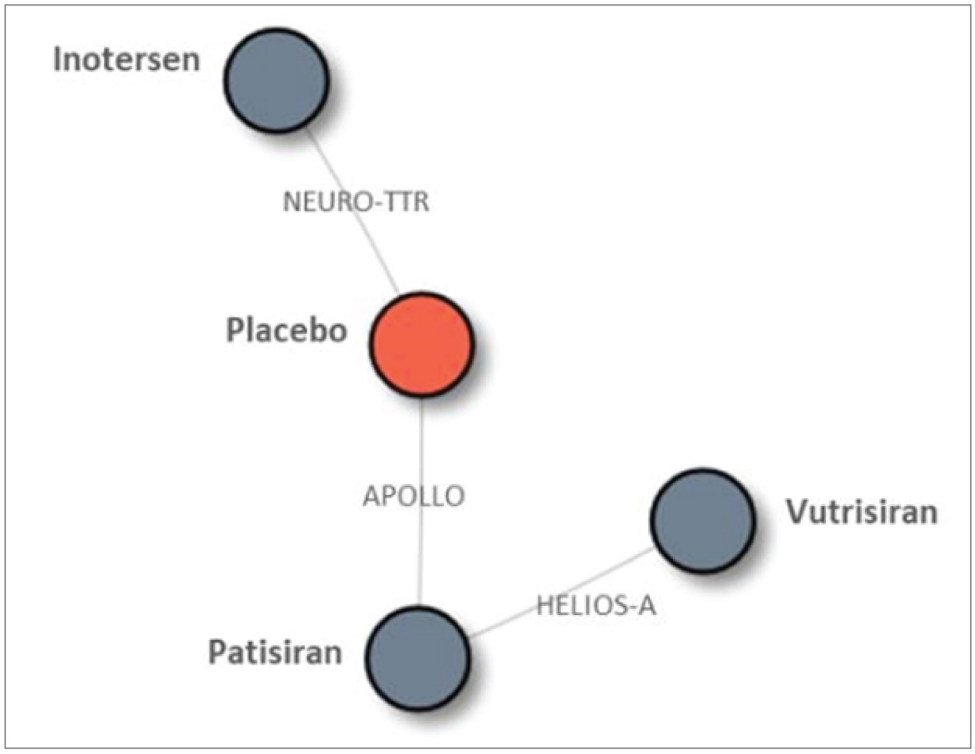
[b]Median posterior estimated mean difference.

Source: Sponsor's ITC.[44]

Critical Appraisal of Sponsor-Submitted ITC

The approach taken to identify relevant evidence, screen, and extract data did not follow a systematic review approach. Importantly, there were no clear inclusion and exclusion criteria with which to systematically screen relevant sources from the literature. One reviewer conducted the screening and data extraction while another performed and data check. Finally, a quality assessment of the risk of bias of the included studies was not conducted. The lack of a systematic review approach increases the overall uncertainty in the presented findings due to increased risk of publication bias, missing relevant evidence, human error in screening and extraction, and not incorporating the assessment of risk of bias through quality assessment. A mitigating factor is the systematic review submitted by the sponsor as a requirement to inform the body of this Clinical Review Report (but not the ITC). The sponsor-submitted systematic review identified the APOLLO and HELIOS-A trials as relevant to the intervention of interest (vutrisiran) but excluded inotersen. As such, there is still uncertainty about whether all inotersen-relevant evidence has been captured in the ITC.

Figure 2: Diagram of Evidence Network



Source: Sponsor's ITC.[44]

Factors that can increase heterogeneity across trials include the open-label design of the HELIOS-A trial, the 15-month end point assessment in the NEURO-TTR trial, the longer time since diagnosis in the NEURO-TTR trial, and the higher proportion of patients in FAP stage II in the APOLLO trial. The extent to which these differences bias the comparative effects within the network meta-analysis is unclear. Furthermore, there is insufficient information on baseline characteristics in the NEURO-TTR trial to provide a proper assessment of the similarity of that population to those of the HELIOS-A and APOLLO trials. These factors further reduce the certainty of the results.

The sponsor ITC used a fixed-effects model to estimate effects between treatment arms, citing the small number of included studies and the fact that only 1 group connected any 2 given studies. A fixed-effects model is typically specified under the assumption that any observed differences in the true effect size between studies is due to sampling error and is not intended to accommodate the variability of the true effects due to the heterogeneity of the populations across trials. This is a strong and untested assumption, given the identified differences between the studies. All results presented from this ITC should be contextualized with the fact that the analysis did not allow room for increased variability due to heterogeneity.

Overall, several of the results show wide 95% CrIs. This was especially observed in the results of vutrisiran versus inotersen and, to a lesser extent, vutrisiran versus placebo. The wide CrIs further suggest low

certainty in the available results, especially when considering that the analysis was conducted using a fixed-effects model.

For the population of patients with hATTR-PN clinically relevant outcomes were not included, such as death, hospitalization, and R-ODS score.

Considering the wide CrIs in the results of vutrisiran versus inotersen in light of all the previously mentioned limitations, the certainty of the comparison of vutrisiran versus inotersen is not sufficiently high to inform decision-making. Indirect results of vutrisiran versus placebo should be used as supportive evidence to the results in the HELIOS-A trial. Indirect results of vutrisiran versus patisiran should be viewed in totality with the noninferiority TTR result in the HELIOS-A trial as well as the post hoc analysis of HELIOS-A outcomes of vutrisiran versus patisiran.

Summary

One sponsor-submitted ITC informed the comparative efficacy of vutrisiran versus placebo, patisiran, and inotersen in patients with hATTR-PN. The ITC used a Bayesian network meta-analysis approach, with noninformative priors, under a fixed-effects model. The measures chosen by the sponsor to inform the comparison of treatments were the PND score (improvement or no change at month 18), mNIS+7 (change from baseline at month 18), and Norfolk QoL-DN (change from baseline at month 18). The sponsor identified evidence through a literature review of phase III RCTs for inotersen, patisiran, and vutrisiran. One reviewer conducted screening and data extraction. No quality assessment of the included studies was conducted.

Three trials — HELIOS-A, APOLLO, and NEURO-TTR — informed the ITC and the estimated effects of vutrisiran, patisiran, and inotersen on the specified outcomes among patients with hATTR-PN.HELIOS-A, An 18-month, phase III, open-label trial, compared vutrisiran to patisiran, with 164 participants randomized to 1 of 2 treatments in a 3:1 ratio, and used the placebo group of the APOLLO trial as an external control. APOLLO, an 18-month, international, double-blind, placebo-controlled trial, assessed the effects of patisiran in 225 patients randomized to either patisiran or placebo in a 2:1 ratio. NEURO-TTR, a phase II/III, double-blind trial, compared the efficacy of inotersen with placebo in 173 patients, randomized in a 2:1 ratio, with hATTR and early-stage polyneuropathy. Notable distinctions between these studies include the assessment time frame (15 months for the NEURO-TTR trial versus 18 months for the APOLLO and HELIOS-A trials) and the study design (double-blind for the NEURO-TTR and APOLLO trials and open-label for the HELIOS-A trial). Each trial sought patients in the early disease stage who had not received prior TTR therapy. Available data from the trials suggest differences in disease duration and stage, with APOLLO participants seemingly at a more advanced disease stage. Information on NEURO-TTR's participants was, however, limited and may not allow proper assessment of clinical heterogeneity.

For the PND score of improvement or no change at 18 months, the median OR for vutrisiran compared to placebo was [redacted], with a 95% CrI of [redacted] to [redacted]. Against patisiran, the median OR was [redacted], with a 95% CrI of [redacted] to [redacted]. When vutrisiran was compared to inotersen, the median OR was [redacted], and the 95% CrI ranged from [redacted] to [redacted]. When using observed data, the results are similar in direction, although numerically lower at the point estimate. In terms of mNIS+7 change

from baseline to 18 months, vutrisiran compared to placebo showed a median mean change from baseline of [redacted], with a 95% CrI of [redacted] to [redacted]. Compared to patisiran, the median mean change from baseline was [redacted], with a 95% CrI of [redacted] to [redacted]. Against inotersen, the median mean change was [redacted], with a 95% CrI of [redacted] to [redacted]. For the Norfolk QoL-DN change from baseline to 18 months, the median mean change for vutrisiran relative to placebo was [redacted] with a 95% CrI of [redacted] to [redacted]. Compared to patisiran, the median mean change was [redacted] with a 95% CrI of [redacted] to [redacted]. Against inotersen, the median mean change was [redacted], and the 95% CrI ranged from [redacted] to [redacted].

Limitations of the ITC are the lack of a systematic review approach, the lack of clear inclusion and exclusion criteria, the use of a single reviewer for screening and data extraction, the lack of quality assessment of the included studies, the varied heterogeneity among the included studies, the lack of comprehensive data to assess clinical heterogeneity, the use of a fixed-effects model, and the wide CrIs of vutrisiran versus inotersen results. Considering the previous limitations, the certainty of the comparison of vutrisiran and inotersen is not sufficiently high to inform decision-making. Indirect results of vutrisiran versus placebo should be used as supportive evidence to the results in the HELIOS-A trial. Indirect results of vutrisiran against patisiran should be viewed in totality with the noninferiority TTR result in the HELIOS-A trial as well as the post hoc analysis of HELIOS-A outcomes of vutrisiran versus patisiran.

Studies Addressing Gaps in the Systematic Review Evidence

No additional studies were available to address gaps in the systematic review evidence.

Discussion

Summary of Available Evidence

A sponsor-submitted systematic review identified 2 studies: HELIOS-A and APOLLO. HELIOS-A was a phase III, randomized, open-label, multicentre study designed to evaluate the efficacy and safety of vutrisiran over 18 months in patients with hATTR-PN. The study had 2 arms: a vutrisiran treatment group and a patisiran treatment group. The HELIOS-A trial used an external placebo control group from the APOLLO trial to assess the efficacy of vutrisiran against placebo. Adult patients with hATTR (N = 164) were randomized in a 3:1 ratio to receive vutrisiran 25 mg SC every 3 months or patisiran 0.3 mg/kg IV infusion every 3 weeks for 18 months.[28] There were 2 HELIOS-A sites in Canada, each with 1 patient (1 patient received vutrisiran and 1 received patisiran). APOLLO was an international, multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of patisiran over 18 months in patients with hATTR-PN. Adult patients with hATTR (N = 225) were randomized in a 2:1 ratio to receive patisiran (n = 148; 0.3 mg/kg every 3 weeks by IV infusion for 18 months) or placebo (normal saline; n = 77). Both the HELIOS-A and APOLLO trials had similar inclusion and exclusion criteria similar outcomes definitions. All patients were diagnosed with hATTR-PN. Patients were excluded if they had advanced disease (NIS > 130) or if they had signs of cardiac involvement (NYHA class > II heart failure).

Additional evidence was included in the form of a post hoc analysis of vutrisiran versus patisiran in the HELIOS-A trial, as well as a sponsor-submitted ITC.

Interpretation of Results

Efficacy

The design of the HELIOS-A trial and the use of the APOLLO external placebo control group to assess the efficacy of vutrisiran was suggested to the sponsor by regulatory authorities, in light of the rarity of the condition and potential ethical considerations. However, this design has inherent limitations compared to a traditional within-trial randomization, due to increased risk of bias from imbalances in baseline prognostic factors, which decreased the certainty of the evidence. The HELIOS-A design attempted to align as much as possible to that of APOLLO. However, certain differences remain; specifically, the open-label design of the HELIOS-A trial, a patient population that appeared more progressed in their disease course in the APOLLO trial than in the HELIOS-A trial, and a numerically better response to patisiran in the APOLLO trial than in the HELIOS-A trial. However, overall, the efficacy results for vutrisiran (HELIOS-A) versus placebo (APOLLO) suggest that vutrisiran may result in relatively large treatment effects (well above established MCID and clinical thresholds) for primary and secondary outcomes in the HELIOS-A trial.

Feedback from the clinical experts suggests that the use of mNIS+7 in clinical practice is very limited. This limits the utility of applying results from the HELIOS-A trial to clinical decision-making. Other outcomes, such as hospitalization and COMPASS 31, were deemed to be clinically relevant by the clinical experts and stakeholders but were not reported in the HELIOS-A trial. However, several other outcome measures that were identified as important by patients and their clinicians were tested as part of the testing hierarchy; these included R-ODS and the Norfolk QoL-DN. The PND score was considered to be an important and clinically relevant outcome by all stakeholders and was used to inform the pharmacoeconomic model submitted to CADTH. However, the PND score was an exploratory outcome in the HELIOS-A trial, which had no formal statistical inferences for PND score.

The treatment landscape of hATTR has changed significantly with the introduction of inotersen and patisiran to the Canadian clinical practice. For appropriate generalizability of the evidence, comparative efficacy results for vutrisiran versus inotersen and patisiran are desirable. The HELIOS-A trial performed a predefined noninferiority test of vutrisiran versus patisiran for the outcome of serum TTR percent reduction from baseline; the results succeeded in establishing the noninferiority margin. The persistent serum TTR reduction observed in patients in the vutrisiran group in the HELIOS-A trial was indicative of vutrisiran's similar biological activity to patisiran and supportive of both, the achieved clinical benefit observed with vutrisiran over placebo, and the less frequent dosing schedule of vutrisiran compared to patisiran (i.e., every 3 months versus every 3 weeks). However, the validity of the TTR precent reduction as a surrogate end point for efficacy end points assessed in the HELIOS-A trial has not been established.

A post hoc analysis of vutrisiran versus patisiran in the HELIOS-A trial was requested by the EMA. The exploratory results do not suggest a trend for 1 drug being better than the other (all 95% CI span the null); overall indicating that vutrisiran likely results in little to no difference in key efficacy outcomes compared to

patisiran. However, the lack of power to detect differences between vutrisiran and patisiran in the HELIOS-A trial, the lack of a predefined noninferiority margin, and the post hoc nature of the analysis limit the validity of these results to be considered on their own. Post hoc analysis results are considered to be supportive in nature.

To further address the lack of efficacy results for vutrisiran versus patisiran and inotersen, the sponsor submitted an ITC that included the 3 drugs plus placebo, which was informed by the HELIOS-A, APOLLO, and NEURO-TTR trials. A number of limitations and a lack of certainty in the evidence prevents firm conclusions to be made on the comparative efficacy of vutrisiran versus inotersen. Despite the limitations (e.g., heterogeneity across study design and patient populations) that led to uncertainty in the comparative efficacy estimates of vutrisiran versus patisiran, there was consistency in the direction of the effects of the ITC, the post hoc analysis results, and the noninferiority TTR result in the HELIOS-A trial, which suggested similar efficacy between vutrisiran and patisiran.

The presented totality of the efficacy results suggests that vutrisiran may have a large effect on halting the progression of hATTR-PN compared to placebo. Similarly, considering the totality of the evidence and the identical mechanism of action for vutrisiran and patisiran, it is likely that vutrisiran and patisiran will have similar efficacy in patients with hATTR-PN. The clinical experts consulted by CADTH on this review have indicated that due to the identical mechanism of action in the 2 drugs, they do not anticipate clinically meaningful differences in effectiveness between vutrisiran and patisiran.

Vutrisiran received an indication for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR. The available evidence from the HELIOS-A trial and the external placebo control group of the APOLLO trial provides evidence of the efficacy of vutrisiran in this patient population. This is evident from the exclusion of patients with NYHA class III or IV heart failure or with advanced-stage polyneuropathy. Given the progressive nature of the disease and the mechanism of action of vutrisiran that aims to halt further progression, the clinical experts consulted by CADTH indicated the limited generalizability of currently available evidence from patients in earlier stages of the disease to patients in late stages of the disease.

Harms

AEs from the HELIOS-A and APOLLO trials indicated a majority of participants experienced at least 1 such event after treatment with either vutrisiran or patisiran. In the HELIOS-A trial, 98% of patients treated with vutrisiran experienced AEs, such as falls, pain in an extremity, and diarrhea; similar rates were seen for patients treated with patisiran. In the APOLLO trial, both patients treated with patisiran (97%) and the placebo group (97%) reported AEs, including diarrhea, peripheral edema, and UTIs. SAEs varied between trials; 26% of patients treated with vutrisiran in the HELIOS-A trial experienced an SAE, as did 43% of patients treated with patisiran. In the APOLLO trial, 36% of the patisiran group and 40% of the placebo group reported SAEs. Treatment discontinuations due to AEs were noted in both trials, with death being a primary reason. Mortality in the HELIOS-A trial was 2% for vutrisiran and 7% for patisiran. In the APOLLO trial, 5% of the patisiran group and 8% of the placebo group died. Notable harms included cardiac arrhythmias, which occurred in 24.6% of patients treated with vutrisiran and 7.1% of patients treated with patisiran in the in the HELIOS-A trial, and in 19% of patients treated with patisiran and 29% of the placebo group in the APOLLO trial. The clinical experts

consulted by CADTH did not raise any concerns that the management of the expected safety profile of vutrisiran would be any different than that of patisiran.

Conclusion

The efficacy and safety of vutrisiran compared to placebo was assessed in the phase III, open-label trial, HELIOS-A, versus an external placebo control group from the APOLLO trial. Both the HELIOS-A and APOLLO trials enrolled patients with hATTR-PN in FAP stage I and stage II. GRADE assessment of clinically relevant outcomes indicated that, compared to placebo, vutrisiran may result in clinically important disease improvements in PND, mNIS+7, R-ODS, and Norfolk QoL-DN scores. The evidence was very uncertain about the effects of vutrisiran on mortality compared to placebo.

The noninferiority comparison of vutrisiran and within-study patisiran was assessed using a biomarker, serum TTR, suggesting that vutrisiran results in little to no difference compared to patisiran.

A post hoc analysis suggested that, compared to patisiran, vutrisiran likely results in little to no difference in mNIS+7, R-ODS, or Norfolk QoL-DN scores, and may result in PND improvement. The lack of power to detect differences between vutrisiran and patisiran in the HELIOS-A trial, the lack of a predefined noninferiority margin, and the exploratory nature of post hoc analyses limit the validity of the results. Post hoc analyses are considered to be supportive evidence.

Given the limited evidence available to inform the comparative efficacy of vutrisiran versus current standards of care (patisiran and inotersen), the sponsor submitted an ITC. A number of limitations (e.g., heterogeneity across study designs, outcome assessments, patient populations, and missing baseline data) prevented firm conclusions to be made on the comparative efficacy of vutrisiran versus inotersen. Despite limitations (e.g., heterogeneity across study design and patient populations) that led to uncertainty about the comparative efficacy estimates of vutrisiran versus patisiran, there was consistency in the direction of the effects of the ITC, the post hoc analysis results, and the noninferiority TTR result in the HELIOS-A trial, which suggested similar efficacy between vutrisiran and patisiran.

The totality of these results, along with the identical mechanism of action of vutrisiran to patisiran, suggests that vutrisiran's efficacy is likely similar to patisiran in the treatment of patients with hATTR and stage 1 or stage 2 polyneuropathy.

Over 18 months of treatment, most participants reported at least 1 AE, and the proportion of patients who experienced SAEs was numerically higher in the patisiran group of the HELIOS-A trial than in the vutrisiran group. A relatively small proportion of patients in both groups discontinued treatment due to AEs. Cardiac arrhythmias were recorded in one-quarter of vutrisiran-treated patients, which is similar to the proportion to that of the placebo (APOLLO) group but higher than the patisiran (HELIOS-A) group. However, due to the small sample size, the deteriorating nature of the disease, and the progressive cardiac involvement, additional data are needed to draw firm conclusions on safety. The clinical experts consulted by CADTH anticipated that the safety profile of vutrisiran would be similar to that of patisiran.

Currently, there is no evidence to support the efficacy or safety of vutrisiran in patients with hATTR-CM or in patients with advanced-stage hATTR-PN. However, the current indication and request for imbursement for vutrisiran is for adult patients with stage 1 or stage 2 polyneuropathy; as such, patients with hATTR-CM and patients with stage 1 or stage 2 polyneuropathy are outside the scope of this review. No appropriate evidence exists to inform the efficacy of vutrisiran in patients who switch from patisiran.

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Vutrisiran (Amvuttra)

Pharmacoeconomic Review

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Abbreviations

AE	adverse event
BSC	best supportive care
hATTR	hereditary transthyretin-mediated
hATTR-CM	hereditary transthyretin-mediated amyloidosis with cardiomyopathy
hATTR-PN	hereditary transthyretin-mediated amyloidosis with polyneuropathy
ICER	incremental cost-effectiveness ratio
LY	life-year
NMA	network meta-analysis
OLT	orthotopic liver transplant
PND	polyneuropathy disability
QALY	quality-adjusted life-year
SC	subcutaneous
TTR	transthyretin

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Vutrisiran (Amvuttra), 25 mg/0.5 mL solution, single-use vial
Submitted price	Vutrisiran, subcutaneous injection: $143,041.00 per 0.5 mL vial
Indication	For the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	October 18, 2023
Reimbursement request	As per indication
Sponsor	Alnylam Netherlands BV
Submission history	Previously reviewed: No

NOC = Notice of Compliance; hATTR-PN = hereditary transthyretin-mediated amyloidosis with polyneuropathy.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with hATTR-PN
Treatment	Vutrisiran
Comparators	• Patisiran • Inotersen
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	NMA; efficacy of vutrisiran informed by the HELIOS-A trial
Submitted results	The ICER for vutrisiran vs. patisiran was $2,811,102 per QALY gained (incremental costs = $1,128,100; incremental QALYs = 0.40)
Key limitations	• It is uncertain whether vutrisiran provides a clinical benefit relative to patisiran or inotersen for hATTR-PN owing to uncertainty in the clinical evidence submitted by the sponsor. The CADTH Clinical Review concluded that the efficacy of vutrisiran is likely similar to patisiran (overall moderate certainty evidence), although limitations in the sponsor-submitted NMA preclude meaningful conclusions being drawn for the efficacy of vutrisiran vs. inotersen. • The impact of AEs on the cost-effectiveness of vutrisiran was not adequately explored in the sponsor's base case owing to the use of naive comparisons and the inclusion of only treatment-related AEs.

Component	Description
	• The sponsor included in its model a benefit associated with SC administration vs. IV administration based on the assumption that less frequent and less invasive treatment will have a reduced negative impact on patients' HRQoL. Approximately 98% of incremental QALYs gained with vutrisiran relative to patisiran were owing to differences in administration route and frequency. The magnitude of any HRQoL benefit that patients may experience because of receiving treatment less frequently and by less invasive means is highly uncertain. • The long-term efficacy of vutrisiran is uncertain, owing to a lack of clinical data beyond 18 months. Potential waning of effectiveness was not explored. • The survival benefit predicted for vutrisiran (incremental LYs = 0.07 and 3.26 relative to patisiran and inotersen, respectively) is highly uncertain. • The model structure, based on PND score, does not adequately reflect hATTR-PN, in that it does not capture autonomic symptoms associated with hATTR (e.g., pain, gastrointestinal symptoms). The validity, reliability, and responsiveness of PND scores to change have not been investigated in patients with hATTR-PN.
CADTH reanalysis results	• Given the limitations identified in the sponsor's economic analysis, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of vutrisiran. Based on the sponsor's analysis, vutrisiran is not a cost-effective treatment option for hATTR-PN at a willingness-to-pay threshold of $50,000 per QALY gained. The probability of vutrisiran being the optimal treatment was 0% in the sponsor's analysis. • There is insufficient clinical evidence to justify a price premium for vutrisiran over currently available treatments for hATTR-PN. To ensure cost-effectiveness, vutrisiran should be priced no more than the lowest-cost treatment used to treat hATTR-PN that is funded.

hATTR = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin-mediated amyloidosis with polyneuropathy; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; PND = polyneuropathy disability; QALY = quality-adjusted life-year; SC = subcutaneous.

Conclusions

The CADTH clinical review concluded that the efficacy of vutrisiran for the treatment hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) will likely be similar to that of patisiran. CADTH judged the certainty of the evidence to be moderate for most outcomes, indicating that vutrisiran will likely have little to no difference compared to patisiran. There have been no head-to-head trials of vutrisiran versus inotersen, and important limitations were identified in the sponsor's network meta-analysis (NMA) that preclude meaningful conclusions from being drawn for this comparison.

As reported in the sponsor's base case, vutrisiran is not a cost-effective treatment for hATTR-PN, with an incremental cost-effectiveness ratio (ICER) of $2,811,102 per quality-adjusted life-year (QALY) gained compared with patisiran. Based on the findings from the CADTH clinical review, the clinical efficacy of vutrisiran is likely similar to patisiran in the treatment hATTR-PN for most outcomes, and uncertainty exists in the comparative clinical data relative to inotersen. As such, there is insufficient evidence to suggest that vutrisiran should be priced higher than other currently reimbursed treatments for hATTR-PN. Thus, to ensure cost-effectiveness, vutrisiran should be priced no more than the lowest-cost treatment option funded in the population to be reimbursed.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient group input was received from TTR Amyloidosis Canada. Input suggests that vutrisiran is more convenient than patisiran for patients, given that administration is less frequent and less time consuming. Patient input suggests that patients may self-inject vutrisiran, which would reduce the clinic visits and time off work required for infusions. Patients expressed hope that falls will be reduced with vutrisiran, which could result in fewer hospital visits and better maintenance of quality of life.

Clinician input was received from the Amyloidosis Program of Calgary. Clinician input noted that vutrisiran represents an improvement over currently approved treatments for hATTR-PN because it is administered less frequently and has the potential to improve patients' quality of life while attenuating disease. Clinician input additionally noted that vutrisiran is currently being evaluated in patients with hATTR cardiomyopathy (hATTR-CM).

Drug plans participating in the CADTH review noted that Alnylam is the market authorization holder for both vutrisiran and patisiran. The drug plans noted that the HELIOS-A trial included patients with hATTR-PN, but that there is the potential for vutrisiran to be used more broadly, including for hATTR-CM. The plans also noted that vutrisiran may additionally be used by patients with hATTR-PN who are presymptomatic, by those with advanced polyneuropathy (e.g., familial amyloid polyneuropathy [FAP] stage III at baseline), and by those who have undergone liver transplant; these groups were excluded from the HELIOS-A trial. The plans indicated that genetic testing is required to confirm the diagnosis of hATTR and to differentiate it from other causes of amyloidosis, and that vitamin A supplementation is advised for patients who initiate vutrisiran. The drug plans expressed concerns regarding the anticipated budget impact of vutrisiran and noted that price negotiations have been completed for both patisiran and inotersen for hATTR-PN.

Several of these concerns were addressed in the sponsor's model:

- Quality of life was incorporated in the sponsor's model, by use of EQ-5D data captured in the vutrisiran trial. The impact of the mode and frequency of administration on HRQoL was incorporated with the use of disutility values.
- Hospital admissions were included as part of health care resource use.
- Loss of productivity was included in a scenario analysis.

CADTH was unable to address the following concerns raised from stakeholder input:

- CADTH was unable to consider falls in the economic model, owing to a lack of clinical data and the model structure.
- CADTH was unable to consider confidential negotiated prices for patisiran or inotersen.
- The sponsor's reimbursement request and the Health Canada indication for vutrisiran does not include use in patients with hATTR-CM. No economic information was provided by the sponsor for hATTR-CM.

Economic Review

The current review is for vutrisiran (Amvuttra) for the treatment of stage 1 and 2 hereditary transthyretin-mediated (hATTR) amyloidosis in adults with polyneuropathy (hATTR-PN).[1]

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The proposed indication for vutrisiran is for the treatment of stage 1 and 2 hATTR-PN.[1] The sponsor submitted a cost-utility analysis of vutrisiran compared with patisiran and inotersen, with the modelled population based on patients enrolled in the HELIOS-A trial.

Vutrisiran is available as a prefilled syringe containing 25 mg vutrisiran in a 0.5 mL solution for subcutaneous (SC) injection, with a recommended dosage of 25 mg once every 3 months.[2] The submitted price of vutrisiran is $143,041 per prefilled syringe (25 mg vutrisiran), which corresponds to an annual per-patient cost of $572,164. The annual per-patient cost of patisiran (0.3 mg/kg every 3 weeks via IV infusion) adopted by the sponsor was $[redacted] (assuming vial sharing), whereas the annual per-patient cost of inotersen (284 mg weekly via SC injection) was $419,698. Patients were assumed to receive best supportive care (BSC) for symptom management (including a mix of drug therapies and procedures, such as treatment and procedures for polyneuropathy, gastrointestinal disorders, bladder dysfunction, ocular disorders) in addition to vutrisiran, patisiran, and inotersen.

The clinical outcomes of interest were QALYs and life-years (LYs). The economic analysis was undertaken over a lifetime (40-year) time horizon from the perspective of the Canadian public health care payer. Discounting (1.5% per annum) was applied to both costs and outcomes.

Model Structure

The sponsor submitted a Markov model with 6 health states based on polyneuropathy disability (PND) scores (PND 0, PND I, PND II, PND IIIA, PND IIIB, PND IV), 2 health states related to orthotopic liver transplant (OLT, post-OLT), and an absorbing death state (Figure 1). Patients entered the model distributed across PND health states and were assumed to receive either vutrisiran, patisiran, or inotersen. In each cycle, patients could remain in the same health state, transition to an improved or worse PND health state, or die. Patients who entered the model in PND I could undergo OLT in cycle 3 and remain there for 1 cycle before transitioning to the post-OLT state, where they were assumed to remain until death. Patients were assumed to remain on vutrisiran or patisiran until discontinuation, after which time they were assumed to receive BSC for the remainder of the model horizon or until death. Patients on inotersen were assumed to remain on inotersen for the entire time horizon or until death. The model assumed a cycle length of 6 months.

Model Inputs

The baseline population characteristics used to inform the model were based on the HELIOS-A trial, which included adult patients with hATTR-PN (mean age = 57.9 years; 35.4% female). The baseline distribution of patients across PND states in the model was informed by the distribution in the HELIOS-A trial.

Clinical efficacy inputs for the model for vutrisiran, patisiran, and inotersen were derived from the HELIOS-A trial and a sponsor-submitted NMA. The probability of transitioning between PND states for patients receiving vutrisiran was informed by the HELIOS-A trial, based on the proportion of patients who improved, had no change, or worsened from baseline to month 18. Efficacy in the model was based on a sponsor-conducted NMA, which was used to estimate the relative risk of worsening, maintaining, or improving PND scores between treatments. These values were maintained over the entire model horizon. Treatment discontinuation was informed by data from the HELIOS-A trial for vutrisiran and patisiran, with parametric models used to extrapolate discontinuation beyond the trial duration. The proportion of patients in the PND I health state deemed eligible for OLT was obtained from a previous CADTH submission,[3] whereas the proportion of the OLT cohort that experienced PND progression was obtained from the literature.[4]

Mortality was assumed to increase by PND health state, with a hazard ratio applied to the risk of mortality for the general population in Canada, based on pooled data from the HELIOS-A[5] and APOLLO[6] trials, the patisiran global open-label extension study,[7] and the patisiran phase II, open-label extension study.[8] The risk of death after OLT was obtained from the literature.[9] Serious treatment-related AEs reported for more than 2% of patients in the HELIOS-A trial (vutrisiran, patisiran) or the NEURO-TTR trial (inotersen) were incorporated into the model with an associated cost and disutility.[10,11]

Health state utility values were derived from the HELIOS-A[5] and APOLLO[6] trials and the patisiran global OLE trials[7,8] for the PND health states, based on EQ-5D-5L data and valued using Canadian tariffs.[12] Utility values for the post-OLT state were obtained from the literature.[13] Utilities were constrained to not exceed the utility of the general population in Canada, based on cohort age.[14] Disutilities were included for administration modes (i.e., SC administration in hospital for vutrisiran, SC administration at home for inotersen, IV administration for patisiran)[15] and for adverse events (AEs).[16,17]

Costs included in the model were those related to drug acquisition and administration, AE management, disease management, disease progression, OLT, and end of life. Drug acquisition costs for vutrisiran were based on the sponsor's submitted price,[1] whereas acquisition costs for the comparators were obtained from the Ontario Exceptional Access Program.[18] Vial sharing was assumed by the sponsor (i.e., no wastage). Administration costs and those related to OLT were obtained from a previous CADTH submission[19] and the Ontario Schedule of Benefits.[20] Costs for AE management were derived from the Ontario Schedule of Benefits,[20] whereas costs associated with disease management were obtained from the Ontario and British Columbia formularies, the Ontario Schedule of Benefits, and the Canadian Institute for Health Information.[20-22] Health care resource use was assumed to vary by PND health state, and included treatments and procedures used to manage symptoms as part of BSC. The frequencies of resource use were obtained from a Delphi panel conducted by the sponsor in the UK and from clinical expert input.[23] The sponsor included a one-time disease progression cost, including items related to assistance with ambulation, mobility, and everyday living. Costs for these items were obtained from private vendors and a previous CADTH report.[19,23] End-of-life costs were derived from literature.[24] Costs were adjusted to 2023 values, if required.[25]

Summary of Sponsor's Economic Evaluation Results

The sponsor's base-case and scenario analyses were run probabilistically (5,000 iterations). The deterministic and probabilistic results were similar. The probabilistic findings are presented here. Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Base-Case Results

In the sponsor's base-case analysis, vutrisiran was more costly and more effective than both inotersen and patisiran, with an estimated cost of $7,551,101 and 9.35 QALYs gained over the 40-year horizon. In sequential analysis, vutrisiran was associated with an ICER of $2,811,102 per QALY gained compared with patisiran (incremental costs = $1,128,100; incremental QALYs = 0.40 QALYs) (Table 3). Vutrisiran had a 0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

Results were driven by the drug acquisition costs of vutrisiran (incremental costs vs patisiran = $1,158,747) and the predicted gain in QALYs (incremental QALYs versus patisiran = 0.40). Compared with patisiran, approximately 98% of incremental QALYs gained with vutrisiran were due to the mode and frequency of administration, and 86% of the incremental QALYs gained were accrued after the HELIOS-A trial period (18 months), indicating that the majority of the incremental benefits were generated through extrapolation beyond the available trial data. At the end of the 40-year time horizon, approximately 1% of vutrisiran patients remained alive.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Inotersen	3,923,523	5.77	Reference
Patisiran	6,423,001	8.95	786,233 vs. inotersen
Vutrisiran	7,551,101	9.35	2,811,102 vs. patisiran

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The submitted analysis is based on the sponsor's submitted price for vutrisiran and publicly available list prices for comparators.

Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analysis Results

The sponsor provided several scenarios and sensitivity analyses, including adopting alternative discount rates, perspective, cohort age, mortality assumptions, and assumptions about efficacy. However, sequential analyses were not provided (i.e., vutrisiran was compared to patisiran or inotersen in a pairwise fashion), limiting the interpretation of the findings. CADTH notes that in all scenarios provided by the sponsor, the ICER for vutrisiran compared to patisiran remained above $1,000,000 per QALY gained.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **The comparative efficacy of vutrisiran is uncertain:** As noted in the CADTH clinical review, the efficacy of vutrisiran for the treatment of hATTR-PN is likely to be similar to that of patisiran. CADTH

judged the certainty of the evidence to be, overall, moderate for most outcomes, suggesting that vutrisiran will likely have little to no difference compared to patisiran. The sponsor's noninferiority analysis of vutrisiran versus patisiran was based serum transthyretin (TTR) reduction and suggested that vutrisiran results in little to no clinically important difference compared to patisiran. However, serum TTR is not a validated surrogate for efficacy outcomes in patients with hATTR-PN. There have been no head-to-head trials of vutrisiran and inotersen. Efficacy in the sponsor's pharmacoeconomic model was informed by NMAs (i.e., which estimated the efficacy of vutrisiran relative to patisiran and to inotersen for the proportion of patients whose PND score improved, worsened, or did not change from baseline to month 18). As noted in the CADTH Clinical Review Report, important limitations were identified in the sponsor's NMA (e.g., lack of a systematic review approach, lack of clear inclusion and exclusion criteria, heterogeneity among the included studies, and wide credible intervals) that preclude meaningful conclusions from being drawn for the efficacy of vutrisiran versus inotersen.

  - It is uncertain whether vutrisiran provides a clinical benefit relative to patisiran or to inotersen based on uncertainty in the clinical evidence submitted by the sponsor. CADTH was unable to address this limitation.

- **The impact of AEs was not adequately considered.** In the economic model, the sponsor included serious treatment-related AEs that occurred in at least 2% of patients who received vutrisiran or patisiran in the HELIOS-A trial (i.e., infusion-site phlebitis, infusion-related reactions, infusion-site cellulitis) or who received inotersen in the NEURO-TTR trial (i.e., glomerulonephritis), based on naive comparison, without adjustment or accounting for differences in patient characteristics. Owing to the direct use of clinical trial data, it is not possible to determine whether any observed differences between the therapies are solely due to the treatment or, rather, due to bias or confounding factors. Additionally, the inclusion of only treatment-related AEs is problematic, given that this relies on investigator judgment as to the cause of the AE. Instead, all AEs that have a clinical or cost consequence should be included in the model.[26] As noted in the CADTH clinical review, approximately 26% of patients who received vutrisiran in the HELIOS-A trial experienced at least 1 serious AE, including falls (approximately 2% of patients), which were noted to be important to patients in the input received by CADTH for this review.
  - CADTH was unable to address this limitation.
- **The magnitude of benefit associated with the mode and frequency of administration is uncertain:** The sponsor assumed that there was an administration-related HRQoL decrement associated with the mode and frequency of treatment administration. That is, the sponsor assumed that treatments administered via SC injection in hospital every 12 weeks (i.e., vutrisiran) would be associated with a disutility of −0.0062, whereas treatments administered via IV infusion in hospital every 3 weeks (i.e., patisiran) or via weekly SC injection (i.e., inotersen) would be associated with a disutility of −[redacted] and −0.0156, respectively. These disutility values were based on a poster[15] that described a vignette-based time trade-off study in the UK not specific to patients with hATTR-PN, which has not been peer reviewed and full study details are unavailable. It is thus uncertain whether the results represent the preferences of patients with hATTR-PN in Canada. CADTH notes that approximately 98% of

incremental QALYs gained with vutrisiran relative to patisiran in the sponsor's base case are due to these administration-related utility decrements. Although clinical expert feedback obtained by CADTH for this review indicated that treatments administered by SC injection at a less frequent interval may be associated with a less deleterious impact on a patient's HRQoL, the magnitude of benefit that will be experienced by patients with hATTR-PN who receive vutrisiran instead of patisiran or inotersen is uncertain.

  - CADTH explored the impact of uncertainty in the magnitude of HRQoL benefit associated with the mode and frequency of administration in scenario analyses. CADTH notes that if the magnitude of benefit with less frequent SC injections is smaller than anticipated by the sponsor, the incremental QALYs gained with vutrisiran compared with patisiran will be lower than predicted in the sponsor's base case, resulting in a higher ICER.

- **Uncertainty in long-term treatment effectiveness of vutrisiran:** Evidence of the long-term effectiveness of vutrisiran beyond 18 months is not available. In the pharmacoeconomic model, the sponsor assumed that patients who remain on vutrisiran treatment maintain the efficacy of vutrisiran estimated from the HELIOS-A trial for the duration of treatment, without consideration of potential waning of the treatment effect. Given that the majority of the incremental QALYs (86%) predicted by the sponsor's model were derived on the basis of extrapolated findings rather than observed benefit, the lack of long-term data and the lack of consideration of potential waning of effectiveness introduces considerable uncertainty into the analysis.
  - CADTH was unable to address this limitation due to a lack of clinical data. The direction and magnitude of the impact of this limitation is unknown, given that the comparative rate of potential effectiveness waning with vutrisiran versus patisiran or inotersen is unknown.
- **The survival benefit predicted for vutrisiran is highly uncertain.** The sponsor's base case predicts a survival benefit with vutrisiran relative to patisiran (incremental LYs = 0.07) and inotersen (incremental LYs = 3.26). As noted in the CADTH clinical review, the certainty of the evidence is very low for the effects of vutrisiran compared to patisiran on mortality, and there has been no comparison of survival between vutrisiran and inotersen. As such, the gain in LYs predicted with the use of vutrisiran in the sponsor's base case is highly uncertain.
  - CADTH was unable to address this limitation.
- **The health states used in the model did not capture all aspects of the condition:** The sponsor submitted a Markov model with health states defined based on PND scores (Figure 1). The PND scale classifies patients based on mobility impairment and does not capture autonomic symptoms associated with hATTR. hATTR is a multifaceted disease that causes motor, sensory, and autonomic neuropathy and leads to progressive muscle weakness and disability, pain, wasting, gastrointestinal symptoms, and other autonomic symptoms, such as orthostatic hypotension, which were not captured using PND health states. In addition, as noted in the CADTH clinical review, PND is not sensitive to small changes,[27] and PND's validity, reliability, and responsiveness to change have not been investigated in patients with hATTR-PN.[28]

- CADTH could not address this limitation associated with the model structure.

Additional limitations were identified, but were not considered to be key limitations:

- **Treatment costs were accrued by patients in the PND IV health state:** Although the sponsor's pharmacoeconomic report indicated that treatment with vutrisiran and patisiran would be discontinued once patients progressed to the PND IV state, drug acquisition costs were still accrued in the pharmacoeconomic model by patients in this health state, thus overestimating the acquisition costs of vutrisiran and patisiran in the model. Clinical expert feedback obtained by CADTH for this review indicated that patients would likely discontinue treatment at this stage; however, use of vutrisiran and patisiran is not precluded in the drug monographs. Testing by CADTH indicates that the exclusion of costs related to the use of vutrisiran and patisiran by patients in PND IV has little impact on the ICER.
- **Health state costs may not be representative of costs to Canadian public payers:** The sponsor's model included costs related to disease management and progression, which included some items unlikely to be covered by public health care payers in Canada. To inform inputs for the pharmacoeconomic model, the sponsor undertook a Delphi panel that involved clinical experts in the UK and focused on treatments available in the UK health system, and assumed that treatment practices would be the same as those in Canada.[23] Potential differences in treatment practices between Canada and the UK were not considered, and the resources included as part of disease management and progression include some that not typically covered by public health care payers in Canada, such as dental care, acupuncture, physiotherapy, and orthotics. The sponsor additionally included a one-time disease progression cost for patients whose condition worsened by 1 PND health state (e.g., from PND 0 to I, I to II). The resources included in this one-time cost included walking frames or chairs, canes, wheelchairs, and home renovations, which may not be covered by public health care payers in Canada.
    - CADTH was unable to address this limitation.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (refer to Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Costs and consequences of genetic testing to confirm a diagnosis of hATTR were not included in the model.	Likely reasonable, given that all comparators require a confirmed diagnosis of hATTR.
Patients who discontinue vutrisiran or patisiran were assumed to receive BSC until death or the end of the time horizon (40 years).	Inappropriate. Clinical expert input received by CADTH indicated that patients who discontinue treatment would likely switch to an alternative treatment. The impact of treatment switching on the ICER is unknown.

Sponsor's key assumption	CADTH comment
Patients on inotersen were assumed to remain on treatment until death or the end of the time horizon (40 years).	Inappropriate. Clinical expert input received by CADTH indicated that patients may discontinue inotersen due to AEs, lack of efficacy, or other factors, including cost and inconvenience. This assumption likely overestimated the costs of inotersen.
Mortality for patients in the PND 0 and I health states was the same as for the general population in Canada.	Uncertain. Clinical expert input received by CADTH indicated that some patients may have an increased risk of undiagnosed cardiac involvement, such as arrythmia, which may increase their risk of death, compared to those in the general population.
To inform treatment costs in the pharmacoeconomic model, the sponsor used treatment discontinuation data from the HELIOS-A trial for vutrisiran and patisiran, with parametric models used to extrapolate discontinuation beyond the trial duration (18 months), resulting in 51% of patients remaining on treatment after 40 years.	Inappropriate. Clinical expert feedback received by CADTH for this review suggests that the proportion of patients remaining on treatment for 40 years is highly uncertain and likely overestimated. CADTH was unable to address this limitation due to the lack of long-term evidence on treatment duration.
Vitamin A costs are not included in the analysis.	Reasonable. Although the sponsor stated that, given vitamin A supplementation is also recommended for patisiran, costs for vitamin A supplementation were not included for simplicity.

AE = adverse event; BSC = best supportive care; hATTR = hereditary transthyretin-mediated amyloidosis; ICER = incremental cost-effectiveness ratio; PND = polyneuropathy disability.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH was unable to address the uncertainty in the comparative clinical data, the impact of AEs on the ICER, the magnitude of benefit associated with the mode and frequency of administration, and the long-term effectiveness of vutrisiran. Given these limitations, CADTH was unable to provide more reliable estimate of the cost-effectiveness of vutrisiran.

Based on the sponsor's submitted results (Table 3), vutrisiran is not a cost-effective treatment for hATTR-PN compared with patisiran, with an ICER of $2,811,102 per QALY gained. The probability that vutrisiran is cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 0%. In the sponsor's analysis, the incremental gain in QALYs associated with vutrisiran compared with patisiran was 0.40, which were accrued almost entirely due to the mode and frequency of administration. That is, 98% of the incremental QALYs gained with vutrisiran were due to vutrisiran being administered less frequently via SC injection compared with patisiran (which is administered more frequently and via IV infusion).

Scenario Analysis Results

CADTH undertook price reduction analyses based on the sponsor's base-case results. The sponsor's base case suggests that a 50.4% reduction in the price of vutrisiran would be required to achieve cost-effectiveness at a $50,000 per QALY threshold (Appendix 4, Table 8).

CADTH undertook sensitivity analyses based on the sponsor's base-case results to explore the impact of uncertainty in the magnitude of HRQoL benefit associated with the mode and frequency of treatment administration. If there is no HRQoL benefit associated with reducing the frequency of administration and changing from IV infusion to SC injection (i.e., administration-related disutility was assumed to be 0 for all

treatments), the ICER for vutrisiran is $163,273,835 (Table 9). If the benefit experienced by patients receiving vutrisiran is 25% lower than assumed in the sponsor's base case (i.e., if the disutility associated with SC injection every 3 months is −0.0080 instead of −0.0062), the ICER for vutrisiran increases by approximately $200,000, compared with the sponsor's base case.

Issues for Consideration

- The sponsor is the market authorization holder for both vutrisiran and patisiran, and the sponsor has indicated that vutrisiran is expected to replace patisiran as treatment for hATTR-PN.[1] The sponsor's analysis is based on the publicly available list price for patisiran and does not consider the negotiated confidential rebate for patisiran.
- Patient input and clinical expert feedback received by CADTH suggests that some patients may self-inject vutrisiran at home. This was not captured in the sponsor's economic evaluation, which assumed that vutrisiran would be administered by SC injection at an infusion clinic.
- Clinical trials investigating the use of vutrisiran for hATTR-CM are ongoing. Patients with hATTR-PN and cardiomyopathy were excluded from the HELIOS-A trial. The cost-effectiveness of vutrisiran in patients with hATTR-PN and cardiomyopathy is unknown.
- The cost-effectiveness of vutrisiran among patients with hATTR-PN who have previously undergone liver transplant is unknown, owing to their exclusion from the HELIOS-A trial. Clinical expert input received by CADTH suggests that vutrisiran may be considered for patients with hATTR-PN after liver transplant.

Overall Conclusions

The CADTH clinical review concluded that the efficacy of vutrisiran for the treatment hATTR-PN will likely be similar to that of patisiran. CADTH judged the certainty of the evidence to be moderate for most outcomes, indicating that vutrisiran will likely have little to no difference compared to patisiran. There have been no head-to-head trials of vutrisiran versus inotersen, and important limitations were identified in the sponsor's NMA that preclude meaningful conclusions from being drawn for this comparison.

CADTH was unable to address the uncertainty related to comparative clinical data, magnitude of HRQoL impact associated with the mode and frequency of treatment administration, predicted survival benefit, and long-term effectiveness. Given these limitations, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of vutrisiran relative to currently available treatment options.

Based on the sponsor's submitted base-case results for the reimbursement population, vutrisiran is not a cost-effective treatment for hATTR-PN, with an ICER of $2,811,102 per QALY gained compared with patisiran, and a 0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. The sponsor's model estimates that treatment with vutrisiran among patients with hATTR-PN will result in an incremental gain of 0.40 QALYs compared to treatment with patisiran over the 40-year time horizon. Most of this benefit (86%) was accrued in the extrapolated period (i.e., after 18 months). In the absence of data beyond 18 months, the incremental QALYs predicted in the sponsor's analysis may be overestimated. Further, 98% of the incremental QALYs gained were due to the reduced frequency of administration and

change in mode of administration compared with patisiran. If the HRQoL benefit of receiving treatment less frequently via SC injection (versus more frequently via IV injection) is less than assumed by the sponsor, the incremental QALYs between vutrisiran and patisiran would be lower and the ICER would be higher than the predicted $2,811,102 per QALY gained in the sponsor's base case.

The clinical evidence submitted by the sponsor suggests that vutrisiran is likely similar to patisiran for the treatment of hATTR-PN; however, no conclusions could be made regarding the comparative efficacy of vutrisiran relative to inotersen. Given that vutrisiran is likely similar to patisiran and the uncertainty in the comparative clinical data relative to inotersen, there is insufficient evidence to suggest that vutrisiran should be priced higher than currently reimbursed treatments for hATTR-PN. Thus, to ensure cost-effectiveness, vutrisiran should be priced no more than the lowest-cost treatment option funded in the population to be reimbursed.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 5: CADTH Cost Comparison Table for Treatment of hATTR-PN

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Average annual cost ($)
Vutrisiran	25 mg	Prefilled syringe for SC injection	143,041.0000[a]	25 mg every 3 months	1,566.50	572,164
Comparators						
Patisiran (Onpattro)	2 mg/mL in a 5 mL vial	Injection solution	2,100.4813 per mL	0.3 mg/kg (to a maximum of 30 mg) every 3 weeks	1,500.34	548,000
Inotersen (Tegsedi)	284 mg per 1.5 mL	Prefilled syringe for SC injection	8,043.4874	284 mg weekly	1,149.07	419,697

SC = subcutaneous.

Note: All prices are from the Ontario Exceptional Access Program (accessed July 2023), unless otherwise indicated, and do not include dispensing fees. For dosing that depends on weight, CADTH assumed 75 kg. Cost estimates include wastage for single-use vials.

[a]Sponsor-submitted price.[1]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

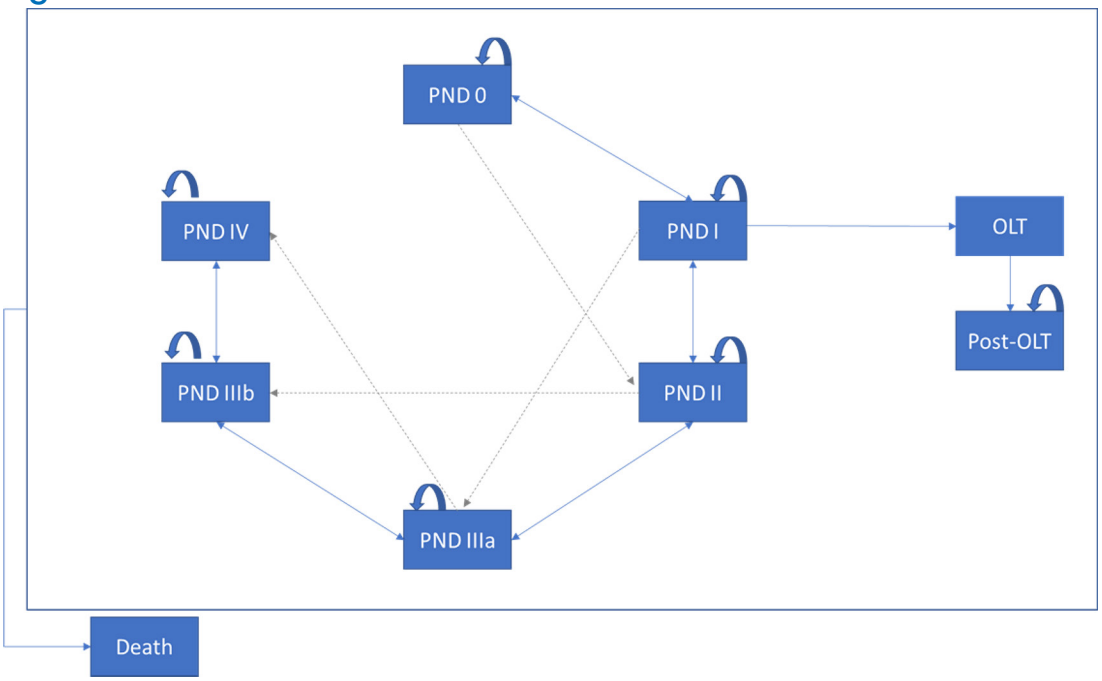
Table 6: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	Yes	No comments.
Model has been adequately programmed and has sufficient face validity	Yes	No comments.
Model structure is adequate for decision problem	No	Health states were defined by PND scores, which do not capture autonomic symptoms associated with hATTR amyloidosis.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comments.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comments.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	Yes	No comments.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Model Structure



OLT = orthotopic liver transplant; PND = polyneuropathy disability.

Source: Sponsor's pharmacoeconomic submission.[1]

Detailed Results of the Sponsor's Base Case

Table 7: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Vutrisiran	Patisiran	Inotersen
Discounted LYs			
PND 0	1.50	1.88	0.21
PND I	3.31	3.30	1.22
PND II	4.00	3.77	2.18
PND IIIA	2.84	2.59	2.26
PND IIIB	1.71	1.61	1.91
PND IV	2.05	2.20	4.39
OLT	0.13	0.13	0.10
Total	**15.54**	**15.48**	**12.28**

Parameter	Vutrisiran	Patisiran	Inotersen
Discounted QALYs			
PND 0	1.21	1.51	0.17
PND I	2.61	2.60	0.97
PND II	2.70	2.55	1.48
PND IIIA	1.57	1.43	1.25
PND IIIB	0.69	0.65	0.77
PND IV	0.56	0.60	1.20
OLT	0.08	0.08	0.07
AEs	0.00	0.00	0.00
Administration	−0.08	−0.47	−0.13
Total	**9.35**	**8.95**	**5.77**
Discounted costs ($)			
Acquisition	7,136,817	5,978,070	3,404,885
Administration	337	37,440	7
Premedication	0	1,039	0
HCRU	385,516	378,007	487,210
AEs	0	74	885
End of life	25,227	25,172	27,523
OLT	3,203	3,200	3,013
Total	**7,551,101**	**6,423,001**	**3,923,523**

AEs = adverse events; ICER = incremental cost-effectiveness ratio; HCRU = health care resource utilization; LY = life-year; NA = not applicable; OLT = orthotopic liver transplant; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Table 8: CADTH Price Reduction Analyses

Price reduction	ICERs for vutrisiran vs. comparators ($/QALY)
No price reduction	WTP < $831,180: inotersen $831,180 < WTP < $2,290,447: patisiran $2,290,447 < WTP: vutrisiran
10%	WTP < $802,225: inotersen $802,225 < WTP: vutrisiran
20%	WTP < $615,401: inotersen $615,401 < WTP: vutrisiran
30%	WTP < $428,576: inotersen $428,576 < WTP: vutrisiran
40%	WTP < $241,752: inotersen $241,752 < WTP: vutrisiran
50%	WTP < $54,928: inotersen $54,928 < WTP: vutrisiran
60%	Vutrisiran dominant

WTP = willingness-to-pay threshold.

Scenario Analyses

Table 9: Scenario Analysis

Stepped analysis	Comparator	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	Inotersen	3,940,830	5.60	Reference
	Patisiran	6,932,110	9.20	831,180 vs. inotersen
	Vutrisiran	7,932,137	9.64	2,290,447 vs. patisiran
CADTH scenario 1: no additional utility benefit associated with administration mode.	Inotersen	3,940,830	5.73	Reference
	Patisiran	6,932,110	9.71	751,102 vs. inotersen
	Vutrisiran	7,932,137	9.72	163,273,835 vs. patisiran
CADTH scenario 2: 25% reduction in the additional utility benefit associated with administration mode.	Inotersen	3,940,830	5.60	Reference
	Patisiran	6,932,110	9.20	831,180 vs. inotersen
	Vutrisiran	7,932,137	9.62	2,402,849 vs. patisiran

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: All analyses were conducted deterministically.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 10: Summary of Key Take-Aways

Key take-aways of the BIA
• CADTH identified the following key limitations with the sponsor's analysis: uncertainty in the number of patients with hATTR-PN eligible for vutrisiran; and uncertainty in the price of drugs paid for by public drug plans. In the absence of more reliable input values related to the eligible population size, the sponsor's base case was maintained. • The net budget impact of reimbursing vutrisiran was estimated to be $4,793,861 in Year 1, $8,173,140 in Year 2, and $10,845,128 in Year 3, for a 3-year incremental cost of $23,812,130. The estimated budget impact is highly sensitive to the number of patients eligible for vutrisiran and reflects its use only by patients with hATTR-PN. • The sponsor is the market authorization holder for both vutrisiran and patisiran, and has indicated that vutrisiran will replace patisiran. The sponsor's budget impact analysis is based on the publicly available list price of patisiran and does not consider the negotiated confidential price of patisiran.

Summary of Sponsor's BIA

The sponsor submitted a budget impact analysis (BIA) estimating the budget impact of reimbursing vutrisiran for patients with hATTR.[29] The BIA was undertaken from the perspective of a Canadian public payer over a 3-year time horizon (January 2023 to January 2026). The number of patients with hATTR-PN eligible for vutrisiran treatment was based on the sponsor's internal estimates and assumptions,[30] and the sponsor assumed that patients with hATTR-CM would receive tafamidis and would not be eligible for vutrisiran. The sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec), as well as the Non-Insured Health Benefits (NIHB) Program. Data to inform the model were obtained from various sources, including the published literature, the sponsor's internal data, and assumptions.

The sponsor compared a reference scenario in which patients with hATTR-PN received patisiran or inotersen to a new drug scenario in which vutrisiran was assumed to be reimbursed for hATTR amyloidosis. In both the reference and new drug scenarios, all treatments were assumed to be received on top of BSC, with no costs attributed to BSC in the analysis. The sponsor's analysis included drug acquisition costs for vutrisiran, patisiran, and inotersen, and premedication costs (patisiran only). The sponsor assumed that all patients would remain on treatment throughout the 3-year BIA time horizon (i.e., no treatment discontinuation). The costs of treatments were obtained from Ontario Exceptional Access Program formulary, Ontario Drug Benefit Formulary, and British Columbia formulary,[18,20,22] with the price of vutrisiran based on the sponsor's submitted price.[29] The market shares for the reference scenario were obtained from sponsor's internal data and assumptions. In the new drug scenario, the sponsor assumed that vutrisiran would capture 86% of the total market share by year 3 based on internal data and assumptions. The sponsor assumed that 50% of patisiran-treated patients will switch to vutrisiran in each year of the analysis. Key inputs to the BIA are documented in Table 12.

Table 11: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
Number of patients with hATTR-PN eligible for drug under review[a]	111 / 136 / 161
Market uptake (3 years)	
Uptake (reference scenario)	
Patisiran	87% / 90% / 91%
Inotersen	13% / 10% / 9%
Uptake (new drug scenario)	
Vutrisiran	55% / 76% / 86%
Patisiran	32% / 13% / 6%
Inotersen	13% / 10% / 9%
Cost of treatment (per patient per year)	
Vutrisiran	$572,164
Patisiran	$[redacted][c]
Inotersen	$419,698

[a]Based on the sponsor's internal data pertaining to the total number of patients treated with patisiran and inotersen as of May 2023, assuming that all patients eligible for treatment are on treatment. An additional 25 patients were assumed by the sponsor to be diagnosed with hATTR amyloidosis each year.

[b]The sponsor assumed that all patients with hATTR-CM will receive tafamidis and would not be eligible for vutrisiran.

[c]Sponsor assumed vial sharing.

Summary of the Sponsor's BIA Results

Results of the sponsor's analysis suggest that the reimbursement of vutrisiran for the treatment for hATTR amyloidosis is expected to be $4,793,861 in Year 1, $8,173,140 in Year 2, and $10,845,128 in Year 3, for a 3-year incremental cost of $23,812,130. CADTH notes that the sponsor's results are predicated on the assumption that no patients with hATTR-CM will receive vutrisiran.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **The number of patients with hATTR-PN eligible for vutrisiran is highly uncertain:** In the BIA, the sponsor assumed that there would be 111, 136, and 161 patients with hATTR-PN eligible for vutrisiran in Year 1, Year 2, and Year 3 of the analysis, based on the number of patients currently receiving treatment with patisiran or inotersen and an estimated growth of 25 newly diagnosed patients per year. However, the sponsor additionally cites a study that estimates the prevalence of hATTR-PN to be between 0.32 per million and 7.52 per million population,[30] noting that the prevalence in Canada likely lies between 1.48 per million and 7.52 per million population.[29] While the true prevalence of hATTR-PN in Canada is uncertain, these prevalence estimates equate to an estimated 53 to 270 patients

with hATTR-PN in Canada (range: 46 to 232 excluding Quebec); however these prevalence estimates may be lower than the true prevalence, owing to, for example, the emergence of survival-extending treatments and improved diagnostic processes and clinician knowledge over time.[30] Although the number of patients estimated by the sponson's internal data lies within the range estimated using these prevalence values, the number of patients with hATTR-PN in Canada remains uncertain.

    - CADTH explored uncertainty in the number of patients with hATTR-PN in scenario analysis.
- **The price of drugs paid for by public drug plans is uncertain:** The sponsor's analysis is based on publicly available list prices for all drugs. Patisiran and inotersen have previously gone through negotiations at pCPA, and actual costs paid by public drug plans are not known. CADTH notes that the sponsor is the market authorization holder for both vutrisiran and patisiran; however, the sponsor's analysis is based on the publicly available list price of patisiran and does not consider the negotiated confidential price of patisiran.
    - This limitation could not be addressed by CADTH.

Additional limitations were identified but were not considered to be key limitations. These limitations include:

- **Costs of BSC were not included in the analysis:** The sponsor assumed the cost of BSC were negligible and they were not included in the BIA. Given that vutrisiran, patisiran, and inotersen are all expected by the sponsor to be used in addition to BSC, the exclusion of BSC costs is unlikely to impact the results of the BIA.
- **No newly diagnosed patients would initiate inotersen:** The sponsor assumed that no newly diagnosed patients would start treatment with inotersen in the 3-years BIA. Clinical experts consulted by CADTH for this review indicated that some patients might chose to start inotersen instead of vutrisiran or patisiran. However, given the small number of patients expected to be treated with inotersen, it is unlikely to impact the results of the BIA.

CADTH Reanalyses of the BIA

In the absence of more reliable estimates to inform the key parameters of the BIA, the sponsor's submitted base case was maintained (Table 12). CADTH expects that the budget impact of reimbursing vutrisiran for the treatment hATTR-PN will be sensitive to more reliable inputs which may affect the market size calculation.

CADTH conducted a scenario analysis to explore the impact of uncertainty in the number of patients with hATTR-PN (Table 11). In this scenario, which assumed a prevalence of 232 patients with hATTR-PN in Canada (excluding Quebec), the budget impact of reimbursing vutrisiran for hATTR-PN was $48,726,388 over the first 3 years of reimbursement.

Table 12: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	Reference	41,413,248	53,752,650	66,092,053	78,431,456	198,276,160
	New drug	41,413,248	58,546,511	74,265,194	89,276,585	222,088,290
	Budget impact	**0**	**4,793,861**	**8,173,140**	**10,845,128**	**23,812,130**
CADTH sensitivity analysis 1: increased prevalence of hATTR-PN[a]	Reference	111,719,4589	124,454,335	137,043,816	149,555,634	411,053,785
	New drug	111,719,459	135,553,635	153,991,063	170,235,475	459,780,173
	Budget impact	**0**	**11,099,300**	**16,947,247**	**20,679,841**	**48,726,388**

BIA = budget impact analysis; hATTR-PN = hereditary transthyretin-mediated amyloidosis with polyneuropathy.

[a]Assumes a prevalence of 232 patients with hATTR-PN in Year 1 and an incidence of 25 newly diagnosed patients per year.

Stakeholder Input

Patient Input

Date: July 12, 2023

To: Whom it may concern

Re: Positive recommendation and reimbursement for Amvuttra

To whom it may concern,

We are a medium sized non-for-profit organization dedicated to educating and supporting patients living with all forms of transthyretin amyloidosis. We primarily represent Canadian patients, caregivers, family and some volunteer health workers, but also have members in the USA, UK and other European countries.

Please accept this letter as TAC's formal submission to CADTH in support of a positive recommendation and subsequent reimbursement of Amvuttra/(Vutrisiran). As you may know, Amvuttra has been approved in many jurisdictions across the globe, with the exception of Canada, which is an immense disservice to Canadian TTR-amyloidosis patients. We have to be leaders in our approach to health care and rare disease treatments. It comes at a cost; however, we should not be discriminated against.

Vutrisiran, previously known as, Amvuttra, is a medication used for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. It is a double-stranded small interfering RNA that interferes with the expression of the transthyretin gene.

Vutrisiran is in a class of medications called small interfering RNAs (siRNAs). It works by decreasing the amount of abnormal proteins and the amount of abnormal protein deposited in the body's tissues, which decreases nerve damage.

Patients have reported the following feedback whilst being on the new drug. Most have previously been receiving Onpattro/Patisiran.

Why it should be available?

Based on qualitative interviews conducted with patients who have previously taken Amvuttra, and prior to that, Onpattro (Patisiran), the following feedback was provided:

- As Amvuttra is administered as a single dose every three months, it is far more convenient than previous options. This allows patients the ability to live their lives as normally as possible, without the disturbances of constant dosing and clinic visits.
- Amvuttra is administered as a subcutaneous injection, rather than an infusion. This means patients are able to learn, and self-administer their therapy, allowing for far more freedom and less reliance on infusion networks and clinic visits. It is important to note, clinic visits are not an individual endeavour, but a dual-effort including a patient's caregiver. Missing a day of work to travel to an infusion centre is also eliminated through self-administration.
- This self-administration also eliminates the necessity of pre-medicine prior to therapy.

- Amvuttra is a more cost-effective option than its predecessor, Onpattro. Cost-effectiveness is always a driving factor in reimbursement decisions, and thus, having a better but cheaper option is undoubtedly desirable for all parties involved.
- Hospital admissions may be decreased with patients on correct therapy, which decreases the pharmacoeconomic burden of illness related to TTR-amyloidosis. At a time where hospitals remain over-burdened due to the pandemic, keeping patients who are typically elderly and already have frail immune systems, away from hospital centres is a key impetus for maintaining optimal health.
- Falls may be lessened, which leads to fewer hospital visits and a higher maintenance of quality of life.

Onpattro is a great therapy and may be preferred and in fact needed by some. However, as an older generation therapy, it does not have the same advantages as Amvuttra. it is administered by infusion once every 3 weeks by a nurse. The procedure takes approximately 3 hours, plus the travel time of the nurse and/or patients. This weighs heavily on patients' limited resources. With health care in Canada suffering and under so much pressure, this adds to the existing burden. Amvuttra/Vutrisiran should be available for patients with his life-threatening rare disease.

Please should you have any questions or should I have missed any important points, please feel free to email or call.

Your sincerely,

Anne Marie Carr

Clinician Input

Date: June 2, 2023

To: Canadian Agency for Drugs, Technology and Health (CADTH)

Re: Vutrisiran

Dear CADTH,

Over the last few years there have been tremendous advances in amyloidosis care, both in recognition and diagnostic approaches, and importantly, new and/or enhanced therapeutic strategies. Because amyloidosis is a relatively rare multi-system disorder, a multi-disciplinary team approach has been demonstrated to be the optimal model of care. Based on this model, we have created the Amyloidosis Program of Calgary (APC) aiming to build the infrastructure for the diagnosis and treatment of amyloidosis in Calgary and the surrounding regions. Furthermore, the APC is engaged in multiple initiatives designed to improve patient care in our center and across Canada, including research, education, quality improvement and clinical pathway development, among others.

As Co-director of the APC, I would like to express support for the public reimbursement of vutrisiran in Canada. Vutrisiran is a micro-RNA inhibitor and transthyretin amyloidosis (ATTR) gene silencer, designed

to attenuate disease progression by suppressing hepatic production of the precursor protein transthyretin. This agent has recently demonstrated efficacy and tolerability in treating patients with hereditary ATTR polyneuropathy (hATTR-PN), a debilitating disease that causes predominantly neuropathic but also multisystem manifestations. Vurtrisiran represents a second generation ATTR gene silencer, and an improvement over the currently approved patisiran in that intravenous infusion dosing is only administered every 3 months, rather than every 3 weeks. This medication has the potential to dramatically improve patients' quality of life while attenuating progression of this devastating disease. Vutrisiran is also currently being evaluated in patients with ATTR cardiomyopathy (ATTR-CM).

Thank you for your consideration and please do not hesitate to contact me if there are any questions.

Sincerely,

Nowell M. Fine, MD SM FRCPC FACC FHFSA FCCS FASE

Associate Clinical Professor of Cardiac Sciences, Medicine and Community Health Sciences

Director of Echocardiography, Heart Failure Cardiologist

Alberta Health Services, Calgary Zone

Clinical Director, Libin Cardiovascular Institute

Co-director, Amyloidosis Program of Calgary

Cumming School of Medicine, University of Calgary

ISSN: 2563-6596

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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.