Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value

Final Evidence Report

October 4, 2018

Prepared for

NOTICE: On October 5, 2018, following final publication of this report, the FDA approved inotersen (Akcea Therapeutics) under the brand name TEGSEDI™ for treatment of polyneuropathy of hereditary transthyretin-amyloidosis in adults. The label includes a black box warning for serious risk of low platelet counts (thrombocytopenia) and kidney inflammation (glomerulonephritis). TEGSEDI is therefore only available through the restricted TEGSEDI Risk Evaluation and Mitigation Strategy (REMS) Program. ICER has made no changes to this report following the FDA approval of inotersen.

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Karen Lasser served as the lead author for this report and wrote the background, other benefits, and contextual considerations sections of the report. Kristin Mickle led the systematic review and authorship of the comparative clinical effectiveness section. Rick Chapman was responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Dan Ollendorf and Steve Pearson provided methodologic guidance on the clinical and economic evaluations. The role of the University of California, Davis (UC Davis) modeling group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of UC Davis. ICER would like to thank Ellie Adair, Laura Cianciolo, Katherine Fazioli, David Fox, Ariel Jurmain, Shelly Kelly, Sonya Khan, Madeline O'Grady, Matt Seidner, and Sumeyye Sumar for their contributions to this report. None of the authors above disclosed any conflicts of interest.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical and academic experts and patient advocacy group provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/amyloidosis-stakeholder-list/.

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List of Acronyms Used in this Report

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ASO	Antisense oligonucleotide
BSC	Best supportive care
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
FAC	Familial amyloid cardiomyopathy
FAP	Familial amyloid polyneuropathy
hATTR	Hereditary transthyretin amyloidosis
ITT	Intention to treat
LSM	Least squares mean
LV	Left ventricle
mBMI	Modified body mass index
mRNA	Messenger RNA
NIS	Neuropathy impairment score
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic protein
NYHA	New York Heart Association
OLE	Open-label extension
PND	Polyneuropathy disability
QALY	Quality-adjusted life year
QOL	Quality of life
RNAi	RNA interference
SAE	Serious adverse event
SF-36	Short-form 36 questionnaire
TTR	Transthyretin
USPSTF	United States Preventive Services Task Force

Executive Summary

Background

Hereditary transthyretin amyloidosis (hATTR) is a multi-system illness caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver. A rare, progressive, and fatal autosomal dominant hereditary disorder, hATTR spans a spectrum of clinical presentations. These presentations include a predominantly neurologic phenotype (formerly known as familial amyloid polyneuropathy [FAP]), and a predominantly cardiac phenotype (formerly known as familial cardiomyopathy), although the majority of cases express both neurologic and cardiac manifestations. hATTR profoundly impacts all aspects of quality of life. Given that the disease may affect multiple organ systems and may progress rapidly, a wide variety of manifestations may include (but are not limited to) weight loss, wasting, difficulty walking, and alternating constipation and uncontrollable diarrhea. The neuropathy-predominant illness affects at least 10,000 people worldwide, and roughly 3,000-3,500 people in the United States (US).[1,2]

Until recently, there was no treatment available that reverses the damage already caused by amyloid deposits, nor was there any FDA-approved treatment available in the US. On August 10, 2018, the United States (US) Food and Drug Administration (FDA) approved patisiran (Onpattro™, Alnylam Pharmaceuticals) for the treatment of peripheral nerve disease (polyneuropathy) caused by hATTR in adult patients.[3] In addition, inotersen (investigational, Akcea Therapeutics) is currently under FDA review for hATTR-associated polyneuropathy, with an expected decision in October 2018.

Two other currently available treatments in the US include liver transplant and diflunisal. Limitations of liver transplant as a treatment for hATTR include allograft availability, neurologic and cardiac disease progression following transplant (e.g., of concurrent hATTR cardiomyopathy at the time of transplant), and substantial morbidity and mortality associated with transplant itself. Diflunisal, a generic nonsteroidal anti-inflammatory drug (NSAID) which stabilizes transthyretin tetramers, is available in the US and is used off-label in hATTR. However, long-term use of diflunisal is limited by risks common to all NSAIDs, such as gastrointestinal bleeding, worsening of renal insufficiency, and cardiovascular events (e.g., MI, stroke). Additionally, diflunisal does not reverse neurologic or cardiac impairment.

Inotersen and Patisiran

There are two new medications for treatment of hATTR: patisiran (Onpattro™, Alnylam Pharmaceuticals; FDA-approved August 2018) and inotersen (TEGSEDI,™ Akcea Therapeutics; under FDA review). Patisiran is an RNA interference (RNAi) therapeutic that is administered by IV infusion every three weeks.[4,5] Inotersen (investigational, Akcea Therapeutics), a once weekly subcutaneous

injection, is an antisense oligonucleotide (ASO) that complexes with messenger RNA (mRNA) that encodes for TTR.[5] Inotersen was approved for use in the European Union in July 2018.[6] Seeking more data from the manufacturer, the US FDA has delayed the approval date for inotersen from July 2018 to a new PDUFA goal date of October 6, 2018.[7]

As the first TTR gene silencers inhibiting production of the protein inducing hATTR, clinical interest in the use of patisiran and inotersen is high. However, there may be uncertainties related to the translation of neurologic outcomes to longer-term clinical benefit, the durability of such benefit, potential harms of treatment, and the costs associated with the use of these medications. Uncertainty also remains regarding when to initiate therapy in a genopositive individual, thereby necessitating treatment for the remainder of the patient's lifetime with attendant costs and recalibration of the risk to benefit ratio. This report reviews the clinical evidence and potential economic impact of inotersen and patisiran for hATTR.

Insights Gained from Discussions with Patients and Patient Groups

Below, we provide a summary of the main themes from discussions with patients and individual patient and caregiver submissions. We note that these themes may not represent the experiences of all patients with hATTR, particularly those who are in the early stages and less burdened by the condition.

We heard from patients, patient advocacy groups, and caregivers that hATTR:

- is a severe disabling illness that profoundly impacts all aspects of quality of life,
- results in loss of independence and a sense of "normalcy,"
- prevents patients from working, having hobbies, and ultimately, leaving their homes and performing activities of daily living (e.g., dressing, feeding, or bathing),
- affects multiple members and generations of families,
- leads to physical disability that makes it difficult for patients to travel to centers of excellence to receive treatment.

Patients describe symptoms such as wasting, difficulty walking, and alternating constipation and uncontrollable diarrhea, which they describe as embarrassing. Patients describe a devastating impact of the illness on family life, with members of multiple generations of the same family affected. Some individuals care for older family members who are affected while also worrying about children who may later develop hATTR. Caretakers describe the emotional burden of "knowing what's to come," and often struggle to balance the responsibilities of working, providing for family members in the home, and transporting patients to medical appointments.

Patients also voice concern that in the face of such suffering, as of July 2018 there are currently no treatments approved in the US specifically for hATTR. Current off-label treatments are of limited efficacy, and patients often have difficulty travelling to a small number of Amyloid Centers of

Excellence at academic medical centers in the US to receive treatment. Therefore, patients and families value convenience of therapies that can be administered in the home. Patients also expressed a willingness to tolerate medication side effects: "The side effects would have to be pretty bad to be worse than the disease." While new treatments for hATTR offer much-needed hope to patients and their families, many patients also voiced concern about potential cost of treatments. While the idea of slowing, stopping, or even reversing disease progression was felt to be a critical advancement, patients were clearly not interested in financially burdening or bankrupting their families to pay for these treatments.

Comparative Clinical Effectiveness

We reviewed the clinical effectiveness of patisiran and inotersen in patients with hATTR in comparison with usual care. Differences in the primary outcome measures and trial population (e.g., race, geographic region, disease severity) precluded direct comparison of the Phase III APOLLO; (patisiran) and NEURO-TTR (inotersen) trials. As a result, we present data on inotersen and patisiran efficacy in relation to their comparators in the clinical trials.

Inotersen

We included four references evaluating the efficacy and safety of inotersen. One peer-reviewed publication[8] and two conference presentations[9,10] reported data from the Phase III NEURO-TTR trial, and the fourth, a full-text publication,[11] included cardiac data from an investigator-initiated, single-arm, open label trial.

NEURO-TTR was a Phase III randomized controlled trial evaluating neurologic function using the mNIS+7$_{Ionis}$ and Norfolk QOL-DN as the primary outcomes after 15 months of treatment.[8] Stabilization was defined as a 0-point change from baseline mNIS +7. Eligibility criteria included FAP stages 1 and 2, NIS scores between 10-130, positive amyloid biopsy, and genotype-verified TTR mutations. Patients who previously received a liver transplant or who met criteria for New York Heart Association (NYHA) heart failure class ≥ 3 were excluded from the trial. Patients using TTR stabilizers (e.g., tafamidis, diflunisal) prior to study enrollment were required to stop treatment prior to receiving their first dose of inotersen (14 and three days before first dose, respectively). Eligible patients were randomized 2:1 to receive either once-weekly 300 mg subcutaneous injections of inotersen or matched placebo. Randomization was stratified by disease stage (FAP Stage 1 vs. 2), TTR mutation (early-onset Val30Met vs. all others including late-onset Val30Met) and prior use of TTR stabilizers (tafamidis and/or diflunisal). All patients received vitamin A supplements at the recommended daily dose.[8] NEURO-TTR is followed by an ongoing open-label extension (OLE) where all patients will receive inotersen for up to five years.

Clinical Benefits

In the NEURO-TTR trial, inotersen treatment slowed the progression of polyneuropathy relative to placebo and stabilized neuropathy-related quality of life. The statistically significant treatment difference in mNIS+7 reflected progression in the placebo group and delayed progression in the inotersen group, though many inotersen patients reported improved neuropathy scores. OLE data suggest sustained delay of progression of polyneuropathy, though neuropathy-related quality of life gains may not be durable. Cardiac endpoints did not differ statistically between the inotersen group and the placebo group after 15 months of intervention; however, the trial was not powered to detect differences in cardiac outcomes. A small single-arm open label study shows minimal worsening of left ventricular mass.

Neurologic Impairment and Quality of Life

The primary outcomes were the change in the modified Neuropathy Impairment Score+7 (mNIS+7; with higher scores indicating poorer function) and the change in the score on the patient-reported Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) questionnaire (with higher scores indicating poorer quality of life). A decrease in scores indicated improvement.

NEURO-TTR inotersen patients experienced a statistically significant delay in neuropathy progression compared to placebo, as measured by mNIS+7_{Ionis} (least-squares mean [LSM] treatment difference: -19.7 points, 95% CI −26.4 to −13.0) (Table ES1).[8] Over 15 months, the placebo group experienced polyneuropathy progression (mNIS+7_{IONIS}: +25.5 points, 95% CI 20.2 to 30.8) while the inotersen group showed a significantly reduced level of progression (mNIS+7_{Ionis} change from baseline: 5.8, 95% CI 1.6 to 10.0)(Table ES1).[8] Significantly more patients in the inotersen group experienced mNIS+7_{Ionis} improvements compared to baseline after 18 months of treatment (Table ES1, $p = 0.033$).[8]

Inotersen treatment also improved neuropathy-related quality of life (QOL), as shown by Norfolk-QOL-DN scores, compared to placebo (Table ES1, $p = 0.0006$). Significantly more patients on inotersen reported improved neuropathy-related QOL after 15 months of treatment compared to those on placebo (Table ES1, $p = 0.008$).[8] Statistically significant improvements in neuropathy-related QOL favoring inotersen compared to placebo were reported in the physical functioning/large fiber neuropathy, activities of daily living, and symptoms domains ($p \leq 0.001$); however, improvements in small fiber and autonomic function neuropathy QOL domains were not statistically significant.[10]

Table ES1. NEURO-TTR Neurologic Impairment and Quality of Life Outcomes

	Inotersen n = 112	Placebo n= 60	Treatment Difference
Mean Change From Baseline[8]			
mNIS+7, points (95% CI)	5.8 (1.6 to 10.0)	25.5 (20.2 to 30.8)	−19.7 (−26.4 to −13.0)*
Norfolk-QOL-DN, points (95% CI)	1.0 (-3.2 to 5.2)	12.7 (7.4 to 17.9)	−11.7 (−18.3 to −5.1)*
Percent Reporting Improvement†			
mNIS+7	36.5%	19.2%	17.2% (2.4 to 32.1)‡
Norfolk-QOL-DN	50.0%	26.9%	23.1% (7.0 to 39.2)‡

NR: not reported. *p < 0.001. Negative changes on both mNIS+7 and Norfolk-QOL-DN indicate improvement
†Improvement defined as no increase from baseline ‡Risk/proportion difference (inotersen-placebo)

Cardiac Outcomes

Assessment of cardiac-specific outcomes in this trial was limited as the study was not powered for these endpoints. NEURO-TTR patients with cardiac involvement were defined as those with an intraventricular septum thickness ≥ 1.3 cm.[8] There was no evidence of improvement versus placebo in global longitudinal strain or other echocardiographic measures, including ejection fraction, posterior wall thickness, and left ventricular mass, with inotersen treatment after 15 months.[8]

Disease Progression

Fifty-eight percent of inotersen and 65% of placebo patients reported improvements or stabilization in PND score. Comparable proportions of patients in the two groups reported worsening disease stage. These results were not compared statistically, however, and data was missing for nearly one-quarter of the inotersen group.

Other Outcomes

Inotersen treatment did not result in significant differences in mBMI compared to placebo.[8] At the time of publication of this draft report, no evidence has been identified on the impact of inotersen on mortality or survival. Mortality was exclusively reported as a safety outcome (see Section on harms).

Patisiran

We included 15 references on patisiran trials. Two peer-reviewed publications,[12,13] four conference presentations,[14-17] and four conference posters[18-21] presented data from the APOLLO Phase III trial. One peer-reviewed publication reported the results of a Phase II dose-ranging study,[22] two conference posters and one presentation reported on the Phase II OLE,[23-25] and two reported findings from the ongoing global OLE study including patients from the Phase II and Phase III trials.[25,26]

APOLLO was a Phase III randomized controlled trial evaluating neurologic function using the mNIS+7 as the primary outcome after 18 months of treatment. Response to treatment was defined as a less than 10-point increase from baseline in the mNIS+7 at 18 months. The trial enrolled 225 hATTR patients with a documented pathogenic variant in TTR, ages 18-85, with NIS scores ranging from 5-130. Patients were required to meet Karnofsky performance status ≥ 60%, PND score ≤IIIb, have anticipated survival of at least two years, adequate blood counts (e.g. absolute neutrophil count ≥ 1,500 cells/mm^3 and platelet count ≥ 50,000 cells/mm^3, liver function (aspartate transaminase and alanine transaminase levels ≤ 2.5 × upper limit of normal; total bilirubin levels within normal limits; international normalized ratio ≤ 2.0), and to be free from hepatitis B and C infection. Patients were excluded if they had a history of liver transplantation, untreated hyper- or hypothyroidism, HIV infection, malignancy in the previous two years (except squamous cell carcinoma or carcinoma in situ of cervix successfully treated), type 1 or 2 diabetes mellitus, uncontrolled cardiac arrhythmia or unstable angina, acute coronary syndrome within the past three months, NYHA classification > 2, or receipt of an investigational device or agent. Participants taking diflunisal or tafamidis prior to enrollment were required to stop stabilizer use 3 and 14 days, respectively, before receiving their first dose of patisiran.

Eligible patients were randomized 2:1 to receive either a 0.3 mg/kg infusion of patisiran every three weeks or matched placebo for 18 months. Randomization was stratified by previous TTR stabilizer use, NIS score (5-49 vs. 50-130), and early-onset Val30Met (defined as before age 50) versus all other mutations, including late-onset Val30Met. Each infusion in both groups was preceded by an injection of dexamethasone, oral acetaminophen, an H2 blocker, and an H1 blocker.

We noted several differences between the patisiran and placebo groups at baseline which may affect the comparability of the two groups. First, there was a statistically significant difference in the proportion of patients with Val30Met (38% of patisiran vs. 52% of placebo) between the two groups ($p < 0.05$).[12] Second, the mean NIS score among patisiran patients was 3.5 points higher, indicating more severe impairment, compared to the placebo group. A difference of 2 points in the NIS score is considered clinically relevant. Patients were stratified at randomization by NIS scores < 50 and ≥ 50, however, placebo and patisiran group NIS mean scores were not compared statistically.[12] Third, there was a 14% absolute difference in the proportion of patients with cardiac involvement between the patisiran (61%) and placebo (47%) groups; this difference was not assessed for statistical significance.[12] These factors suggest the potential for imbalances in baseline disease severity and natural history between the two groups. Statistical analyses controlled for some, but not all of these differences. We also noted a difference in the proportion of patisiran and placebo patients who completed the study, with 7% of patisiran and 29% of placebo patients discontinuing the study through 18 months of respective treatment. Differences in reasons for discontinuation included AEs (9% of placebo vs. 2% of patisiran patients) and disease progression (5% of placebo vs. < 1% of patisiran patients), defined as a ≥ 24-point increase in the mNIS+7 from baseline and FAP stage progression relative to baseline at nine months.

Clinical Benefits

Data from the APOLLO Phase III trial show evidence of functional improvement, as measured by patients' ability to walk. A substantial proportion of patisiran patients reported stable or improved neuropathy stage. APOLLO data demonstrate a statistically significant mean improvement in neurologic function and neuropathy-related quality of life with patisiran treatment compared to placebo. About half of patisiran patients showed neurological improvement by mNIS+7 score. Post-hoc evidence suggests a decreased risk of the composite endpoint of all-cause mortality (based on AE case report forms) and hospitalization among those with cardiac involvement. Baseline data indicate statistically significant imbalances in TTR genotype and potentially clinically relevant differences in disease severity with unknown statistical significance between patisiran and placebo groups, which may impact study generalizability.

Neurologic Impairment and Quality of Life

The primary outcome was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7, with higher scores indicating more impairment) at 18 months. After 18 months of treatment, patisiran demonstrated a least-squares (LS) mean improvement of 34.0 points (95% CI −39.9 to −28.1) in the mNIS+7 compared to placebo (Table ES2).[12] During this time, patisiran patients improved by a mean of −6.0 points, while placebo patients worsened by 28.0 points (Table ES2).[12] Binary analysis (improvement vs. no improvement) of mNIS+7 score shows 56% of patisiran patients experienced neurological improvement, defined as decrease in mNIS+7 score, versus 4% of placebo patients (odds ratio: 39.9, 95% CI 11.0 to 144.4; $p < 0.0001$).[12] Statistically-significant improvements in mNIS+7 component favoring patisiran were seen in all five sub-scores covering muscle weakness, sensory function, reflexes, nerve conduction, and postural blood pressure compared to placebo.[12] The treatment effects of patisiran appear to increase over time; improvement during months 10 to 18 was double that of the first nine months (4 vs. 2 points).[12]

Neuropathy-related QOL measured by the Norfolk-QOL-DN also significantly improved after 18 months of patisiran treatment compared to placebo (−6.7 vs. +14.4 points, $p < 0.001$; decrease reflects improvement, Table ES2).[12] Individual Norfolk-QOL-DN domains show patisiran patients reported modest improvements in three neuropathy domains after 18 months of treatment: physical function/large fiber neuropathy, symptoms, and autonomic, though statistical analysis was not available.[15] Placebo patients reported worsening Norfolk-QOL-DN scores in all five domains; this worsening was the main driver of the differences seen between the patisiran and placebo groups.[15]

Table ES2. APOLLO Neurologic Impairment and Quality of Life Outcomes

	Phase II OLE[25]	APOLLO[12]		
	Patisiran n = 27	Patisiran n = 148	Placebo n = 77	Treatment difference
Mean Change From Baseline				
mNIS+7 (SEM or 95% CI)	−7.0 (2.0)	−6.0 (1.7)	28.0 (2.6)	−34.0 (−39.9 to −28.1)*
Norfolk-QOL-DN (SEM)	NR	−6.7 (1.8)	14.4 (2.7)	−21.1 (−27.2 to −15.0)*
Percent Reporting Improvement (95% CI)†				
mNIS+7	70.4%†	56 (48 to 64)	4 (0 to 8)	OR: 39.9 (11.0 to 144.4)*
Norfolk-QOL-DN	NR	51.4 (43 to 59)	10.4 (4 to 17)	OR: 10.0 (4.4 to 22.5)*

NR: not reported; OR: odds ratio; SEM: standard error of the mean *p < 0.001; Improvement defined as a change < 0 points. †Calculated from available data.

Cardiac Outcomes

Cardiac outcomes were evaluated as exploratory endpoints among a subgroup of patients with a left ventricle wall thickness of ≥ 13 mm at baseline and without a medical history of aortic valve disease or hypertension. Disproportionately more patisiran patients met these criteria compared to placebo patients (90 [61%] vs. 36 [47%], respectively). We also noted potential imbalances between the patisiran and placebo patients in the subset with cardiac involvement, including more severe polyneuropathy (NIS score) and FAP stage 2 patients in the placebo group, and more patients with NYHA class II heart failure in the patisiran group. Patisiran patients with cardiac involvement were similar to all patients in the trial in baseline polyneuropathy and disease stage but showed more severe heart failure. Placebo patients had considerably worse polyneuropathy and disease stage compared to all trial patients.

We reviewed APOLLO NT-pro-BNP data, an exploratory endpoint, as this biomarker has been shown to predict mortality in hATTR patients with cardiac involvement.[28] NT-proBNP modestly decreased by a median of 49.9 ng/L with patisiran treatment compared to increases in blood concentrations (median 320.4 ng/L) in the placebo group. This treatment difference was statistically significant (difference: 370.2, p < 0.0001);[16] however, the median NT-proBNP concentration in both groups prior to treatment initiation as well as after 18 months of treatment was below the 3,000 ng/L cut-off associated with increased risk of death (Table 3.8).[15,27] Nearly one-third (31.6%) of patisiran patients showed improved NT-proBNP levels (defined as ≥ 30% and ≥ 300 mg/L decrease at 18 months), nearly half (47.3%) remained stable, and the remaining patients (21.1%) had higher concentrations of NT-proBNP after 18 months of treatment (Table 3.9).[19] However, data on the proportion of placebo and patisiran patients with clinically relevant NT-proBNP levels (i.e. > 3,000 ng/L vs. ≤ 3,000 ng/L) through 18 months of treatment were unavailable. Further, data were not available on use of diuretics, which could also lower NT-proBNP levels.

Disease Progression

FAP stage remained stable in nearly three-quarters (76%) of patisiran patients, and five patients (3%) reported improved FAP stage. No placebo patients reported improved FAP stage. As assessed by PND score, ambulation improved in 12 (8%) patisiran patients.[20] No placebo patients reported improved ambulation. Of those whose ambulation worsened, five times as many placebo patients progressed by two PND stages compared to patisiran patients (50% vs. 10%, respectively). Disease progression measures were not compared statistically.

Other Outcomes

mBMI data showed patisiran patients experienced statistically significant stabilization of nutritional status compared to placebo (LSM treatment difference: 115.7 kg/m2 x g/L, $p < 0.0001$).[12] Considerably more patisiran patients showed improved mBMI, defined as > 0 kg/m^2 x g/L, compared to placebo (41% vs. 7%, respectively), though results of statistical testing were not reported.[17] There is no definition of the minimal change in mBMI that is clinically important.

Mortality was assessed as a safety endpoint only. However, a post-hoc analysis of mortality and hospitalization data was recently presented (and additional data provided in confidence) for the cardiac subpopulation. There was an approximate 50% reduction in the composite rate of all-cause hospitalization and mortality (patisiran: 34.7 [95% CI: 27.5 to 43.1], placebo: 71.8 [95% CI: 56.1 to 90.1], HR: 0.48 [95% CI 0.30 to 0.79]) observed for patisiran relative to placebo.[13,14] There was also a trend reported for the composite of cardiovascular hospitalization and all-cause mortality, although findings were not statistically significant. However, we identified no analysis of all-cause mortality alone, nor did we find any description of whether or how baseline differences were controlled for in this analysis. Furthermore, the trial population had few cardiomyopathy-dominant patients, which may inadequately represent cardiac outcomes in such patients.

Harms

Inotersen

Table ES3 summarizes harms associated with inotersen. Five deaths were reported during the study, all of which occurred in the inotersen group, through 15 months of treatment. Four deaths were considered related to disease progression and one death was considered possibly inotersen-related.

Safety data show two key concerns with inotersen treatment: thrombocytopenia and glomerulonephritis. Frequent platelet and renal monitoring implemented during the NEURO-TTR trial suggests thrombocytopenia and decreased renal function may be manageable through enhanced monitoring. AEs considered related to treatment were more frequently reported by inotersen patients compared to placebo patients.

Anti-inotersen antibodies were reported in 30.4% of NEURO-TTR patients.[29] These antibodies typically developed after a median of 200 days of treatment and did not appear to affect drug efficacy, but patients with such antibodies reported more injection site reactions.[29]

Table ES3. Inotersen Harms

	NEURO-TTR[8]	
	Placebo n = 60	**Inotersen** n = 112
Treatment Duration	15 months	
Any Adverse Event	60 (100)	111 (99)
Study-Related Adverse Event	23 (38)	87 (78)
Serious Adverse Event	13 (22)	36 (32)
Study-Related Serious Adverse Event	1 (2)	8 (7)
Discontinuations Due to Adverse Event	1 (2)	14 (13)
Deaths	0	5 (4.5)*
Common Adverse Events†		
Nausea	7 (12)	35 (31)
Headache	7 (12)	26 (23)
Pyrexia	5 (8)	22 (20)
Vomiting	3 (5)	17 (15)
Anemia	2 (3)	15 (13)
Thrombocytopenia	1 (2)	15 (13)
Decreased Platelet Count	8 (13)	60 (54)

All data are n (%). NR: not reported. *One death considered possibly drug-related. †Defined as those reported by ≥ 10% and twice as frequently in inotersen group versus placebo.

Patisiran

Table ES4 summarizes harms associated with patisiran. Data from APOLLO indicate treatment discontinuations due to AEs were more common among placebo than patisiran patients through 18 months of treatment. Most AEs were mild or moderate. The most common AEs reported in APOLLO were peripheral edema and infusion-related reactions; the latter led to treatment discontinuation in one patient. Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in patisiran-treated patients, including 3 cases of complete AV block. No serious occurrences of AV block were reported in placebo-treated patients. Seven of 194 (3.6%) patients developed anti-drug antibodies during treatment with patisiran (APOLLO and OLE studies).

No treatment-related deaths were reported during any of the patisiran trials. A total of 13 deaths were reported during the APOLLO trial. All deaths in the patisiran group were due to cardiovascular causes (e.g. congestive heart failure), while reasons for death in the placebo arm varied. No further explication of the cardiovascular deaths was available in the trial publication or other materials.

Table ES4. Patisiran Harms

	Phase II OLE[22,25]	APOLLO[12]		Global OLE[26]
Treatment Group	**Patisiran** n = 25	**Placebo** n = 77	**Patisiran** n = 148	**Patisiran** n = 211
Treatment Duration	Up to 48 months	18 months		Up to 48 months
Any Adverse Event	25 (100)	75 (97)	143 (97)	189 (90)
Serious Adverse Event	6 (24)	31 (40)	54 (36)	55 (26)
Atrioventricular (AV) Block	NR	0	4 (2.7)	NR
Severe Adverse Event	3 (12)	28 (36)	42 (28)	38 (18)
Discontinuations Due to Adverse Event	0	11 (14)	7 (5)	16 (8)
Deaths	0	6 (8)	7 (5)	11 (5)
Common Adverse Events				
Peripheral Edema	3 (11)	17 (22)	44 (30)	NR
Infusion-Related Reactions	6 (22)	7 (9)	28 (19)	NR (10)
Flushing	7 (25)	NR	NR	NR

NR: not reported. All data reported are n (%).

Comparator: Diflunisal

One randomized, double-blind, placebo-controlled trial evaluated the efficacy of diflunisal in treating hATTR polyneuropathy.[30] Inclusion and exclusion criteria were similar to NEURO-TTR and APOLLO. Eligible patients were randomized 1:1 and stratified by Val30Met versus non-Val30Met mutation to receive either 250 mg of diflunisal or placebo twice daily for 24 months. Approximately half of the study population discontinued treatment prior to the study conclusion at 24 months, and more placebo patients discontinued treatment compared to diflunisal patients (61% vs. 42%).[30] Although both groups experienced progression of polyneuropathy, additional longitudinal analysis of the intention-to-treat (n = 130) population showed diflunisal patients experienced significantly less neuropathy progression as assessed by the NIS+7 score compared to placebo patients at both 12 months (treatment difference: 6.4 points, 95% CI: 1.2 to 11.6) and 24 months. Likewise, QOL measured by the SF-36 showed modest but statistically significant improvement in QOL related to physical symptoms for diflunisal patients compared to placebo after 24 months of treatment. There were no differences in treatment-related AEs or SAEs.[30] Four (6%) diflunisal and two (3%) placebo patients discontinued treatment due to treatment-related AEs.[30] Four (6%) diflunisal and nine (14%) placebo patients died during the 24-month follow-up period, with 12 of 13 deaths occurring off study drug.[30] Cardiac outcomes data for the diflunisal study have not been reported.

Controversies and Uncertainties

Historically, hATTR has been diagnosed as two separate conditions affecting two separate organ systems. As a result, most literature details the two predominant manifestations – polyneuropathy and cardiomyopathy – in isolation, and there is little, if any, literature regarding how these two pathologies of a multi-system disease interact. Many of the studies we identified through our

search evaluated primary outcomes related to polyneuropathy rather than cardiac involvement, which provides limited statistical power to identify treatment differences in cardiac outcomes in clinical trials.

Due to the lack of validated thresholds for the mNIS+7 assessment and neuropathy-related QOL, data from the NEURO-TTR and APOLLO trials must be interpreted without a context of what constitutes a clinically relevant improvement. Older neuropathy impairment assessments (e.g., NIS and NIS+7) do have established minimal clinically important differences defined; however, these assessments were judged to be unable to adequately reflect polyneuropathy symptoms resulting from hATTR.[31] Furthermore, because the mNIS+7 is a composite measure of motor, autonomic, and sensory function, total score changes provide a coarse measurement of total neuropathy rather than specific sensory, autonomic, and motor nerve function. As a result, it is difficult to extrapolate mNIS+7 score changes into clinical changes, particularly for a patient population with a diverse spectrum of polyneuropathy symptoms.

Generalizability of APOLLO and NEURO-TTR study findings is potentially limited based on trial design and populations. First, only 20% of APOLLO and 48% of NEURO-TTR participants were from the US, which has a different genotype mix than other regions; therefore, findings of these trials may not be generalizable to the US population. Both trials included very few patients with the most common mutation in the US, Val122Ile. Inclusion of very few patients with the Val122Ile mutation may be due in part to both trials' inclusion criterion of polyneuropathy-predominant hATTR. Thus, neither trial is representative of the US hATTR and cardiomyopathy-predominant hATTR populations. Second, liver transplant recipients and individuals who were currently receiving treatment with TTR stabilizers (and did not wish to stop such treatment) were excluded from both trials. Thus, findings may not be generalizable to such patients, and the safety and efficacy of treatment in these patient populations is unknown.

We also noted differential discontinuations in the APOLLO trial: 29% of placebo patients discontinued compared to 7% of patisiran patients. Nearly half of all discontinuations were otherwise unexplained patient withdrawals, which limits our understanding of why placebo patients discontinued study treatment. Differential study discontinuations may have under- or over-estimated the treatment difference between patisiran and placebo in key outcomes and may not reflect true treatment benefits in hATTR patients.

Due to the chronic and progressive nature of hATTR, long-term use of patisiran and inotersen is expected. Both inotersen and patisiran trials were of relatively short duration, however, which provides limited information on the safety of long-term use of these new drugs; this is an important concern, given the potential signals that have been highlighted regarding renal and hematologic safety for inotersen, and cardiovascular safety for patisiran. In addition, patisiran is the first RNAi therapeutic approved by the US FDA, and the long-term effects of RNA interference are unknown. Inotersen would join three other approved antisense oligonucleotide drugs.

Finally, input from patients included concerns about affordability and access to these new therapies. Many patients recognized the high cost of developing inotersen and patisiran and their perceived clinical benefit but felt these treatments should be priced in alignment with what patients can afford. Patients voiced additional uncertainties about potential decisions to end treatment due to cost despite improved disease symptoms and quality of life.

Summary and Comment

Limitations of inotersen and patisiran clinical evidence include study populations that limit the generalizability of clinical outcomes to all hATTR patients, clinical outcome measures (mNIS+7 and Norfolk-QOL-DN) without defined thresholds for clinical significance, limited functional outcomes such as disease stage progression, and limited data on patients with cardiac involvement, especially among cardiac-dominant patients who are at a higher risk for mortality than patients with neuropathy-predominant hATTR. For both medications, we were unable to interpret the clinical relevance of changes in polyneuropathy measured by the mNIS+7 and neuropathy-related quality of life (Norfolk-QOL-DN) without established thresholds for meaningful clinical change.

Despite these limitations, we found the following in our review of the clinical evidence:

Inotersen

- Both primary efficacy assessments (polyneuropathy [mNIS+7 $_{Ionis}$], and neuropathy-related quality of life [Norfolk-QOL-DN] favored inotersen; on average, inotersen patients' neuropathy remained stable while placebo patients' neuropathy worsened
- 36% of the patients in the inotersen group had an improvement (no increase from baseline) in the mNIS+7 $_{Ionis}$ and 50% had an improvement in the Norfolk QOL-DN score
- Relative to best supportive care, no evidence of improved stabilization of disease progression, as measured by PND score.
- Potential for continued delayed progression of polyneuropathy and declines in neuropathy-related quality of life through nearly two years of inotersen treatment.
- Potential safety signals including thrombocytopenia and glomerulonephritis. One of five deaths among inotersen patients in NEURO-TTR is considered possibly drug-related.

Relative to placebo patients, inotersen patients had more favorable outcomes on the mNIS+7 and Norfolk QOL-DN measures. However, on average, inotersen patients did not experience improvement from baseline in neuropathy symptoms, as measured by the mNIS+7, but rather a slowing in worsening of neuropathy relative to placebo. Regarding safety, there remains some uncertainty given that:

1. All deaths in the Phase III trial occurred in the inotersen arm, one of which was considered possibly-drug related;

2. Other antisense oligonucleotides (nusinersen, volanesorsen) have demonstrated similar risks of thrombocytopenia; and
3. Anti-inotersen antibodies were reported in 30.4% of NEURO-TTR patients, the long-term significance of which is unknown at this point.

The enhanced monitoring protocol added to the trial provides some reassurance that thrombocytopenia risks can be managed. However, the long-term implications of the other safety and antibody concerns are currently unknown. In summary, we have moderate certainty of a comparable, small, or substantial net health benefit relative to best supportive care, with high certainty of at least a comparable net health benefit, and therefore rate the clinical evidence for inotersen to be comparable or better (C+; note that ICER does not change its approach to rating evidence for ultra-rare conditions).

Patisiran

- Mean improvement in polyneuropathy (mNIS+7), and neuropathy-related quality of life (Norfolk-QOL-DN), with statistically significant differences compared to best supportive care (placebo).
- Baseline imbalances in TTR genotype and clinically relevant differences in disease severity (based on NIS) between patisiran and placebo groups, which may impact study validity and generalizability.
- Exploratory endpoint of neuropathy stage stable or improved compared to best supportive care (placebo).
- Statistically significant evidence of lowered cardiac biomarker (NT-proBNP) with unclear clinical relevance.
- Post-hoc evidence of a statistically significant reduction in the composite rate of all-cause hospitalization and mortality compared to best supportive care among patients with cardiac involvement.
- In general, a decreased frequency of AEs compared to best supportive care; no differences in mortality between treatment arms, but all deaths in the patisiran arm were cardiovascular in nature, a phenomenon that has not been otherwise explained. Potential safety signal of complete heart block, though heart block can be observed with cardiac involvement in hATTR.

On average, patients on patisiran demonstrated improvement in neuropathy symptoms, as measured by the mNIS+7. Regarding safety, we deemed the risk of concomitant steroid administration to be low-moderate risk, depending on patient characteristics, based on analogous steroid use in other therapeutic areas. While the rate of death did not differ between the treated and placebo groups, the finding that all deaths in the patisiran group were cardiovascular-related is an additional uncertainty related to use of patisiran, and there has been little explication of this

phenomenon in the trial publication or other materials. Four cases of heart block were observed among patisiran patients, and while this finding represents a potential safety signal, it could also represent disease progression. However, no cases of heart block were observed among placebo patients. In summary, we have moderate certainty of a substantial net health benefit with high certainty of at least a small net health benefit compared to best supportive care, and therefore rate the clinical evidence for patisiran to be incremental or better ("B+").

Long-Term Cost Effectiveness

We conducted a cost-effectiveness analysis using a *de novo* Markov model featuring FAP disease stages and a one-month cycle length over a lifetime time horizon. Research reporting a high mortality hazard ratio for patients with NT-proBNP > 3,000 motivated the introduction of a separate set of disease states to keep track of the increased cost, decreased quality of life and elevated mortality associated with elevated levels of this biomarker among patients with cardiac manifestations of hATTR. The model was developed with dual base cases (a health care sector perspective and a societal perspective) under the ultra-rare disease adaptation of ICER's value framework, with costs and outcomes discounted at 3% annually. A comprehensive list of choices and assumptions made in the model, along with the rationale for each, is available in Section 4 of the report.

Since differences in the primary outcome measures and trial populations (e.g., disease severity) precluded direct comparison of the NEURO-TTR and APOLLO trials, there are two separate cohorts for the base case models—one for each drug, with characteristics based on each trial's baseline population. The target population for the first economic evaluation was adults with hATTR with an indication for treatment with inotersen (as reflected in the NEURO-TTR trial). The target population for the second economic evaluation was adults with hATTR with an indication for treatment with patisiran (as reflected in the APOLLO trial). Both diflunisal and tafamidis were excluded from consideration, as neither has received FDA approval for the treatment of hATTR amyloidosis, and indirect comparisons with diflunisal were infeasible due to differences in trial design, outcome measure, and study populations.

Annual transition probabilities were created by mapping the PND score (a variable collected in both trials) to FAP stage. The same method was used for both inotersen and patisiran when converting PND to FAP stage. The sex-weighted, age-specific death rate for both models was taken from the United States life tables. The weights for the weighted average of female and male mortality rates came from the drug-specific trials. Mortality for FAP stages 1, 2 and 3 were approximated by the "without neuropathy" curve, the "with neuropathy" curve, and the "with weight loss" curve, respectively, from a natural history study published by Swiecicki et al.[32] The death rate related to severe cardiac involvement (NT-proBNP > 3,000) was estimated based on data from the APOLLO trial. [18] Importantly, however, an effect of treatment on the proportion of patients with severe cardiac involvement was not assumed for the base case given a lack of data on these effects from

the trials. Instead, potential benefits from treatment on this outcome were assessed in scenario analyses.

Health state utility weights assigned to each FAP stage were adjusted by a quality of life decrement to serve as a "toll" for severe cardiac involvement (NT-proBNP > 3,000). The utilities for FAP stages 1 and 2 were from the trial data reported by Denoncourt et al.[33] The missing FAP stage 3 utility value was taken from the "by stage" estimation of Disease Stage 3 in the tafamidis report produced by the York Economic Review Group (ERG).[34] The utility decrement for severe cardiac involvement (NT-proBNP > 3,000) was assumed to be a 10% disutility, reflecting the 10% decrement estimated for heart failure reported by Sullivan and Ghushchyan, 2006.[35] The utility parameters were varied in both scenario and sensitivity analyses to explore the impact of uncertainty.

Table ES5. Utility Values for Health States

Health State	Utility Value If NT-proBNP ≤ 3,000	Utility Value If NT-proBNP > 3,000
FAP Stage 1	0.710	0.639
FAP Stage 2	0.570	0.513
FAP Stage 3	0.170	0.153

Patients in the both trials taking active treatment with inotersen or patisiran reported improvements in Norfolk QOL-DN compared to placebo. In previous economic evaluation models of hATTR,[34] Norfolk QOL-DN scores have been mapped to EQ-5D utilities, allowing differences in QoL score to be converted into a utility value. Using the "crosswalk equations" in the York report, we converted Norfolk QOL-DN gains into QALY utility gains. Thus, in the model patients accrue utility gains through QoL improvements over the time period for which there is evidence of a QoL benefit (i.e., 15 months for inotersen and 18 months for patisiran); after building to the maximum amount, the utility gain plateaus. From this point onward, patients continue to receive the plateau level "bonus" utility for as long as they are on treatment. This utility benefit is above and beyond the utility gain seen from improvement in FAP stage.

Drug costs for patisiran were assumed to be $345,000 per year, consistent with reported net price estimates.[36] We assumed the same level for inotersen in the absence of a published price. Please see Section 4 for our estimates of additional treatment-related costs (e.g., infusion and facility mark-up for patisiran, training visits and blood monitoring for inotersen).

Previous cost-effectiveness analyses of hATTR did not include AEs in the base case, and we similarly decided that including them would be unlikely to change the findings materially. Drug discontinuation was set equal to that seen in the trials for patients taking new treatments (e.g., discontinuation rates of 22.3% over 15 months for inotersen and 6.8% over 18 months for patisiran). All costs were adjusted to 2018 US dollars using the Consumer Price Index.

Model outputs include quality-adjusted life years (QALYs), life years (LYs), and total costs for intervention and BSC, as well as incremental costs per additional QALY gained and per additional LY gained for each intervention relative to BSC. While the base case for the modified societal perspective only altered the costs (i.e., there were no changes to the utilities or the transition probabilities), we explored the potential effect of including a possible caregiver QALY utility burden. In addition to the dual base case analysis that includes the health system and a modified societal perspective, sensitivity and scenario analyses were conducted, with detailed descriptions of these additional analyses presented in Section 4 of the report.

Base Case Results

Inotersen

For the base case focused on the health care sector perspective, undiscounted total costs were $1,709,977 for inotersen and $404,059 for BSC, with corresponding life years of 9.6 years and 8.7 years, respectively. Given the severity of hATTR, this corresponds to 5.44 QALYs for inotersen and 4.56 QALYs for BSC. When discounting both costs and outcomes at 3%, total costs were $1,507,450 for inotersen and $329,858 for BSC, with corresponding life years of 7.9 years and 7.3 years, respectively. Quality adjustment of these life years produced estimates of 4.54 QALYs for inotersen and 3.86 QALYs for BSC.

For the base case focused on the modified societal perspective, undiscounted total costs were $1,843,473 for inotersen and $534,183 for BSC. When discounting both costs and outcomes at 3%, total costs were $1,608,862 for inotersen and $431,261 for BSC.

Table ES6. Results for the Base Case for Inotersen Compared to Best Supportive Care

	Undiscounted			Discounted		
	Total Costs	Life Years	QALYs	Total Costs	Life Years	QALYs
Health Care Sector Perspective						
Inotersen	$1,709,977	9.6	5.44	$1,507,450	7.9	4.54
Best Supportive Care	$404,059	8.7	4.56	$329,858	7.3	3.86
Modified Societal Perspective						
Inotersen	$1,843,473	9.6	5.44	$1,608,862	7.9	4.54
Best Supportive Care	$534,183	8.7	4.56	$431,261	7.3	3.86

The model produces incremental cost-effectiveness ratio estimates for inotersen of approximately $1.7 million per QALY gained. On a per life-year basis, the incremental cost-effectiveness ratio was about $1.95 million per LY. Likewise, the results show that the incremental cost-effectiveness ratios computed from a modified societal perspective are also high for inotersen. While not evident because of the rounding, incremental cost-effectiveness ratios calculated from the modified societal perspective are slightly higher than those from the health care sector perspective. This is because valuing the greater productivity in the treatment cohort does not fully cancel out the

greater informal costs associated with caring for patients with hATTR, as productivity gains are somewhat limited due to the older age and the infirmity of the cohort.

Table ES7. Incremental Cost-Effectiveness Ratios for Inotersen Compared to Best Supportive Care, Discounted at 3%

Incremental	Inotersen vs. BSC
Incremental Costs	
Health Care Sector Perspective	$1,177,592
Modified Societal Perspective	$1,177,601
Incremental Outcomes	
Life Years (LY)	0.61 years
QALYs	0.68 QALYs
Incremental Cost-Effectiveness Ratios (Life years)*	
Health Care Sector Perspective	$1,950,000
Modified Societal Perspective	$1,950,000
Incremental Cost-Effectiveness Ratios (QALYs)*	
Health Care Sector Perspective	$1,730,000
Modified Societal Perspective	$1,730,000

* Note: Incremental cost-effectiveness ratios reported may not be identical to those computed because of rounding.

Patisiran

For the base case focused on the health care perspective, undiscounted total costs were $3,946,706 for patisiran and $371,946 for BSC, with corresponding life years of 12.3 years and 7.4 years, respectively. Given the severity of hATTR, this corresponds to 8.31 QALYs for patisiran and 3.62 QALYs for BSC. When discounting both costs and outcomes at 3%, total costs were $3,173,084 for patisiran and $312,062 for BSC, with corresponding life years of 9.7 years and 6.3 years, respectively. Quality adjustment of these life years produced estimates of 6.54 QALYs for patisiran and 3.11 QALYs for BSC.

For the base case focused on the modified societal perspective, undiscounted total costs were $4,182,277 for patisiran and $517,420 for BSC. When discounting both costs and outcomes at 3%, total costs were $3,355,304 for patisiran and $432,031 for BSC.

Table ES8. Results for the Base Case for Patisiran Compared to Best Supportive Care

	Undiscounted			Discounted		
	Total Costs	Life Years	QALYs	Total Costs	Life Years	QALYs
Health Care Sector Perspective						
Patisiran	$3,946,706	12.3	8.31	$3,173,084	9.7	6.54
Best Supportive Care	$371,946	7.4	3.62	$312,062	6.3	3.11
Modified Societal Perspective						
Patisiran	$4,182,277	12.3	8.31	$3,355,304	9.7	6.54
Best Supportive Care	$517,420	7.4	3.62	$432,031	6.3	3.11

The model produced incremental cost-effectiveness ratio estimates of approximately $835,000 per QALY gained. On a per life-year basis, results were approximately $850,000 for patisiran. The results in the table below show that the incremental cost-effectiveness ratios computed from a modified societal perspective are also high, at approximately $850,000. On a per life-year basis, corresponding results were approximately $870,000.

Table ES9. Incremental Cost-Effectiveness Ratios for Patisiran Compared to Best Supportive Care, Discounted at 3%

Incremental	Patisiran vs. BSC
Incremental Costs	
Health Care Sector Perspective	$2,861,022
Modified Societal Perspective	$2,923,273
Incremental Outcomes	
Life Years (LY)	3.36 years
QALYs	3.43 QALYs
Incremental Cost-Effectiveness Ratios (Life years)*	
Health Care Sector Perspective	$852,000
Modified Societal Perspective	$871,000
Incremental Cost-Effectiveness Ratios (QALYs)*	
Health Care Sector Perspective	$835,000
Modified Societal Perspective	$853,000

* Note: Incremental cost-effectiveness ratios reported may not be identical to those computed because of rounding.

Sensitivity and Scenario Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per QALY. While there were no data about the effect of new treatments on reducing the percentage of patients with severe cardiac involvement (defined as NT-proBNP > 3,000), we did vary this parameter from 0% to 50% in sensitivity analyses. In other words, at 50%, the model assumes that of those taking the new treatments, 50% transition from NT-

proBNP > 3,000 to NT-proBNP < 3,000 and have improved survival, better quality of life, and lower costs as a result. However, this change had only a modest impact on cost-effectiveness given the relatively small size of the cardiac subset; the resulting cost-effectiveness estimates were approximately $1.3 million per QALY for inotersen and $780,000 per QALY for patisiran. The tornado diagrams (see Section 4) illustrated that for both treatments drug cost and hATTR disease progression are key drivers of the economic results. This finding holds for both the health care sector and the modified societal perspectives.

The scenario analyses change multiple variables at once to consider different scenarios. Assumptions about utility values increased the incremental cost-effectiveness ratio by over $100,000. In addition, the model was sensitive to other utility assumptions. We assumed that the difference in Norfolk QOL-DN by FAP stage by treatment could be represented by a difference in quality of life utility scores (i.e., patients in the same FAP stage could have different QALY utility scores due to treatment). The scenario analyses explore the effect of this assumption by varying the size of the benefit and the time over which the benefit accrues. The results show that our base case assumptions are consequential; without them the incremental cost-effectiveness ratio estimate is more than $2.4 million for inotersen and more than $1.1 million for patisiran.

Varying all parameters at once, in a probabilistic sensitivity analysis, clarifies the likelihood that the incremental cost-effectiveness ratio is within conventional levels of willingness to pay. The table below shows the probability that each drug is cost-effective compared to BSC. Cost-effectiveness acceptability curves (CEACs) are presented in Appendix D, where we explored the probability of cost-effectiveness by varying willingness to pay up to $1 million per QALY gained.

Table ES10. Probability New Treatment is Cost-Effective: Inotersen versus Best Supportive Care and Patisiran versus Best Supportive Care, Health Care Sector Perspective

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
Inotersen	< 1%	< 1%	< 1%	< 1%	< 1%
Patisiran	< 1%	< 1%	< 1%	< 1%	< 1%

Threshold Analyses

The results suggest that significant discounts from the assumed prices are necessary to reach standard cost-effectiveness thresholds. The inotersen results suggest an annual drug cost of approximately $96,103 would be required to achieve a threshold of $500,000 per QALY. The patisiran results suggest that an annual drug cost of approximately $200,000 would be required to achieve a threshold of $500,000 per QALY. Both estimates are far below estimated net price of $345,000 per year for patisiran (note: inotersen does not yet have a published price as it is still under FDA review). To reach more modest thresholds between $50,000 per QALY and $150,000

per QALY, inotersen's annual drug cost should be between $5,000 and $25,000. For patisiran, the corresponding annual drug cost should be between $3,000 and $46,000. Similar magnitudes of reduction are needed when considering annual drug cost from a societal perspective.

Summary and Comment

The economic models produced results suggesting improved quality-adjusted life years accompanied by increased costs from the new treatments for hATTR amyloidosis. In all four of the base cases, the incremental cost-effectiveness ratios were beyond levels normally considered good value for money. Given the high additional treatment cost (i.e., $345,000 *each year* in drug costs alone), new treatments will need to be accompanied by extremely large corresponding QALY benefits (or drug price reductions) in order to obtain incremental cost-effectiveness ratios below standard thresholds.

A big driver of the value of the new treatments appears to be the drugs' cost. The disease has profound quality of life impacts, and quality of life assumptions do appear to impact the results according to the scenario analysis results. However, the model's optimistic assumptions (compared with those made by others reporting utilities used for QALYs), do not result in incremental cost-effectiveness ratio estimates near conventional cost-effectiveness thresholds.

For ultra-rare diseases, it should be noted that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that may lead to coverage and funding decisions at higher cost-effectiveness thresholds. However, at the current assumed prices, neither treatment option is economically attractive at either conventional or higher cost-effectiveness thresholds. As a result, substantial price discounts and additional study are indicated.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below. As inotersen and patisiran were evaluated under ICER's framework for a serious ultrarare condition (https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-ValueFramework-for-Rare-Diseases.pdf) additional elements appear in the table that are assessed for such conditions.

Potential Other Benefits

Table ES11. Potential Other Benefits

Other Benefits	Description
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	Patient testimony indicates substantial work, family, social, and psychological effects, which may be improved by treatment but not fully captured by traditional utility estimation.
This intervention offers reduced complexity that will significantly improve patient outcomes.	Patients and families value convenience of therapies that can be administered in the home (e.g., subcutaneous administration of inotersen).
This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	These therapies also the potential to reduce health disparities in the future. The V122I mutation disproportionately affects African Americans in the US, causing a cardiomyopathy-predominant presentation. If these therapies are able to improve cardiac outcomes, this could lead to a reduction in racial disparities in heart failure-related morbidity and mortality. Yet if the cost of treatment is significant, those with limited financial resources may find it difficult to afford treatment.
This intervention will significantly reduce caregiver or broader family burden.	Because patisiran and inotersen have the potential to slow and/or reverse disease progression, these new treatments may positively impact caregiver and family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Inotersen and patisiran offer a novel mechanism of action as the first TTR gene silencers inhibiting production of the protein inducing hATTR.
This intervention will have a significant impact on improving return to work and/or overall productivity.	Having a more effective therapy should improve patient and caregiver ability to remain at work which may in turn affect productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	New treatments offer hope for younger generations of individuals who carry hATTR genes and watch their parents and grandparents suffer from the disease with no currently approved therapies in the US.
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	By reducing symptom burden and disease progression, these agents may enable patients and their caretakers to spend more time outside the home and medical care system, and therefore participate more fully in their communities (e.g., schools, civic activities).
This intervention will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	With more efficacious treatments available, individuals at risk for hATTR may be more likely to undergo screening and pursue diagnosis of hATTR.

Contextual Considerations

Table ES12. Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	hATTR creates substantial burdens that affect quality of life and can also affect length of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Given that hATTR is a hereditary illness, patients often are caregivers for sick family members prior to, or during, their own illness.
This intervention is the first to offer any improvement for patients with this condition.	As of July 2018, there was no treatment available that reverses the damage already caused by amyloid deposits.
Compared to usual supportive care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Both inotersen and patisiran trials were of relatively short duration, which provides limited information on the magnitude or durability of the long-term benefits of these interventions. Additionally, the long-term effect of anti-inotersen antibodies on drug efficacy is unknown. The long-term effects of steroid administration with patisiran is also unknown.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	Patisiran and inotersen represent the first new treatments to address the underlying cause of symptoms and that have the potential to reverse the damage already caused by amyloid deposits. The arrival of any new treatment option is seen as a positive in a disease with no known cure.

Value-Based Benchmark Prices

Our annual value-based price benchmarks for inotersen's and patisiran's use in adults with hereditary ATTR (hATTR) amyloidosis are presented in Table ES13. As noted in the ICER methods document (https://icer-review.org/material/final-vaf-2017-2019/), the value-based benchmark price for a therapy is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For inotersen, price discounts of 94% to 97% from the assumed placeholder list price would be required to reach the $100,000 to $150,000 per QALY thresholds. For patisiran, price discounts of 90% to 95% from the list price would be required to reach the $100,000 to $150,000 per QALY thresholds.

Table ES13. Value-Based Benchmark Prices for Inotersen and Patisiran

	List Price	Net Price	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Discount from List Price to Reach Threshold Prices
Inotersen	$450,000*	$345,000*	$15,275	$25,379	94% to 97%
Patisiran	$450,000	$345,000	$24,700	$46,488	90% to 95%

QALY: quality-adjusted life year

*Assumed placeholder price for inotersen

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. ICER's methods for estimating potential budget impact are described in detail in Section 7.2 and have recently been updated; additional information can be found at https://icer-review.org/material/final-vaf-2017-2019/. The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including therapy costs) minus any offsets in these costs from averted health care events.

The potential budget impact analysis included the candidate population eligible for treatment: adults with hATTR amyloidosis. To estimate the size of the potential candidate population for treatment, we used an estimate of 1 per 100,000 in the US, which would put the US prevalence at approximately 3,250 individuals.[37] We assumed equal rates of initiation over each of the five years, meaning 650 patients would initiate treatment each year. A detailed description of our methods in estimating budget impact, including the determination of eligible population, is available in Section 7.2 of the report.

Table ES14 illustrates the per-patient budget impact calculations for inotersen in adults with hATTR amyloidosis, compared to best supportive care. Potential budget impact is presented based on the placeholder list price ($450,000 per year), the placeholder net price ($345,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($25,379, $15,275, and $5,171 per year, respectively).

Table ES14. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Inotersen Treatment of Adults with hATTR Amyloidosis

	Average Annual Per Patient Budget Impact				
	Placeholder List Price	Placeholder Net Price	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Inotersen + Best Supportive Care	$359,655	$284,129	$54,230	$46,962	$39,694
Best Supportive Care	$36,741				
Difference	$322,914	$247,388	$17,489	$10,221	$2,953

QALY: quality-adjusted life year

Table ES15 illustrates the per-patient budget impact calculations for patisiran in adults with hATTR amyloidosis, compared to best supportive care. Potential budget impact is presented based on the announced average list price ($450,000 per year), the expected average net price ($345,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($46,488, $24,700, and $2,911 per year, respectively).

Table ES15. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Patisiran Treatment of Adults with hATTR Amyloidosis

	Average Annual Per Patient Budget Impact				
	List Price	Net Price	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Patisiran + Best Supportive Care	$458,772	$361,574	$85,243	$65,074	$44,903
Best Supportive Care	$39,300				
Difference	$419,472	$322,274	$45,943	$25,774	$5,603

QALY: quality-adjusted life year

For each of the drugs, the annual potential budgetary impact of treating the entire eligible population over five years did not exceed the $991 million ICER budget impact threshold at any of these prices, largely due to the relatively small number of patients eligible for treatment. As such, ICER is not issuing an access and affordability alert for these treatments. However, the potential budget impact reached 59% of the threshold with inotersen treatment using the estimated placeholder list price of $450,000 per year, and 80% of the threshold with patisiran treatment when using the list price of $450,000 per year, suggesting an outsized impact relative to the number of individuals affected.

Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on September 13, 2018 in Chicago, IL. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1) Is the evidence adequate to demonstrate that the net health benefit of inotersen plus best supportive care is superior to that provided by best supportive care alone?

Yes: 9 votes	**No: 2 votes**

2) Is the evidence adequate to demonstrate that the net health benefit of patisiran plus best supportive care is superior to that provided by best supportive care alone?

Yes: 10 votes	**No: 1 vote**

3) Is the evidence adequate to distinguish the net health benefit between inotersen and patisiran when added to best supportive care?

Yes: 1 vote	***No: 10 votes***

4) When compared to best supportive care alone, does the addition of inotersen or patisiran offer one or more of the following "other benefits"?

Other Benefits	Number of Votes
This intervention offers reduced complexity that will significantly improve patient outcomes.	3/11
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	0/11
This intervention will significantly reduce caregiver or broader family burden.	10/11
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	11/11
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.	8/11
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	3/11
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	4/11
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	4/11

5) Are any of the following contextual considerations important in assessing inotersen's or patisiran's long-term value for money in patients?

Contextual Considerations	Number of Votes
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	10/11
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	11/11
This intervention is the first to offer any improvement for patients with this condition.	8/11
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	9/11
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	10/11
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	2/11

6) For adults with hereditary transthyretin amyloidosis, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of inotersen plus best supportive care compared with best supportive care alone?

High: 0 votes	**Intermediate: 0 votes**	***Low: 11 votes***

7) For adults with hereditary transthyretin amyloidosis, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of patisiran plus best supportive care compared with best supportive care alone?

High: 0 votes	**Intermediate: 0 votes**	***Low: 11 votes***

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on inotersen and patisiran for hATTR amyloidosis to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, one payer, and two representatives from manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Manufacturers

- Manufacturers should bring the price for innovative treatments for hATTR down to a level that aligns fairly with the added benefits for patients. Pricing aligned with clinical value is more likely to provide superior access for patients over the long term, and in the short term would lessen the financial toxicity experienced by patients and families.
- The high level of uncertainty regarding the long-term safety and effectiveness of patisiran and inotersen suggests that a reasonable price should be lower at the launch of these drugs and only rise to full value-based levels after further demonstration of the overall added benefits to patients and families.

Payers

- Given that the price of new therapies for hATTR do not align with their value, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments. Payers may weight others factors in their coverage decision, such as the ultra-rare nature of the disease and the lack of other approved treatment options.
- Payers should negotiate discounts to seek the best value for patients and the health system by bringing the net price closer to traditional cost-effectiveness ranges. Given that patients do not have low-cost alternative treatments available, payers should seek to work with employers and other purchasers of insurance to limit the financial toxicity to patients. While the overall cost of treating the 3,000-3,500 hATTR patients in the US with new therapies may be affordable to the health care system as a whole, the US health care system *cannot* afford to pay for multiple drugs for multiple ultra-rare disorders.
- Given that clinicians cannot predict which treatment will be most effective for any individual patient, and evidence is not able to distinguish the overall net health benefit of patisiran and inotersen, payers may be able to achieve lower prices for the health system and for patients by applying a step therapy policy favoring the less expensive treatment. Careful consideration should be given, however, to the differences in delivery mechanism for these drugs and other reasons that may lead one drug to be highly preferable for certain patients.
- Prior authorization criteria should be based on clinical evidence with input from clinical experts and patient groups. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.
- Payers and other policymakers seeking to judge the value of patisiran and inotersen should recognize the heightened responsibility to consider contextual considerations, including the potential for broader benefits to patients and society, while simultaneously working to maintain affordability of health insurance for all patients now and in the future.

- Outcomes based contracts for hATTR treatments might help address some of the uncertainty around longer-term outcomes but would be complicated by the lack of easily defined measures of treatment response.

Manufacturers and Payers

- Patients fully desire to pay a reasonable amount for a prescription for one of the new treatments for hATTR. However, co-insurance with high deductibles and other benefit design features leave patients at high risk for financial toxicity, especially since these treatments do not cure the illness and likely must be taken for life. Payers, manufacturers, and those who design health benefits need to recognize the seriousness of financial toxicity for patients and families and seek new approaches to eliminate this burden.

Patient Advocacy Organizations

- Patient organizations that have a leading role in funding, organizing, and promoting innovative research on new treatments should demand commitments from manufacturers for sustainable pricing of the products patients helped bring to the market.
- Patient organizations should also work with payers to ensure that they utilize the best available evidence in designing coverage criteria and understand how diverse the patient population with hATTR is, and how important access to effective treatments will be for individuals and their families.

Providers

- Specialists involved in the care of hATTR should rapidly convene, in partnerships with patients, manufacturers, and payers, to develop evidence-based guidelines for appropriate use of new agents.
- Professional societies should highlight the impact on their patients of failed pricing and insurance policies and demand to be part of the public process that should guide pricing to balance the needs for affordability and for investments in future innovation.

Researchers

- Future research should address the durability of improvements in neurological function, longer-term safety, and cardiac outcomes.
- Future research is needed to validate modified outcome measures used as the basis for regulatory approval. For hATTR amyloidosis, research and policy development are needed to specify the absolute or relative point changes in the modified mNIS+7 that represent significant clinical differences.

1. Introduction

1.1 Background

Hereditary transthyretin amyloidosis (hATTR) is a multi-system illness caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver that is present in all human serum. TTR is also known as prealbumin, owing to its electrophoretic mobility. Genetic mutations increase the likelihood of TTR misfolding into insoluble beta-pleated sheets that deposit in body tissues and disrupt the function of major organs.

A rare, progressive, and fatal autosomal dominant hereditary disorder, hATTR spans a spectrum of clinical presentations. These presentations include a predominantly neurologic phenotype (formerly known as familial amyloid polyneuropathy [FAP]), and a predominantly cardiac phenotype (formerly known as familial cardiomyopathy), although the majority of cases express both neurologic and cardiac manifestations. Disease symptoms, age of onset, and rate of progression are highly variable from patient to patient,[38] and many patients have both cardiac and neurologic involvement. In addition, other organ systems may be affected (e.g., gastrointestinal, renal, and ocular effects), particularly as the disease progresses.[38] Renal involvement is rare in hATTR, and most frequently manifests as protein loss in the urine.[39] The neuropathy-predominant illness affects at least 10,000 people worldwide, and roughly 3,000-3,500 people in the United States (US).[1 2] Due to under-diagnosis and a lack of population-based data, the true number of affected individuals is likely greater. It is important to distinguish hATTR amyloidosis from wild-type ATTR amyloidosis (ATTRwt), a disease that is largely restricted to cardiac manifestations. ATTRwt amyloidosis, while sharing the pathway of TTR misfolding and amyloidogenesis with hATTR, is not heritable, appears to affect predominantly elderly males, and has a different disease course.

The prevalence of hATTR-associated cardiomyopathy has also been problematic to estimate. Any one of more than 130-point mutations in the TTR gene can cause this disease, with the most frequent mutation in the US being the V122I variant. This variant is most common among African Americans, with a prevalence of 3.4% in the general population.[40] Phenotypic penetrance is related to age, with limited data suggesting that the allele is associated with cardiomyopathy in up to 60% of cases.[39,40] Based on US Census data, approximately 1.3 million carriers of the V122I allele are living in the US. Quarta et al. found that the prevalence of overt cardiac disease did not differ between carriers and non-carriers, possibly because symptoms may present later in life as varying degrees of heart failure, and there may be other risk factors for heart failure in older individuals that are unrelated to TTR mutations.[41] There is some indication that biomarkers are worsened in carriers, and that carriers may have a higher risk of incident heart failure. However, estimates of clinical prevalence vary substantially. Estimates of the percentage of patients with overt clinical

cardiac disease vary widely, from 7 to 80%, depending on age.[41] Higher estimates of "clinical penetrance" appear to come from studies with very small samples of carriers.

Outside of the US, the Val30Met is the most common hATTR mutation, with the phenotype varying by region.[43] Val30Met is the most common TTR mutation in patients with hATTR with polyneuropathy, especially in Portugal, South America, Sweden, and Japan. Prevalence of the mutation may approach 1 in 1,000 in Portugal, 100 times the prevalence of neurologic-predominant hATTR in the U.S.[44]

Several different tests are used to diagnose hATTR, with laser capture tandem mass spectrometry considered the gold standard for diagnosis. Demonstration of amyloid deposition on biopsied tissues also confirms the diagnosis of amyloidosis, but not its etiology. Tissues appropriate for biopsy include subcutaneous fatty tissue of the abdominal wall ("abdominal fat pad"), skin, gastric or rectal mucosa, cardiac, sural nerve, and connective tissue from specimens obtained at carpal tunnel surgery. Anti-TTR antibody staining identifies amyloid deposits as TTR-derived.[45] The specific diagnosis of hATTR may be confirmed with genetic testing. The TTR gene, located on chromosome 18, has more than 130 mutations that confer disease, including single mutations, compound heterozygotes, and deletions.[46] Approximately 100 mutant TTR gene products are amyloidogenic.[44] The age at onset varies from the second to ninth decade of life.[32] For example, with the Val30met mutation, there is a bimodal age of symptom onset, with persons of younger age presenting with predominantly neurologic symptoms, and older persons with predominantly cardiac symptoms.[47] The natural history of the illness also varies according to patient sex, geographic region, and genotype.[48]

While the neurologic symptoms of hATTR are among the most physically disabling, cardiac manifestations are most predictive of early death. Circulating misfolded forms of TTR protein and deposition of TTR-derived amyloid fibrils produce severe sensorimotor disturbances (loss of sensation, pain, muscle weakness and loss of ambulation) and autonomic dysfunction, altering control of blood pressure, bowel and bladder function.[49] Autonomic neuropathy is also a common feature resulting in labile blood pressures and debilitating orthostatic hypotension (a drop in blood pressure when changing position). The cardiac manifestations of hATTR include arrhythmias, conduction system disease which may require pacemaker implantation, and an enlarged heart (cardiomegaly) which results in heart failure. If the disease is untreated, median survival for patients with predominantly neuropathic symptoms is 5-15 years, while patients with predominantly cardiomyopathic symptoms have a median survival of 2.5-6 years.[42,48]

Few data on health care utilization among patients with hATTR are available. A recent analysis of patients enrolled in a randomized controlled trial of patisiran found that patients had high rates of primary and specialty care, emergency department use, and hospitalization in the year prior to study enrollment. For patients with early-onset symptoms associated with the Val30Met mutation, researchers have estimated mean lifetime health care costs of 125,645€ ($154,819) per untreated

patient, although these patients typically do not have cardiac manifestations or their associated costs.[51]

As of July 2018, there was no treatment available that reverses the damage already caused by amyloid deposits, nor was there any FDA-approved treatment available in the US.

Currently-Available Treatments

Liver Transplantation

The liver produces virtually all the body's TTR; the brain and eyes produce the remainder of the TTR. Therefore, liver transplantation, which removes the abnormal TTR, is one potential treatment. On average, only 120 hATTR patients with polyneuropathy worldwide receive a liver transplant each year, though this rate has been declining more recently.[52] The Familial Amyloidotic Polyneuropathy World Transplant Registry shows that 129 liver transplants were performed in the US since the early 1990s. The Transthyretin Amyloidosis Outcomes Survey registry data show a transplant rate of 3.3% among patients with hATTR in the US. However, a retrospective cross-sectional study performed at the Mayo Clinic demonstrated a higher frequency of liver transplants. Between 1970 and 2013, 54 of 266 patients with hATTR received a liver transplant, with varying frequency by hATTR genotype. Finally, an analysis of two commercial insurance claims databases covering 2012-2016 found that between 5-13% of patients identified with hATTR had a liver transplant.[53,54] It is likely that rates of receipt of liver transplant vary by geographic region of the US (as well as worldwide according to genotype). Liver transplant benefits only patients with nerve and heart amyloid deposition, such as those with early-onset of amyloidosis caused by the Val30Met mutation.[55] Because the Val30Met mutation is less prevalent in the US, liver transplant is less frequently utilized in the US than in other countries.

Limitations of liver transplant as a treatment for hATTR include allograft availability, neurologic and cardiac disease progression following transplant (e.g., of concurrent hATTR cardiomyopathy at the time of transplant), and substantial morbidity and mortality associated with transplant itself.

TTR Stabilizers

Diflunisal, a generic nonsteroidal anti-inflammatory drug (NSAID) which stabilizes transthyretin tetramers, is available in the US and is used off-label in hATTR. In a randomized trial of 130 patients with symptomatic hATTR, diflunisal significantly reduced progression of neurologic impairment at two years and preserved quality of life compared to placebo.[30] However, long-term use of diflunisal is likely limited by risks common to all NSAIDs, such as gastrointestinal bleeding, worsening of renal insufficiency, and cardiovascular events (e.g., MI, stroke), and as noted above, diflunisal does not reverse neurologic or cardiac impairment.

Tafamidis, a TTR stabilizer administered orally once daily, is the only medicine currently approved to treat stage 1 (early) hATTR neuropathy, and is marketed in the European Union and several South American and Asian countries.[56-58] However, the US FDA did not approve its use during a filing in 2012, due to limited efficacy data.[59] In a randomized, double-blind trial that compared tafamidis to placebo, the co-primary endpoints were not met in the intent-to-treat population.[60] Pfizer recently completed a second trial, a Phase III, multi-center, randomized double-blind, placebo-controlled trial comparing tafamidis 20 mg daily, tafamidis 80 mg daily, or placebo daily (all via oral route). The primary outcome of the trial is a combination of all-cause mortality and frequency of cardiovascular-related hospitalizations versus placebo at 30 months. A press release in March 2018 announced that the study has met its primary endpoint. However, the magnitude of the difference was not described, and results have not yet been presented at scientific meetings or published.

A recent non-randomized cohort study of TTR stabilizer therapy (both diflunisal and tafamidis) for ATTR amyloidosis (both hATTR and ATTRwt) demonstrated a mortality benefit with treatment.[61] Whether these results will be reproduced in the aforementioned randomized prospective trial remains to be determined.

Treatments on the Horizon

As mentioned above, tafamidis is a new treatment on the horizon in the US.

Several new treatments for hATTR are currently in preclinical development. These include investigational monoclonal antibodies designed to target and clear the misfolded TTR amyloid protein (PRX004, and GSK2135698+GSK2398852)[60,61] as well as AG10, a small molecule that binds and stabilizes TTR in the blood.[64]

Inotersen and Patisiran

There are two new medications for treatment of hATTR: patisiran (Onpattro,™ Alnylam Pharmaceuticals; FDA-approved August 2018) and inotersen (TEGSEDI,™ Akcea Therapeutics; under FDA review). Patisiran is an RNA interference (RNAi) therapeutic that was approved by the US FDA for the treatment of peripheral nerve disease (polyneuropathy) caused by hATTR in adult patients. Administered by IV infusion every three weeks, patisiran suppresses the production of both mutant and wild-type forms of TTR by initiating mRNA degradation through the RNA-Induced Silencing Complex (RISC).[4,5] Inotersen is an antisense oligonucleotide (ASO) that complexes with messenger RNA (mRNA) that encodes for TTR. A once weekly subcutaneous injection, inotersen binds TTR mRNA inducing its degradation by RNAase.[5] Inotersen was approved for use in the European Union in July 2018.[6] Seeking more data from the manufacturer, the US FDA has delayed the approval date for inotersen from July 2018 to a new PDUFA goal date of October 6, 2018.[7]

In Phase III clinical trials, both agents significantly improved or reduced worsening in measures of neuropathy impairment, a primary study outcome in both studies, and health-related quality of life,

in comparison to placebo.[8,12] Secondary outcomes included modified body mass index (mBMI; the product of serum albumin concentration and BMI) and N-terminal pro-B-type natriuretic protein (NT-proBNP), a diagnostic and prognostic marker in heart failure, both of which have been found to be predictors of survival in hATTR.[27,49,64] Other exploratory cardiomyopathy outcomes (e.g., ejection fraction, left ventricular size) were also included in the studies and were considered relevant for this evaluation.

As the first TTR gene silencers inhibiting production of the protein inducing hATTR, clinical interest in the use of patisiran and inotersen is high. However, there may be uncertainties related to the translation of neurologic outcomes to longer-term clinical benefit, the durability of such benefit, potential harms of treatment, and the costs associated with the use of these medications. Uncertainty also remains regarding when to initiate therapy in a genopositive individual, thereby necessitating treatment for the remainder of the patient's lifetime with attendant costs and recalibration of the risk-to-benefit ratio. Further, it is possible that some TTR is needed in the body for other purposes, and that treatments that lower TTR beyond a certain threshold level could cause harm.

All stakeholders will therefore benefit from a comprehensive review of the comparative clinical effectiveness, safety, and economic impact of patisiran and inotersen relative to standard care for hATTR.

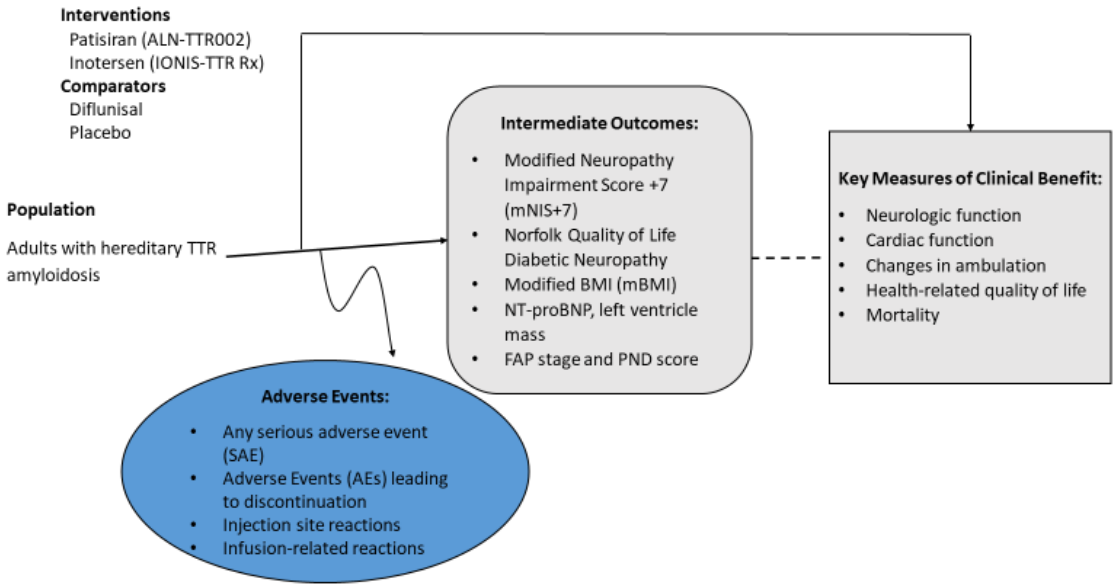
1.2 Scope of the Assessment

This report assesses both the comparative clinical effectiveness and economic impacts of patisiran and inotersen monotherapy for patients with hATTR. The assessment aims to systematically evaluate the existing evidence, taking uncertainty and patient-centered considerations into account. To that aim, the assessment is informed by two research components – a systematic review of the existing evidence and an economic evaluation – developed with input from a diverse group of stakeholders, including patients and their families, clinicians, researchers, representatives from patient advocacy organizations, and manufacturers of the agents of focus in this review. Below, we present the review's scope in terms of the research questions, PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design) elements, and an analytic framework diagram.

Analytic Framework

The general analytic framework for assessment of therapies for hATTR is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Therapies for Hereditary TTR Amyloidosis (hATTR)



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., neuropathy impairment score), and those within the squared-off boxes are key measures of benefit (e.g., quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.

Populations

The population of focus for the review was adults with hereditary ATTR (hATTR) amyloidosis.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Patisiran
- Inotersen

Comparators

The comparator in clinical trials was placebo, reflecting best supportive care. While not a formal comparator, we also summarized data on diflunisal due to its off-label use in the condition. Tafamidis was not deemed to be in scope, however, as it is not currently approved in the US and the manufacturer has yet to formally file with the FDA for approval.

Outcomes

The outcomes of interest are described in Table 1.1 below.

Table 1.1. Key Outcomes and Harms

Outcomes	Key Harms
Neuropathy (e.g., Modified Neuropathy Improvement Score + 7 [mNIS+7])	Significant adverse events
Modified BMI (BMI x albumin)	Adverse events leading to discontinuation
Ambulation/mobility (e.g., FAP stage and PND score)	Injection site reactions
Health-related quality of life (e.g., Norfolk-QOL-DN)	Thrombocytopenia (platelet count decrease) causing significant bleeding
Cardiac function (e.g., echocardiographic measures , NT-proBNP, NYHA Class)	Infusion-related reactions
Mortality	Grades 3 and 4 serious adverse events
	Death

Timing

Evidence on intervention effectiveness was derived from studies of at least one year's duration and evidence on harms from studies of at least three months' duration.

Settings

All relevant settings were considered, including both outpatient and inpatient settings.

Value Framework Considerations

ICER is assessing the clinical effectiveness and value of inotersen and patisiran for hATTR under a modified value assessment framework for treatments of ultra-rare conditions (http://icer-review.org/material/final-ultra-rare-adaptations/) because we believe the assessment meets the following proposed criteria:

- An eligible population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals

- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals

The conservative estimate is that the US candidate population potentially eligible for treatment may be as small as 3,000 to 3,500 patients, although the prevalence of truly hATTR-attributable cardiac amyloidosis is currently unknown. However, key opinion leaders in the field believe drug approval will lead to identification of twice those numbers of eligible patients.

1.3 Definitions

Karnofsky performance status: Karnofsky performance status measures a patient's functional status. With a range from 0 to 100, lower numbers indicate worse status (e.g., 0 is death), and higher numbers indicate higher levels of function (100 is normal function). This measure is frequently used to assess functional status among cancer patients.[66]

Eastern Cooperative Oncology Group (ECOG) performance status: Assesses a patient's function with regard to their ability to care for themselves, perform activities of daily living, walk, and work. With a range from 0 to 5, a lower score indicates higher functioning.[67]

FAP stage: Coutinho et al. developed a clinical staging system for the neuropathy symptoms of hATTR (formerly termed familial amyloid neuropathy). The scale ranges from 1 to 3, as follows:[49]

- FAP Stage 1: Walking without assistance, mild neuropathy (sensory, autonomic, and motor) in lower limbs
- FAP Stage 2: Walking with assistance, moderate impairment in lower limbs, trunk, and upper limbs
- FAP Stage 3: wheelchair or bed-ridden, severe neuropathy

Modified BMI (mBMI): the product of BMI (weight in kilograms divided by the square of height in meters) and serum albumin (g/L). mBMI is a predictor of survival in the predominantly neurologic phenotype of hATTR (formerly known as familial amyloid polyneuropathy).[68] A lower score is associated with worse survival.

Modified neuropathy impairment score +7 (mNIS+7): A composite score measuring motor strength, reflexes, sensation, nerve conduction, and autonomic function. Two versions of this composite measure were adapted from the NIS+7 to better reflect hATTR polyneuropathy and have been used as primary outcomes in inotersen and patisiran clinical trials. Key differences between these two versions are summarized in Table 1.2. Neither version of the mNIS+7 has a defined threshold for clinical relevance. A 2-point change has been suggested as the minimum clinically important difference for the NIS+7;[8] however, we were unable to find literature reporting any

validation specific to either version of the mNIS+7. In both scales, a lower score represents better neurologic function (e.g., an increase in score reflects worsening of neurologic impairment).

Table 1.2. Modified Neuropathy Impairment Score + 7

mNIS+7		mNIS+7$_{Ionis}$	
Motor strength	192 points	Motor strength	192 points
Reflexes	20 points	Reflexes	20 points
QST	80 points	Sensation	32 points
NCS	10 points	QST	80 points
Postural blood pressure	2 points	NCS	-18.6 to 18.6 points
Total	**304 points**	HRdb	-3.72 to 3.72 points
		Maximum score	**346.6 points**

HRdb: heart rate response to deep breathing, NCS: nerve conduction score, QST: quantitative sensory testing

Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire: Assesses quality of life in diabetic polyneuropathy. Vinik et al. have validated this scale to assess quality of life in hATTR patients with neurologic symptoms.[69] However, there is no minimum clinically important difference defined in the literature for Norfolk-QOL-DN. A higher score indicates poorer quality of life.

NT-proBNP: N-terminal pro-BNP (NT pro-BNP) is a fragment of the hormone brain natriuretic peptide (BNP). The heart releases both BNP and NT pro-BNP in patients with heart failure. Elevated levels of NTpro-BNP may be used to diagnose heart failure.[70] While associated strongly with outcomes in hATTR amyloidosis, the marker is not specific for this disease thus its utility in diagnosis is limited.

NYHA Class: The New York Heart Association (NYHA) Functional Classification is the most commonly used heart failure classification system. Ranging from I to IV, the scale measures the severity of a patient's heart failure symptoms. Patients with class I heart failure have no limitations of physical activity, while patients with class IV have symptoms of heart failure at rest.

Polyneuropathy disability score (PND)*:* A five-stage measure of neuropathy impairment ranging from 0 (no impairment) to 4 (confined to a wheelchair or bedridden).[49]

- Stage 0: no impairment
- Stage I: sensory disturbances but preserved walking capability
- Stage II: impaired walking capability but ability to walk without a stick or crutches
- Stage IIIA: walking only with the help of one stick or crutch
- Stage IIIB: walking with the help of two sticks or crutches
- Stage IV: confined to a wheelchair or bedridden

Thrombocytopenia: A low platelet level that can cause bleeding.

1.4 Insights Gained from Discussions with Patients and Patient Groups

We received comments from patients with hATTR and their caregivers, and reviewed survey data collected by the Amyloidosis Research Consortium.[71] The survey included 101 patients with hATTR, over half whom were from the US. Similar themes emerged from the comments and survey data.

We heard from patients and caregivers that hATTR is a severe disabling illness that profoundly impacts all aspects of quality of life. Given that the disease may affect multiple organ systems and may progress rapidly, a wide variety of manifestations may include (but are not limited to) weight loss, wasting, difficulty walking, and alternating constipation and uncontrollable diarrhea, which patients describe as embarrassing. Patients with hATTR are frustrated by loss of independence and a sense of "normalcy" in their lives. Not only are patients unable to work or engage in hobbies, but they may also have difficulty leaving the house and ultimately, may become bed-bound and unable to dress, feed, or bathe themselves.

Patients describe a devastating impact of the illness on family life, with members of multiple generations of the same family affected. Some individuals care for older family members who are affected while also worrying about children who may later develop hATTR. Caretakers describe the emotional burden of "knowing what's to come," and often struggle to balance the responsibilities of working, providing for family members in the home, and transporting patients to medical appointments.

Patients also voiced concern that in the face of such suffering, there were no treatments approved in the US specifically for hATTR until just recently. Following the approval of patisiran, many patients commented on their worry that access may be an issue because of the announced high price of the drug. Patients commented that there needs to be a balance between revenue for future innovation, and affordability for patients now.

Current off-label treatments are of limited efficacy, and patients often have difficulty travelling to a small number of Amyloid Centers of Excellence at academic medical centers in the US to receive treatment. Therefore, patients and families value convenience of therapies that can be administered in the home. Patients also expressed a willingness to tolerate medication side effects: "The side effects would have to be pretty bad to be worse than the disease." New treatments for hATTR offer much-needed hope to patients and their families.

1.5. Potential Cost-Saving Measures in Hereditary Transthyretin Amyloidosis

As described in its *Final Value Assessment Framework for 2017-2019*, ICER will now include in its reports information on wasteful or lower-value services. Such services could be reduced or eliminated to create room in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with hATTR or related conditions that could be reduced, eliminated, or made more efficient.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for hATTR treatment, we reviewed National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs) from the Centers for Medicare and Medicaid Services (CMS), and coverage policies and formularies for Missouri's state Medicaid program (MO Healthnet) and representative commercial plans (Blue Cross Blue Shield Kansas City, Cigna Missouri, United Healthcare, CVS Caremark, Anthem Blue Cross Blue Shield, and Aetna) at the national and regional level. We surveyed each plan's coverage policies for three pharmacologic agents for hATTR: diflunisal, inotersen, and patisiran. There are no coverage policies for inotersen, as it is not FDA-approved; since patisiran was just approved in August 2018, we were unable to identify any coverage policies. Alnylam has announced that is working to implement outcomes-based contracts for coverage of patisiran with willing payer partners. According to a press release from Alnylam, "the goal of these agreements is to ensure that Alnylam is paid based on the ability of ONPATTRO [patisiran] to deliver outcomes in the real world setting comparable to those demonstrated in clinical trials."[72]

We were unable to identify any NCDs or LCDs for diflunisal in CMS regions 6, 7, and 8, which represent the Midwestern states.[73] MO Healthnet, Missouri's state Medicaid program, listed diflunisal as a non-preferred agent and requires patients to have a documented adverse effect or therapeutic failure with ibuprofen, naproxen, or piroxicam before diflunisal will be covered. One exception to the aforementioned rule is that coverage is provided for patients who are currently being treated with diflunisal and are adherent (i.e., they do not need to re-attempt therapy with another agent to receive authorization for diflunisal). Although the policy, as written, applies to the use of diflunisal for any indication, it is unclear whether this would be the case for hATTR as diflunisal is used for its ability to stabilize the mutant protein rather than its anti-inflammatory effect.

Diflunisal was covered as a tier 1 generic drug with no preferred alternative in all surveyed national and Midwestern commercial plans.[74-79]

2.2 Clinical Guidelines

There are few available guidelines on the treatment of hATTR or TTR-FAP. These guidelines focused on the pathogenesis, diagnosis, monitoring, and pharmaceutical treatment of hATTR. Below, we have summarized a consensus statement from the European Network for TTR-FAP (ATTReuNET) and a guideline based on the Transthyretin Amyloidosis Outcomes Survey (THAOS).

European Network for TTR-FAP (ATTREeuNET), 2016[80]

The 2016 ATTReuNET consensus statement focused on the polyneuropathy that patients with hATTR experience and did not include guidance related to inotersen or patisiran. Treatment recommendations were based on the age, stage of disease, and possibility of liver transplant. For stage I TTR-FAP tafamidis was recommended, and liver transplant was recommended if disease progression occurred following treatment. Diflunisal was recommended for stage II TTR-FAP and, if liver transplant was contraindicated, as a second-line treatment for stage I patients. Liver transplant was recommended for stage I TTR-FAP with disease progression on tafamidis, and combined kidney/liver transplant was recommended for patients with severe nephropathy or cardiomyopathy. ATTReuNET recommended monitoring, including an annual review of disease stability for patients on pharmaceutical treatment. If disease stability was achieved, continuation of current pharmacological treatment was recommended. Conversely, if objective disease progression was detected, alternative treatments such as liver transplant or enrollment in clinical trials were recommended.

Ando Y, Coelho T, Berk JL, et al., 2013[49]

This 2013 guideline was based on the authors' opinions and information from THAOS, a TTR amyloidosis patient registry, and focused on the diagnosis and symptom management of TTR-FAP. Treatment recommendations were based on stage of disease and possibility of liver transplant but were limited by a paucity of evidence.

Tafamidis and diflunisal were recommended for patients with stage I TTR-FAP and, in the context of a clinical trial, for patients whose disease is in stage 0, II, or III, or who have had a domino liver transplant. The guideline recommended that all patients with stage I TTR-FAP be placed on a liver transplant list.

For stage I patients, the guideline recommended the use of any approved drugs for TTR-FAP regardless of liver transplant status. The consensus statement notes that diflunisal and tafamidis may prolong the time to disease progression based on available data, although there was scant data on the durability of this therapeutic effect. Monitoring is recommended for patients on pharmaceutical treatment, including disease progression assessment every six months. If objective disease progression occurred, liver transplant should be considered. The statement did not include guidance for the treatment of patients with stable disease.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our review of the clinical effectiveness of patisiran and inotersen in patients with hereditary transthyretin amyloidosis (hATTR) in comparison with usual care, we extracted evidence from available clinical studies meeting our inclusion criteria, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). We focused on efficacy, safety, and effectiveness data in comparison to placebo in our target population of adults age 18 and older with hATTR. Our review focused on assessing the intermediate and long-term outcomes and harms evaluated in available studies. We sought evidence on the following outcomes:

- Modified Neuropathy Impairment Score + 7 (mNIS+7)
- Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) scores
- FAP stage and PND scores
- Modified BMI (mBMI)
- Mortality
- Cardiac outcomes (e.g., echocardiographic measures, NT-proBNP, NYHA class)
- Adverse events (AEs)
- Serious adverse events (SAEs) and severe adverse events
- Treatment discontinuations due to AEs
- Deaths

When reviewing clinical evidence in ultra-rare populations, ICER acknowledges the challenges of study design, recruitment, and availability of data on long-term outcomes. We recognize the difficulty in validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. As such, we aim to add specific context to our findings regarding potential challenges in study design, when possible.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for hATTR followed established best research methods.[79,80] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[83] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated using the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

Study Selection

We included all relevant randomized clinical trials, nonrandomized comparative studies, and single-arm or open-label studies of any size if they evaluated efficacy for at least one year and/or harms for three or more months. We excluded studies with trial populations of less than 50% hATTR participants (e.g., studies with a mixed population of wild-type amyloidosis and hATTR), and trials evaluating additional treatments (e.g., tafamidis) without analysis stratified by the treatments, as such studies were outside the scope of this review. *In vitro* and non-human studies were excluded, as were single-dose and pharmacokinetic studies. We excluded conference proceedings and abstracts reporting data also available in full-text peer-reviewed publications.

Data Extraction and Quality Assessment

Main trial data were extracted directly into Microsoft Word tables (see Appendix C). We extracted data on patient populations, sample size, duration of follow-up, study design features (e.g., randomized controlled trial, open-label trial, etc.), interventions (drug, dosage, frequency, and schedule), outcome assessments (e.g., timing, definitions, and methods of assessment), results, and quality for each study. Data were extracted from the full-text articles by a single reviewer and validated by a second reviewer.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix Figure C1).

Assessment of Bias

Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for hATTR therapies using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. We did not find any indication of studies completed more than two years ago that would have met our inclusion criteria and were without associated publications.

3.3 Results

Study Selection

We captured 64 potentially relevant references through our literature search (date of last search August 23, 2018), of which three met eligibility criteria. The primary reasons for study exclusion included non-clinical outcomes (e.g., *in vitro* studies), lack of outcomes of interest, and duplicate data found in published literature. We found additional data from 12 publicly-available peer-reviewed manuscripts, manufacturer press releases, and conference abstracts, posters, and presentations not yet available through the databases used in our literature review. In all, 19 references were included, of which 15 reported on patisiran trials and four reported on inotersen trials.

Quality of Individual Studies

Using criteria from the US Preventive Services Task Force (USPSTF), we rated the APOLLO study to be of fair quality due to differential drop-out between treatment groups; the NEURO-TTR study to be of fair quality based on baseline differences in autonomic and sensorimotor neuropathy severity between treatment groups; and one randomized controlled trial of diflunisal to be of fair quality based on differential attrition between the placebo and diflunisal arms (see Appendix C for details on quality rating criteria).[84] We did not assign a quality rating to non-comparative studies or references obtained from grey literature sources (e.g., conference proceedings).

Key Studies

We identified single Phase III trials for inotersen and patisiran, both of which are summarized in Table 3.1. Differences in the primary outcome measures and trial population (e.g., race, geographic

region, disease severity) precluded direct comparison of the APOLLO and NEURO-TTR trials. NEURO-TTR evaluated efficacy based on a co-primary endpoint which included a modified neuropathy impairment score (mNIS+7) that differed substantially from the mNIS+7 used in the APOLLO trial (see also Section 1.3). Key differences in the score components (e.g., nerve conduction component, autonomic function) and total scoring (346.3 vs. 304 points, see Section 1.3) prevented the direct comparison of neurological outcomes between the two trials. As a result, we present data on inotersen and patisiran efficacy in relation to their comparators in the clinical trials.

Table 3.1 Comparability of Inotersen and Patisiran Randomized Controlled Trials

	NEURO-TTR Inotersen	APOLLO Patisiran
Baseline characteristics	**Geographic region** N. America: 47.7% Europe: 34.9% Other: 17.4% **Race** White: 91.9% Asian: 2.3% Black: 2.3% Other: 3.5%	**Geographic region** N. America: 20.9% Europe: 43.6% Other: 35.6% **Race** White: 72.4% Asian: 23.1% Black: 2.2% Other: NR
TTR Genotype†	**Val30Met**: 50.0% **non-Val30Met**: 50.0%	**Val30Met**: 42.7% **non-Val30Met**: 57.3%
FAP Stage†	**Stage 1**: 66% **Stage 2**: 34%	**Stage 1**: 46.2% **Stage 2**: 53.3%
Cardiac Subpopulation	67%	56.0%
Prior Use of TTR Stabilizers*†	56%	52.9%

FAP: familial amyloid polyneuropathy, NR: not reported, TTR: transthyretin. *APOLLO stratified at randomization †NEURO-TTR stratified at randomization.

Clinical Benefits

Inotersen

In the NEURO-TTR trial, inotersen treatment slowed the progression of polyneuropathy relative to placebo and improved neuropathy-related quality of life versus placebo. The statistically significant treatment difference in mNIS+7 reflected progression in the placebo group and delayed progression in the inotersen group, though many inotersen patients reported improved neuropathy scores. OLE data suggest sustained delay of progression of polyneuropathy, though neuropathy-related quality of life appears to decline slightly through an additional 52 weeks of treatment. Cardiac endpoints did not differ statistically between the inotersen group and the placebo group after 15 months of intervention; however, the trial was not powered to detect differences in cardiac outcomes. A small single-arm open label study shows minimal worsening of left ventricular mass.

We included four references evaluating the efficacy and safety of inotersen (Table 3.2). One peer-reviewed publication [8] and two conference presentations[9,10] reported data from the Phase III NEURO-TTR trial, and the fourth, a full text publication,[11] included cardiac data from an investigator-initiated, single-arm, open label trial.

NEURO-TTR was a Phase III randomized controlled trial evaluating neurologic function using the mNIS+7$_{Ionis}$ and Norfolk QOL-DN as the primary outcomes after 15 months of treatment.[8] Stabilization was defined as a 0-point change from baseline mNIS +7. Eligibility criteria included FAP stages 1 and 2, NIS scores between 10-130, positive amyloid biopsy, and genotype-verified TTR mutations. Patients who previously received a liver transplant or who met criteria for New York Heart Association (NYHA) heart failure class ≥ 3 were excluded from the trial. Patients using TTR stabilizers (e.g., tafamidis, diflunisal) prior to study enrollment were required to stop treatment prior to receiving their first dose of inotersen (14 and 3 days before first dose, respectively). Eligible patients were randomized 2:1 to receive either once-weekly 300 mg subcutaneous injections of inotersen or matched placebo. Randomization was stratified by disease stage (FAP Stage 1 vs. 2), TTR mutation (Val30Met vs. non-Val30Met) and prior use of TTR stabilizers (tafamidis and/or diflunisal). All patients received vitamin A supplements at the recommended daily dose.[8] NEURO-TTR is followed by an ongoing open-label extension (OLE) where all patients will receive inotersen for up to five years.

Table 3.2 NEURO-TTR Baseline Characteristics

	NEURO-TTR[8] Randomized controlled trial Duration: 15 months	
Baseline Characteristics	**Inotersen** 300 mg weekly by subcutaneous injection	**Matched placebo**
No. of Participants	112	60
Trial Discontinuation, (%)	22.3	13.3
Mean Age, Years (SD)	59.0 (12.5)	59.5 (14.1)
Females, n (%)	35 (31.2)	19 (31.7)
mNIS+7 Score, Mean (SD)	79.2 (37.0)	74.8 (39.0)
Norfolk-QoL-DN Score, Mean (SD)	48.2 (27.5)	48.7 (26.7)
FAP Stage, n (%)*		
FAP Stage 1	74 (66)	42 (70)
FAP Stage 2	38 (34)	18 (30)
Cardiac Sub-Populations, n (%)†	75 (67.0)	33 (55.0)
TTR Genotype, n (%)*		
Val30Met	56 (50)	33 (55)
non-Val30Met	56 (50)	27 (45)
Previous Tetramer Stabilizer Use*	63 (56)	36 (60)

NR: not reported; SD: standard deviation; Matched placebo=identical treatment except study drug. *Stratification factor at randomization. †NYHA class not reported.

The inotersen and placebo groups were balanced with regard to previous use of TTR stabilizers, TTR genotype, quality of life, and age (Table 3.2). There were some differences at baseline noted in the available published literature (e.g., sensorimotor and autonomic neuropathy were more severe in the inotersen group), however, the statistical significance of these differences was not reported.[8] The proportion of patients with cardiac symptoms of hATTR was notably higher in the inotersen group compared to placebo (67% vs. 55%). Statistical analyses adjusted for baseline values of the outcome evaluated (i.e., analysis of mNIS+7 adjusted for baseline mNIS+7 values).

Half of the trial population carried the Val30Met mutation, likely because the trial design focused on polyneuropathy patients and outcomes; however, the Val122Ile mutation, which is the most prevalent mutation in the US, was largely under-represented (n = 3, 1.7%). Treatment discontinuations occurred more frequently among inotersen patients compared to placebo (22.3% vs. 13.3%). Inotersen patients discontinued most commonly due to AEs while placebo patients discontinued most commonly due to voluntary withdrawal and disease progression (n = 3, 5% each).[8]

The single-arm, investigator-initiated trial enrolled eight hATTR patients to receive 300 mg of inotersen weekly by subcutaneous injection for 12 months.[11] Patients had a mean age of 63 and one patient (12.5%) carried the Val30Met mutation.

Mortality

At the time of publication of this draft report, no evidence has been identified on the impact of inotersen on mortality or survival. Mortality was exclusively reported as a safety outcome (see section on harms).

Disease Progression

Disease progression measured by PND score is presented in Table 3.3. As described in Section 1.3, decreases in PND score reflect worsening ambulation. Fifty-eight percent of inotersen and 65% of placebo patients reported improvements or stabilization in PND score. Comparable proportions of patients in the two groups reported worsening disease stage. These results were not compared statistically, however, and data was missing for nearly one-quarter of the inotersen group.

Table 3.3 NEURO-TTR Disease Progression by PND score[85]

	Placebo	Inotersen
No. Randomized	60	112
No. Completed*	52 (86%)	87 (78%)
PND Score Change From Baseline		
Improved, n (%)	2 (3)	9 (8)
No Change, n (%)	37 (62)	56 (50)
Worsened, n (%)	13 (22)	21 (19)
Missing, n (%)	8 (13)	26 (23)

*Number of participants who completed the trial

Neurologic Impairment and Quality of Life

NEURO-TTR inotersen patients experienced a statistically significant delay in neuropathy progression compared to placebo, as measured by mNIS+7_{Ionis} (least-squares mean [LSM] treatment difference: -19.7 points, 95% CI −26.4 to −13.0) (Table 3.4).[8] Over 15 months, the placebo group experienced polyneuropathy progression (mNIS+7_{Ionis}: +25.5 points, 95% CI 20.2 to 30.8) while the inotersen group showed a significantly reduced level of progression (mNIS+7_{Ionis} change from baseline: 5.8, 95% CI 1.6 to 10.0)(Table 3.4).[8] Significantly more patients in the inotersen group experienced mNIS+7_{Ionis} improvements compared to baseline after 15 months of treatment (Table 3.4, p = 0.033).[8]

Table 3.4 NEURO-TTR Neurologic Impairment and Quality of Life Outcomes

	Inotersen n = 112	Placebo n= 60	Treatment Difference
Mean Change From Baseline[8]			
mNIS+7, points (95% CI)	5.8 (1.6 to 10.0)	25.5 (20.2 to 30.8)	−19.7 (−26.4 to −13.0)*
Norfolk-QOL-DN, points (95% CI)	1.0 (-3.2 to 5.2)	12.7 (7.4 to 17.9)	−11.7 (−18.3 to −5.1)*
Percent Reporting Improvement†			
mNIS+7	36.5%	19.2%	17.2% (2.4 to 32.1)‡
Norfolk-QOL-DN	50.0%	26.9%	23.1% (7.0 to 39.2)‡

NR: not reported. *p < 0.001. Negative changes on both mNIS+7 and Norfolk-QOL-DN indicate improvement
†Improvement defined as no increase from baseline ‡Risk/proportion difference (inotersen-placebo)

Inotersen treatment also improved neuropathy-related quality of life (QOL), as shown by Norfolk-QOL-DN scores, compared to placebo (Table 3.4, p = 0.0006). Significantly more patients on inotersen reported improved neuropathy-related QOL after 15 months of treatment compared to those on placebo (Table 3.4, p = 0.008).[8] Statistically-significant improvements in neuropathy-related QOL favoring inotersen compared to placebo were reported in the physical functioning/large fiber neuropathy, activities of daily living, and symptoms domains (p ≤ 0.001); however, improvements in small fiber and autonomic function neuropathy QOL domains were not

statistically significant.[10] Neither the mNIS+7$_{Ionis}$ nor the Norfolk-QOL-DN have a validated threshold of what magnitude of improvement or worsening is clinically relevant. Benson and colleagues suggest a 2-point change in the mNIS+7 is the minimum clinically important difference; [8] however, the sources cited by Benson actually refer to the NIS and NIS+7. As a result, it is uncertain whether these changes represent meaningful improvements for patients.

Patients who completed NEURO-TTR were eligible to enroll in the open-label extension study to receive inotersen treatment for up to five years. Data through an additional 52 weeks show continued delay of polyneuropathy progression in the 54 inotersen patients rolling over to OLE (mNIS+7$_{Ionis}$ increased by an estimated 3 points from the end of NEURO-TTR), but suggest stabilization of neuropathy-related QOL may not be sustained (worsened by an estimated 3.6 points from the end of NEURO-TTR).[9]

Subgroup Analyses

Subgroup analyses by TTR mutation (Val30Met vs. non-Val30Met), disease stage, and previous TTR stabilizer treatment (i.e., stratification factors) showed a consistent and statistically significant benefit with inotersen in mNIS+7$_{Ionis}$ (all $p < 0.001$) and Norfolk-QOL-DN (all $p \leq 0.05$) versus placebo.[8] Likewise, inotersen patients showed benefits in neuropathy and disease-related quality of life regardless of whether cardiomyopathy was present. Patients with milder disease (FAP stage 1) at baseline also reported a statistically smaller LSM change from baseline in mNIS+7 (-14.2, 95% CI -22.5 to -5.9) compared to patients with more severe disease (-29.1, 95% CI -40.2 to -18.0; $p = 0.035$).[8]

Cardiac Outcomes

Assessment of cardiac-specific outcomes in this trial was limited as the study was not powered for these endpoints. NEURO-TTR patients with cardiac involvement were defined as those with an intraventricular septum thickness ≥ 1.3 cm.[8] There was no evidence of improvement versus placebo in global longitudinal strain or other echocardiographic measures, including ejection fraction, posterior wall thickness, and left ventricular mass, with inotersen treatment after 15 months compared to placebo.[8]

In addition, Benson and colleagues reported outcomes related to heart structure and function in an 8-patient, single-arm study. Because this study was uncontrolled, no formal statistical analysis was reported. At baseline, the seven hATTR patients with available data had a mean LVM (measured by MRI) of 202 g (standard error of the mean [SEM] ± 15). These patients largely showed stable LVM after 12 months of inotersen treatment.[11] Similar stabilization was reported across eight patients in left ventricle (LV) wall thickness, global systolic strain, and 6-minute walk test (6MWT). All eight patients had NYHA class data; four improved from class 2 to class 1 and four remained stable in class 1.

Other Outcomes

Inotersen treatment did not result in significant differences in mBMI compared to placebo.[8]

Harms

Five deaths were reported during the study, all of which occurred in the inotersen group, through 15 months of treatment (Table 3.5). Four deaths were considered related to disease progression and one death was considered possibly inotersen-related. Safety data show two key concerns with inotersen treatment: thrombocytopenia and glomerulonephritis. Frequent platelet and renal monitoring implemented during the NEURO-TTR trial suggests thrombocytopenia and decreased renal function may be monitorable and manageable. AEs considered related to treatment were more frequently reported by inotersen patients compared to placebo patients.

As described previously, mortality was analyzed as a safety outcome only. Five deaths occurred during NEURO-TTR, all in the inotersen group. One death was due to intracranial hemorrhage associated with serious (Grade 4) thrombocytopenia (platelet count less than 10,000/mm^3) that occurred before the implementation of frequent platelet monitoring and four were considered related to disease progression.[8]

Three SAEs (Grade 4 severity) of thrombocytopenia occurred in three patients, one of whom died due to intracranial hemorrhage, during the NEURO-TTR trial. [8] One additional inotersen recipient discontinued study treatment following a non-serious thrombocytopenia event. Decreased platelet counts (below 140,000 cells/mm^3) were reported in 54% of inotersen patients and 13% of placebo patients.[8] These decreases developed over several weeks and generally peaked between three and six months after starting inotersen. Decreased platelet counts (undefined) were also reported in the investigator-initiated study.[11] Other antisense oligonucleotides (e.g., mipomersen [Kynamro®], nusinersen [Spinraza®], drisapersen, volanesorsen) have been associated with thrombocytopenia, presenting either as a mild decline over time or as a rapid and severe decrease in platelets resulting in hospitalization.[5,86] Safety evaluations of the severe thrombocytopenia events in NEURO-TTR suggest evidence of an immune-mediated mechanism, and ruled out effects on platelet production.[8]

Three inotersen patients (3%) experienced glomerulonephritis.[8] Two placebo and one inotersen patients discontinued after meeting defined renal function stopping rules.[8] After identifying this renal signal, additional monitoring (every two to three weeks) was added to the NEURO-TTR study protocol.

Table 3.5. Inotersen Harms

	NEURO-TTR[8]	
	Placebo n = 60	**Inotersen** n = 112
Treatment Duration	15 months	
Any Adverse Event	60 (100)	111 (99)
Study-Related Adverse Event	23 (38)	87 (78)
Serious Adverse Event	13 (22)	36 (32)
Study-Related Serious Adverse Event	1 (2)	8 (7)
Discontinuations Due to Adverse Event	1 (2)	14 (13)
Deaths	0	5 (4.5)*
Common Adverse Events†		
Nausea	7 (12)	35 (31)
Headache	7 (12)	26 (23)
Pyrexia	5 (8)	22 (20)
Vomiting	3 (5)	17 (15)
Anemia	2 (3)	15 (13)
Thrombocytopenia	1 (2)	15 (13)
Decreased Platelet Count	8 (13)	60 (54)

All data are n (%). NR: not reported. *One death considered possibly drug-related. †Defined as those reported by ≥ 10% and twice as frequently in inotersen group versus placebo.

The inotersen group reported higher rates of SAEs (32%) relative to the placebo group (22%) (Table 3.5). Common AEs reported by at least 10% of NEURO-TTR patients and twice as frequently in the inotersen group versus placebo included thrombocytopenia or platelet count decrease, nausea, vomiting, fever, chills, and anemia (Table 3.5). Anti-inotersen antibodies were reported in 30.4% of NEURO-TTR patients.[29] These antibodies typically developed after a median of 200 days of treatment and did not appear to affect drug efficacy, but patients with such antibodies reported more injection site reactions.[29] Injection site reactions occurred following less than 1% of all injections and resulted in no discontinuations. Injection site reactions were slightly more common in the investigator-initiated study.[11]

A respective 9% and 4% of inotersen-inotersen and placebo-inotersen patients discontinued inotersen treatment due to AEs in the OLE.[9] Rates of SAEs were similar in both groups of patients (26% among inotersen-inotersen patients vs. 22% among placebo-inotersen patients).[9]

Patisiran

Data from the APOLLO Phase III trial show the first evidence of functional improvement, as measured by patients' ability to walk. A substantial proportion of patients reported stable or improved neuropathy stage. APOLLO data demonstrate a statistically significant mean improvement in neurologic function and neuropathy-related quality of life with patisiran

treatment compared to placebo. About half of patisiran patients showed neurological improvement by mNIS+7 score. Post-hoc evidence suggests decreased risk of the composite endpoint of all-cause mortality (based on adverse event case report forms) and hospitalization among those with cardiac involvement. Baseline data indicate statistically significant imbalances in TTR genotype and potentially clinically relevant differences in disease severity with unknown statistical significance between patisiran and placebo groups, which may impact study generalizability.

We identified and included 15 references on patisiran trials. One peer-reviewed publication,[12] four conference presentations,[14-17] and four conference posters[18-21] presented data from the APOLLO Phase III trial. One peer-reviewed publication reported the results of a Phase II dose-ranging study[22], two conference posters and one presentation reported on the Phase II OLE,[23-25] and two reported findings from the ongoing global OLE study including patients from the Phase II and Phase III trials.[25,26]

A Phase II open-label multiple-dose escalation trial evaluating patisiran safety included 29 patients who received two infusions at one of the following doses: 0.01 mg/kg (n = 4), 0.05 mg/kg (n = 3), 0.15 mg/kg (n = 3), or 0.3 mg/kg (n = 7) every four weeks or 0.3 mg/kg every 3 weeks (n = 12).[22] The subsequent Phase II OLE included patients who completed the Phase II dose-ranging study and who chose to continue receiving patisiran. All patients received 0.3 mg/kg of patisiran by infusion once every three weeks for 24 months.[24] Primary outcomes included safety and tolerability; mNIS+7 score, cardiac biomarkers and echocardiography were included as secondary outcomes.

APOLLO was a Phase III randomized controlled trial evaluating neurologic function using the mNIS+7 as the primary outcome after 18 months of treatment. Response to treatment was defined as a less than 10-point increase from baseline in the mNIS+7 at 18 months. The trial enrolled 225 hATTR patients with a documented pathogenic variant in TTR, ages 18-85, with NIS scores ranging from 5-130. Patients were required to meet Karnofsky performance status ≥ 60%, PND score ≤IIIb, have anticipated survival of at least two years, adequate blood counts (e.g. absolute neutrophil count ≥ 1,500 cells/mm3 and platelet count ≥ 50,000 cells/mm^3, liver function (aspartate transaminase and alanine transaminase levels ≤ 2.5 × upper limit of normal; total bilirubin levels within normal limits; international normalized ratio ≤ 2.0), and to be free from hepatitis B and C infection. Patients were excluded if they had a history of liver transplantation, untreated hyper- or hypothyroidism, HIV infection, malignancy in the previous two years (except squamous cell carcinoma or carcinoma in situ of cervix successfully treated), type 1 or 2 diabetes mellitus, uncontrolled cardiac arrhythmia or unstable angina, acute coronary syndrome within the past three months, NYHA classification > 2, or receipt of an investigational device or agent. Participants taking diflunisal or tafamidis prior to enrollment were required to stop stabilizer use 3 and 14 days, respectively, before receiving their first dose of patisiran.

Eligible patients were randomized 2:1 to receive either a 0.3 mg/kg infusion of patisiran every three weeks or matched placebo for 18 months. Randomization was stratified by previous TTR stabilizer use, NIS score (5-49 vs. 50-130), and early-onset Val30Met (defined as before age 50) versus all other mutations, including late-onset Val30Met. Each infusion in both groups was preceded by an injection of dexamethasone, oral acetaminophen, an H_2 blocker, and an H_1 blocker. Baseline characteristics of APOLLO participants are shown in Table 3.6.

The ongoing global OLE study includes 211 patients who completed the Phase II or III trials. All patients enrolled receive a 0.3 mg/kg infusion of patisiran every three weeks, preceded by the pre-treatment medication described above. Preliminary data available at the time of report drafting show 44% of included patients have completed 52 weeks of treatment.

Table 3.6. APOLLO Baseline Characteristics

	APOLLO[12,14,21] Randomized controlled trial Duration: 18 months	
Baseline Characteristics	Patisiran 0.3 mg/kg by infusion every 3 weeks	Matched placebo
No. of Participants	148	77
Trial discontinuation, (%)	7	29
Median Age, years (range)	62 (24-83)	63 (34-80)
Females, n (%)	39 (26%)	19 (24%)
Geographic Region, n (%)		
North America	37 (25%)	10 (13%)
Europe	62 (41%)	36 (46%)
Other	49 (33%)	31 (40%)
Race, n (%)		
White/Caucasian	113 (76%)	50 (65%)
Asian	27 (18%)	25 (33%)
Black	4 (3%)	1 (1%)
Other	1 (< 1)	0
> 1 Race	1 (< 1)	0
Missing data	2 (1)	1 (< 1)
mNIS+7 Score, mean (SD)	80.9 (41.5)	74.6 (37.0)
NIS Score, mean (range)*	60.5 (6.0-141.6)	57.0 (7.0-125.5)
Norfolk-QoL-DN Score, mean (SD)	59.6 (28.2)	55.5 (24.3)
FAP Stage, n (%)		
FAP Stage 1	67 (45%)	37 (48%)
FAP Stage 2	81 (55%)	39 (51%)
FAP Stage 3	0	1 (1%)
Cardiac Sub-Populations, n (%)	90 (61%)	36 (47%)
NYHA Class I	34 (38%)	16 (44%)
NYHA Class II	56 (62%)	20 (56%)
TTR Genotype, n (%)		
Val30Met	56 (38%)	40 (52%)
non-Val30Met	92 (62%)	37 (48%)
TTR Genotype Class, n (%)*		
early-onset Val30Met	13 (9%)	10 (13%)
all others (including late onset Val 30Met)	135 (91%)	67 (87%)
Previous Tetramer Stabilizer Use*	78 (53%)	41 (53%)

NR: not reported; SD: standard deviation; Matched placebo=identical treatment except study drug. *Stratification factor at randomization, NIS score stratified by 5-49 and 50 to 130

Importantly, we noted several differences between the patisiran and placebo groups at baseline which may affect the comparability of the two groups (Table 3.6). First, there was a statistically-significant difference in the proportion of patients with Val30Met (38% of patisiran vs. 52% of placebo) between the two groups ($p < 0.05$).[12] Second, the mean NIS score among patisiran patients was 3.5 points higher, indicating more severe impairment, compared to the placebo group. A difference of 2 points in the NIS score is considered clinically relevant. Patients were stratified at

randomization by NIS scores < 50 and ≥ 50, however, placebo and patisiran group NIS mean scores were not compared statistically.[12] Third, there was a 14% absolute difference in the proportion of patients with cardiac involvement between the patisiran (61%) and placebo (47%) groups; this difference was not assessed for statistical significance.[12] These factors suggest the potential for imbalances in baseline disease severity and natural history between the two groups. Statistical analysis using a mixed-effects model for repeated measures of the primary, secondary, and exploratory endpoints adjusted for treatment group, baseline values, visit (month nine vs. 18), treatment by visit interaction, age at symptom onset as well as for stratification factors (early onset Val30Met vs. others and previous TTR stabilizer use) and geographic region (North America, Western Europe, and rest of the world).[12]

We also noted a difference in the proportion of patisiran and placebo patients who completed the study, with 7% of patisiran and 29% of placebo patients discontinuing the study through 18 months of respective treatment (Table 3.6). Notable differences in reasons for discontinuation included AEs (9% of placebo vs. 2% of patisiran patients) and disease progression (5% of placebo vs. < 1% of patisiran patients), defined as a ≥ 24-point increase in the mNIS+7 from baseline and FAP stage progression relative to baseline at nine months.

Mortality

As with the NEURO-TTR trial of inotersen, mortality was assessed as a safety endpoint only. However, a post-hoc analysis of mortality and hospitalization data was recently presented (and additional data provided in confidence) for the cardiac subpopulation. There was an approximate 50% reduction in the composite rate of all-cause hospitalization and mortality (patisiran: 34.7 [95% CI: 27.5 to 43.1], placebo: 71.8 [95% CI: 56.1 to 90.1], HR: 0.48, 95% CI 0.30 to 0.79) observed for patisiran relative to placebo.[14] There was also a trend reported for the composite of cardiovascular hospitalization and all-cause mortality, although findings were not statistically significant. However, we identified no analysis of all-cause mortality alone, nor did we find any description of whether or how baseline differences were controlled for in this analysis. Furthermore, the trial population had few cardiomyopathy-dominant patients, which may inadequately represent cardiac outcomes in such patients. Finally, while none of the deaths in APOLLO were considered attributable to study drug, we note that all deaths in the patisiran arm were attributed to cardiovascular causes, while causes of death in the placebo arm varied. The significance of this finding is uncertain; [12] no further explication of the cardiovascular deaths was available in the trial publication or other materials.

Disease Progression

We also reviewed data on changes in disease stage defined by a patient's ability to walk (Table 3.7). We noted differential missing ambulation data for placebo and patisiran patients (22 [29%] and 10 [7%], respectively); for the former, missing data was due primarily to death or early study discontinuation.[20] We looked at two disease stage measures – polyneuropathy disability (PND)

score and familial amyloid polyneuropathy (FAP) stage – where disease progression is marked by increasing score or stage (see Section 1.3 for details). Both measures showed similar results, though neither outcome was analyzed for statistical significance between the patisiran and placebo groups. FAP stage remained stable in nearly three-quarters (76%) of patisiran patients, and five patients (3%) reported improved FAP stage (Table 3.7). No placebo patients reported improved FAP stage. As assessed by PND score, ambulation improved in 12 (8%) patisiran patients (Table 3.7).[20] Ten of the 12 patients (83%) improved from requiring one or two crutches while walking (PND IIIa/b) to walking unimpaired (PND I). No placebo patients reported improved ambulation. Of those whose ambulation worsened, five times as many placebo patients progressed by two PND stages compared to patisiran patients (50% vs. 10%, respectively).

Table 3.7 APOLLO Disease Progression by FAP Stage and PND Score[12,20]

	Placebo	Patisiran
No. Randomized	77	148
No. Completed (%)*	55 (71)	138 (93)
FAP Stage		
Improved, n (%)	0	5 (3)
No Change, n (%)	34 (44)	112 (76)
Worsened, n (%)	21 (27)	21 (14)
Missing*, n (%)	22 (29)	10 (7)
PND Score		
Improved, n (%)	0	12 (8)
No Change, n (%)	23 (30)	96 (65)
Worsened, n (%)	32 (42)	30 (20)
Missing†, n (%)	22 (29)	10 (7)

* Number of participants who completed the trial. †Missing includes all deaths before 18-month assessments.

Neurologic Impairment and Quality of Life

After 18 months of treatment in the APOLLO trial, patisiran demonstrated a least-squares (LS) mean improvement of 34.0 points (95% CI −39.9 to −28.1) in the mNIS+7 compared to placebo (Table 3.8).[12] During this time, patisiran patients improved by a mean of −6.0 points, while placebo patients worsened by 28.0 points (Table 3.8).[12] Binary analysis (improvement vs. no improvement) of mNIS+7 score shows 56% of patisiran patients experienced neurological improvement, defined as decrease in mNIS+7 score, versus 4% of placebo patients (odds ratio: 39.9, 95% CI 11.0 to 144.4; $p < 0.0001$)(Table 3.8).[12] Statistically-significant improvements in mNIS+7 component favoring patisiran were seen in all five sub-scores covering muscle weakness, sensory function, reflexes, nerve conduction, and postural blood pressure compared to placebo.[12] The treatment effects of patisiran appear to increase over time; improvement during months 10 to 18 was double that of the first nine months (4 vs. 2 points).[12]

Table 3.8. APOLLO Neurologic Impairment and Quality of Life Outcomes

	Phase II OLE[25]	APOLLO[12]		
	Patisiran n = 27	Patisiran n = 148	Placebo n = 77	Treatment difference
Mean Change From Baseline				
mNIS+7 (SEM or 95% CI)	−7.0 (2.0)	−6.0 (1.7)	28.0 (2.6)	−34.0 (−39.9 to −28.1)*
Norfolk-QOL-DN (SEM)	NR	−6.7 (1.8)	14.4 (2.7)	−21.1 (−27.2 to −15.0)*
Percent Reporting Improvement (95% CI)				
mNIS+7	70.4%†	56 (48 to 64)	4 (0 to 8)	OR: 39.9 (11.0 to 144.4)*
Norfolk-QOL-DN	NR	51.4 (43 to 59)	10.4 (4 to 17)	OR: 10.0 (4.4 to 22.5)*

NR: not reported; OR: odds ratio; SEM: standard error of the mean *p < 0.001 Improvement defined as a change < 0 points. †Calculated from available data.

As a whole, the patisiran group showed improvement in hATTR polyneuropathy compared to baseline, as demonstrated by reductions from baseline in the mNIS+7 score. It is difficult to be certain, however, what magnitude of mNIS+7 change is clinically relevant because no previous trial has used this composite measure, and a minimum clinically important difference has yet to be defined. Due to the magnitude of neurological impairment progression among placebo patients, and evidence of mean *improvement* among patisiran patients, we anticipate these findings are clinically relevant.

Preliminary 52-week data from the global OLE show continued delay of neuropathy progression for patients rolling over from Phase II extension or APOLLO patisiran groups (additional 21 and 11 months of post-trial treatment, respectively). Twenty-five patients who completed 36 months of patisiran treatment experienced a 4.1-point mean improvement compared to baseline mNIS+7.[26] Patients initiating patisiran after receiving placebo during APOLLO showed small improvements in mNIS+7 after 52 weeks of treatment, similar to results seen in APOLLO.[26]

Neuropathy-related QOL measured by the Norfolk-QOL-DN questionnaire in APOLLO also significantly improved after 18 months of patisiran treatment compared to placebo (−6.7 vs. +14.4 points, p < 0.001; decrease reflects improvement, Table 3.8).[12] Individual Norfolk-QOL-DN domains show patisiran patients reported modest improvements in three neuropathy domains after 18 months of treatment: physical function/large fiber neuropathy, symptoms, and autonomic, though statistical analysis was not available.[15] Placebo patients reported worsening Norfolk-QOL-DN scores in all five domains; this worsening was the main driver of the differences seen between the patisiran and placebo groups.[15]

Phase II OLE data showed patients were similarly diverse in age (mean age 61.3) in comparison to APOLLO patients but had less severe disease (mean mNIS+7 score of 77 [range 3-199]).[26] About half of patients (46.4%) had the Val30Met mutation. Available data showed a mean improvement of 7.0 points in mNIS+7 (standard error of the mean (SEM): 2.0) among the 26 participants with data at 24

months (Table 3.8).[25] Tafamidis and diflunisal use were permitted during the study, and 13 (50%) and 7 (26.9%) patients, respectively, were treated with these stabilizers in combination with patisiran.[25]

Subgroup Analysis

Pre-specified subgroup analyses, including groups defined by baseline age (≥ 65 vs. < 65 years), sex, race (white vs. non-white), region, NIS score, genotype, previous TTR stabilizer use, and FAP stage showed consistent clinical benefits on the mNIS+7 and Norfolk-QOL-DN favoring patisiran over placebo ($p < 0.05$), though the subgroup analysis for early onset Val30Met versus all other mutations did not favor patisiran, as the confidence interval crossed zero.[12]

Cardiac Outcomes

Cardiac outcomes in the APOLLO trial were evaluated as exploratory endpoints among a subgroup of patients with a left ventricle wall thickness of ≥ 13 mm at baseline and without a medical history of aortic valve disease or hypertension. Disproportionately more patisiran patients met these criteria compared to placebo patients (90 [61%] vs. 36 [47%], respectively). Baseline characteristics of patients included in the cardiac subgroup are shown in Table 3.9. We also noted potential imbalances between the patisiran and placebo patients in the subset with cardiac involvement, including more severe polyneuropathy (NIS score) and FAP stage 2 patients in the placebo group, and more patients with NYHA class II heart failure in the patisiran group (Table 3.9). Patisiran patients with cardiac involvement were similar to all patients in the trial in baseline polyneuropathy and disease stage but showed more severe heart failure. Placebo patients had considerably worse polyneuropathy and disease stage compared to all trial patients.

Table 3.9 APOLLO Cardiac Subgroup Baseline Characteristics [18,20]

	Patisiran n = 90	Placebo n = 36	All Patients
Baseline			
Median Age (range), years	60 (24-79)	62 (43-80)	62 (24-83)
Val30Met Genotype, n (%)	22 (24.4)	12 (33.3)	96 (42.7)
Mean NIS Score	60.9	68.7	59.3
FAP Stage, n (%)	**Stage 1:** 42 (46.7) **Stage 2**: 48 (53.3)	**Stage 1**: 13 (36.1) **Stage 2**: 23 (63.9)	**Stage 1**: 104 (46.2) **Stage 2**: 120 (53.3)
NYHA Class, n (%)	**Class I**: 34 (37.8) **Class II**: 56 (62.2)	**Class I**: 16 (44.4) **Class II**: 20 (55.6)	**Class I**: 110 (48.9) **Class II**: 113 (50.2)
Median NT-proBNP (SD), ng/L	756.4 (NR)	845.7 (NR)	NR

NR: not reported, NT-proBNP: N-terminal pro-B-type brain natriuretic peptide, SD: standard deviation. *Least squares mean change from baseline through 18 months.

We reviewed APOLLO NT-pro-BNP data, an exploratory endpoint, as this biomarker has been shown to predict mortality in hATTR patients with cardiac involvement.[28] Increased risk of death with NT-proBNP levels above 3,000 ng/L at baseline was also demonstrated in APOLLO cardiac patients, where patients with an NT-proBNP level > 3,000 ng/L (n = 29, 12.9%) had a statistically significant 19.3-fold (95% CI: 5.9 to 62.8) increased risk of death compared to patients with baseline levels ≤ 3,000 ng/L (n = 196, 87.1%).[18]

NT-proBNP modestly decreased by a median of 49.9 ng/L with patisiran treatment compared to increases in blood concentrations (median 320.4 ng/L) in the placebo group. This treatment difference was statistically significant (difference: 370.2, $p < 0.0001$);[16] however, the median NT-proBNP concentration in both groups prior to treatment initiation as well as after 18 months of treatment was below the 3,000 ng/L cut-off associated with increased risk of death (Table 3.9).[15,27] Nearly one-third (31.6%) of patisiran patients showed improved NT-proBNP levels (defined as ≥ 30% and ≥ 300 mg/L decrease at 18 months), nearly half (47.3%) remained stable, and the remaining patients (21.1%) had higher concentrations of NT-proBNP after 18 months of treatment (Table 3.10).[19] However, data on the proportion of placebo and patisiran patients with clinically relevant NT-proBNP levels (i.e., > 3,000 ng/L vs. ≤ 3,000 ng/L) through 18 months of treatment were unavailable. Further, data were not available on use of diuretics, which could also lower NT-proBNP levels.

Cardiac outcome data from APOLLO showed statistically significant improvements (LSM difference vs. placebo [SEM]) favoring patisiran for mean left ventricle (LV) wall thickness (-0.9 [0.4], $p = 0.02$) and left ventricular longitudinal strain (-1.37 [0.56], $p = 0.015$).[12] Data for 10-minute walk test gait speed showed improvement with patisiran (0.31 [0.04], $p < 0.001$).[12] The proportions of patients meeting thresholds of improvement and worsened heart structure and function are shown in Table 3.10. The clinical significance of the observed changes and thresholds of improvement is unclear.

Patisiran and placebo patients had similar left ventricle mass and ejection fraction at baseline, and no statistically significant differences were seen with patisiran treatment compared to placebo.[16]

Table 3.10 APOLLO Cardiac Outcomes [19]

		Patisiran	Placebo
Mean LV Wall Thickness*	Improved, %	29.1	4.0
	Stable, %	64.6	88.0
	Worsened, %	6.3	6.3
Mean Global Longitudinal Strain†	Improved, %	21.3	8.0
	Stable, %	53.4	48.0
	Worsened, %	25.3	44.0
NT-proBNP‡	Improved, %	31.6	0
	Stable, %	47.3	41.7
	Worsened, %	21.1	58.3

*Improved defined as > 2 mm decrease and worsened defined as > 2 mm increase from baseline thickness.
†Improvement defined as > 2% decrease and worsened defined as > 2% increase from baseline strain.
‡Improved defined as ≥ 30% + 300 ng/L decrease and worsened defined as ≥ 30% + 300 ng/L increase from baseline NT-proBNP.

Finally, as described earlier, we found post-hoc evidence of a trend towards reduction in cardiac hospitalizations (patisiran: 8.2 [95% CI: 5.0 to 12.6], placebo: 15.6 [95% CI: 9.0 to 24.9]), the composite rate of cardiac hospitalization and all-cause mortality compared (patisiran: 10.1 [95% CI: 6.4 to 14.9], placebo: 18.7 [95% CI: 11.4 to 28.8]) to best supportive care (p = NS), and an approximate 50% reduction in the composite rate of all-cause hospitalization and mortality (patisiran: 34.7 [95% CI: 27.5 to 43.1], placebo: 71.8 [95% CI: 56.1 to 90.1], HR: 0.48 [95% CI 0.30 to 0.79]).[13,14]

Additional Outcomes

Modified BMI data showed patisiran patients experienced statistically significant stabilization of nutritional status compared to placebo (LSM treatment difference: 115.7 kg/m^2 x g/L, $p < 0.0001$).[12] Considerably more patisiran patients showed improved mBMI, defined as > 0 kg/m^2 x g/L, compared to placebo (41% vs. 7%, respectively), though results of statistical testing were not reported.[17] There is no definition of the minimal change in mBMI that is clinically important. Patisiran's label also notes 7 of 194 (3.6%) patients treated with patisiran during placebo-controlled and open-label trials tested positive for anti-drug antibodies. Available evidence shows these antibodies do not affect patisiran's efficacy or safety; however, additional data to establish longer-term efficacy and safety are needed.[87]

Harms

Data from APOLLO indicate treatment discontinuations due to AEs were more common among placebo than patisiran patients through 18 months of treatment. Most AEs were mild or moderate, with the exception of four serious adverse reactions of atrioventricular (AV) heart block which occurred in patients who received patisiran. The most common AEs reported in APOLLO were peripheral edema and infusion-related reactions; the latter led to treatment discontinuation in one patient.

No treatment-related deaths were reported during any of the patisiran trials. A total of 13 deaths were reported during the APOLLO trial. All deaths in the patisiran group were due to cardiovascular causes (possibly heart-failure related), while reasons for death in the placebo arm varied. This significance of this observation is unclear; however, all deaths in both groups were considered consistent with the natural history of the disease.[12] Among patients with cardiac hATTR involvement, the rates of cardiac AEs (28% vs. 36%) and cardiac SAEs (14% vs. 13%) were similar between the patisiran and placebo groups, while cardiac arrythmias were less common among patisiran patients (19% vs. 29%).

AEs reported more frequently by patisiran than placebo patients included infusion reactions and peripheral edema (Table 3.11); all of these AEs were deemed mild to moderate. The rate of infusion-related reactions decreased over time.[12] Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in patients treated with patisiran, including 3 cases of complete AV block. No serious occurrences of AV block were reported in placebo patients.[87]

Table 3.11 Patisiran Harms

	Phase II OLE[22,25]	APOLLO[12]		Global OLE[26]
Treatment Group	**Patisiran** n = 25	**Placebo** n = 77	**Patisiran** n = 148	**Patisiran** n = 211
Treatment Duration	Up to 48 months	18 months		Up to 48 months
Any Adverse Event	25 (100)	75 (97)	143 (97)	189 (90)
Serious Adverse Event	6 (24)	31 (40)	54 (36)	55 (26)
Atrioventricular (AV) Block	NR	0	4 (2.7)	NR
Severe Adverse Event	3 (12)	28 (36)	42 (28)	38 (18)
Discontinuations Due to Adverse Event	0	11 (14)	7 (5)	16 (8)
Deaths	0	6 (8)	7 (5)	11 (5)
Common Adverse Events				
Peripheral Edema	3 (11)	17 (22)	44 (30)	NR
Infusion-Related Reactions	6 (22)	7 (9)	28 (19)	NR (10)
Flushing	7 (25)	NR	NR	NR

NR: not reported. All data reported are n (%).

Global OLE data show a similar rate of AEs leading to study withdrawal among patients on patisiran in the OLE study compared to patients treated with patisiran during the APOLLO study (8% vs. 5%), and a much lower rate of discontinuation compared to placebo treatment during APOLLO (Table 3.11).[26] Infusion-related reactions were less common in the Phase II dose-ranging study and global OLE study compared to the APOLLO trial (10% vs. 19%) (Table 3.11).[21,25] Limited Phase II OLE data suggest the frequency of flushing (7/20, 35%) and infusion-related reactions (5/20, 25%) is higher in patients taking patisiran plus a TTR stabilizer compared to patisiran alone (0/5 for both harms).[24]

Finally, 7 of 194 (3.6%) patients developed anti-drug antibodies during treatment with patisiran (APOLLO and OLE studies).

Diflunisal

Diflunisal, a TTR stabilizer, is frequently used on an off-label basis for hATTR in the US. We found one randomized, double-blind, placebo-controlled trial evaluating the efficacy of diflunisal in treating hATTR polyneuropathy.[30] Inclusion and exclusion criteria were similar to NEURO-TTR and APOLLO. Eligible patients were randomized 1:1 and stratified by Val30Met versus non-Val30Met mutation to receive either 250 mg of diflunisal or placebo twice daily for 24 months.

At baseline, the diflunisal and placebo groups were balanced on age, sex, race, TTR genotype (Val30Met vs. non-Val30Met), mBMI, and quality of life assessed by the Short-Form 36 (SF-36) questionnaire.[30] The placebo group (n = 66) had slightly more severe polyneuropathy, as assessed by PND score, NIS+7 score, and NIS score compared to the diflunisal group (n = 64). There were no statistically-significant differences between the groups in any of the neuropathy measures. However, we consider this study to be of fair quality due to a high rate of study discontinuation that was differential between study arms.

Approximately half of the study population discontinued treatment prior to the study conclusion at 24 months, and more placebo patients discontinued treatment compared to diflunisal patients (61% vs. 42%).[30] Study discontinuation was associated with increased disease severity and worsened QOL measured by the SF-36 questionnaire at 12 months compared to those continuing study treatment (p = 0.023 and 0.002, respectively). The most common reasons for study discontinuation were disease progression and receipt of liver transplant.

Although both groups experienced progression of polyneuropathy, additional longitudinal analysis of the intention-to-treat (ITT) (n = 130) population showed diflunisal patients experienced significantly less neuropathy progression as assessed by the NIS+7 score compared to placebo patients at both 12 months (treatment difference: 6.4 points, 95% CI: 1.2 to 11.6) and 24 months (Table 3.12). Likewise, QOL measured by the SF-36 showed modest but statistically significant improvement in QOL related to physical symptoms for diflunisal patients compared to placebo after 24 months of treatment.

Table 3.12 Diflunisal Efficacy

	Diflunisal n = 64	Placebo n = 66	Treatment Difference
Longitudinal Analysis (ITT)			
NIS+7 (95% CI)	8.2 (2.9 to 13.6)	26.3 (20.2 to 32.4)	-18.0 (9.9 to 26.2)*
SF-36 Physical (95% CI)	1.2 (−1.2 to 3.7)	−4.9 (−7.6 to −2.1)	−6.1 (−9.8 to −2.5)*
SF-36 Mental (95%)	3.5 (0.4 to 6.7)	−0.9 (−4.4 to 2.5)	−4.5 (−9.2 to 0.2)

All data reported are mean change from baseline through 24 months. *p ≤ 0.001

Sensitivity analyses (e.g., multiple imputations, last observation carried forward, and "worst case scenario imputation") demonstrated similar findings to the longitudinal analysis. Two-year responder analysis, which compared treatment response (< 2-point increase in the NIS+7) to treatment failure (increase of ≥ 2 points), showed diflunisal patients experienced significantly less disease progression compared to placebo (p =0.007). Finally, analysis of patients completing study treatment also showed statistically and clinically significant benefits for NIS+7 scores, with a magnitude of treatment difference similar to that found in the longitudinal analysis (7.1 points, 95% CI 3.2 to 11.1, p < 0.001). The drug effect was evident across mutation, sex, study sites, and severity of neurologic disease at enrollment.

Three additional single-arm, open-label studies were included per our PICOTS criteria. Two additional references reported outcomes for primarily late-onset Val30Met Japanese patients and showed findings similar to the trial described above. In addition, a single-arm, open-label study of late-onset hATTR patients with moderate to severe polyneuropathy with cardiac involvement showed PND score worsened by one stage in 8 of 18 patients (44%) through 24 months of diflunisal treatment.[88] Cardiac progression was reported to occur in 2 of 21 patients; however, the conference abstract did not define "progression" or provide details on the differing number of participants in each group.[88]

Harms

Randomized controlled trial data showed no differences in treatment-related AEs or SAEs.[30] Four (6%) diflunisal and two (3%) placebo patients discontinued treatment due to treatment-related AEs.[30] Four (6%) diflunisal and nine (14%) placebo patients died during the 24-month follow-up period, with 12 of 13 deaths occurring off study drug.[30] Cardiac outcomes data for the diflunisal study have not been reported. In general, long-term use of diflunisal is often limited by risks common to all NSAIDs, such as gastrointestinal bleeding, worsening of renal insufficiency, and cardiovascular events (e.g., MI, stroke).

Controversies and Uncertainties

Historically, hATTR has been diagnosed as two separate conditions affecting two separate organ systems. As a result, most literature details the two predominant manifestations – polyneuropathy

and cardiomyopathy–in isolation, and there is little, if any, literature regarding how these two pathologies of a multi-system disease interact. For example, cardiac-related QOL in hATTR patient populations is largely under-researched, while polyneuropathy-related QOL was collected by nearly all the studies included in our search. Additionally, many of the studies we identified through our search evaluated primary outcomes related to polyneuropathy rather than cardiac involvement, which provides limited statistical power to identify treatment differences in cardiac outcomes in clinical trials.

We identified uncertainties pertaining to clinical data for patisiran and inotersen. Due to the lack of validated thresholds for the mNIS+7 assessment and neuropathy-related QOL, data from the NEURO-TTR and APOLLO trials must be interpreted without a context of what constitutes a clinically relevant improvement. Older neuropathy impairment assessments (e.g., NIS and NIS+7) do have established minimal clinically important differences defined; however, these assessments were judged to be unable to adequately reflect polyneuropathy symptoms resulting from hATTR.[31] Furthermore, because the mNIS+7 is a composite measure of motor, autonomic, and sensory function, total score changes provide a coarse measurement of total neuropathy rather than specific sensory, autonomic, and motor nerve function. As a result, it is difficult to extrapolate mNIS+7 score changes into clinical changes, particularly for a patient population with a diverse spectrum of polyneuropathic symptoms.

Generalizability of APOLLO and NEURO-TTR study findings is potentially limited based on trial design and populations. First, only 20% of APOLLO and 48% of NEURO-TTR participants were from the US, which has a different genotype mix than other regions; therefore, findings of these trials may not be generalizable to the US population. Both trials included very few patients with the most common mutation in the US, Val122Ile. The NEURO-TTR and APOLLO studies included a respective three (1.7%) and two (0.9%) Val122Ile patients.[8,12] Inclusion of very few patients with the Val122Ile mutation may be due in part to both trials' inclusion criterion of polyneuropathy-predominant hATTR. Thus, neither trial is representative of the US hATTR and cardiomyopathy-predominant hATTR populations. Second, liver transplant recipients and individuals who were currently receiving treatment with TTR stabilizers (and did not wish to stop such treatment) were excluded from both trials. Thus, findings may not be generalizable to such patients, and the safety and efficacy of treatment in these patient populations is unknown. While limited Phase II data suggest combination treatment with patisiran and tafamidis and/or diflunisal does not reduce patisiran's pharmacological activity in reducing serum TTR, further study is required.[22]

We also noted differential discontinuations in the APOLLO trial: 29% of placebo patients discontinued compared to 7% of patisiran patients. Most of the placebo patients discontinued prior to the 18-month assessments, and a higher proportion of placebo patients discontinued due to AEs and disease progression compared to patisiran patients. However, nearly half of all discontinuations were otherwise unexplained patient withdrawals, which limits our understanding of why placebo patients discontinued study treatment. Differential study discontinuations may

have under- or over-estimated the treatment difference between patisiran and placebo in key outcomes and may not reflect true treatment benefits in hATTR patients; the interaction of these effects and the treatment group imbalances noted above are also unclear.

Due to the chronic and progressive nature of hATTR, long-term use of patisiran and inotersen is expected. Both inotersen and patisiran trials were of relatively short duration, however, which provides limited information on the safety of long-term use of these new drugs. Patisiran trials, for instance, included premedication with steroids and anti-histamine drugs. The dose of dexamethasone used with patisiran is equivalent to approximately 6.3 mg/day of prednisone, which is a low-to-moderate-dose (≤ 5mg/day is considered low-dose). Patients on this dose for years are at increased risk for infection, osteoporosis, early cataracts, weight gain, diabetes, hypertension, skin fragility, and avascular necrosis of the hip. However, the overall risk would not be considered high given the dose.[89] Certain patients, such as those with diabetes, may be at higher risk. However, this remains an uncertainty as such patients were excluded from the patisiran trials. While the rate of death did not differ between the treated and placebo groups, the finding that all deaths in the patisiran group were cardiovascular-related is an additional uncertainty related to use of patisiran. Finally, both inotersen and patisiran reduce transthyretin protein levels by 80-90%.[5,44] Transthyretin functions as an indirect vitamin A (via retinol binding protein) transport protein. Patients who took patisiran in the Phase I trial experienced decreased vitamin A levels.[90] Both the NEURO-TTR and APOLLO trials required patients to take daily vitamin A supplements.

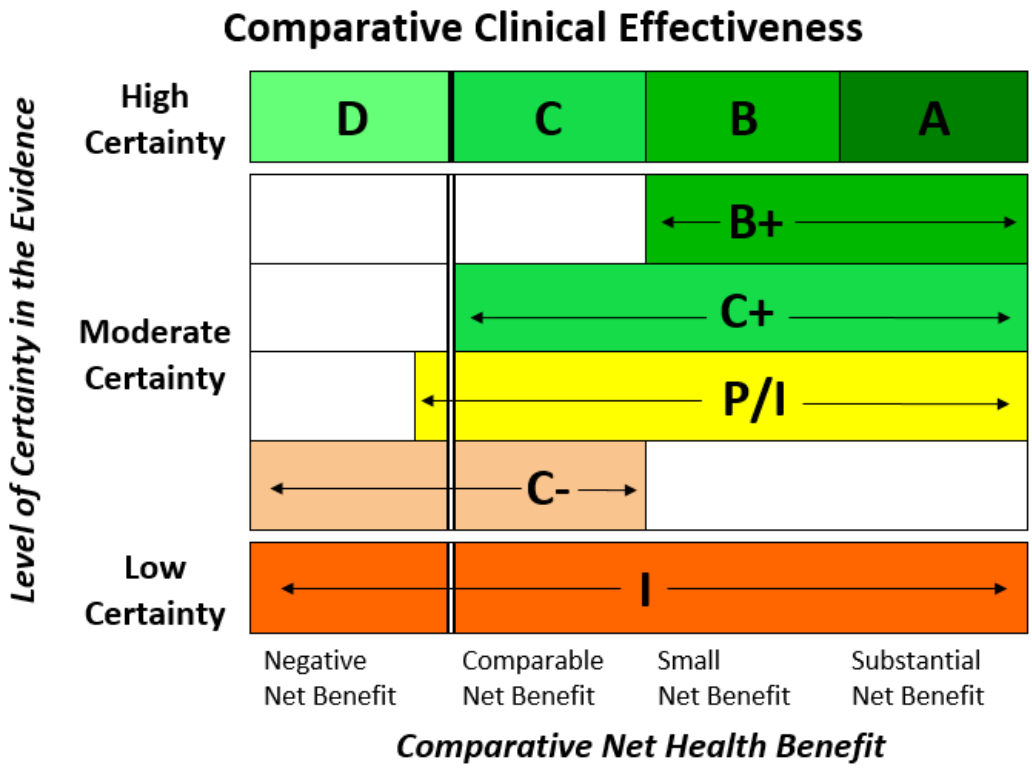
Long-term safety is also a key uncertainty. As novel therapies for an ultra-rare disorder, it is not surprising that we lack such evidence for inotersen and patisiran. Patisiran is the first RNAi therapeutic approved by the US FDA, and the long-term effects of RNA interference are unknown. Inotersen would join three other approved antisense oligonucleotide drugs. Additional investigational antisense oligonucleotides (e.g., volanesorsen) have also been shown to induce thrombocytopenia, similar to inotersen.[48,84] The mechanism of ASO-induced thrombocytopenia has not been identified, though some suggest platelet activation, anti-platelet immunogenicity, and dose-dependent effects not seen with more commonly used lower doses may explain this adverse effect.[50]

Finally, input from patients included concerns about affordability and access to these new therapies. Many patients recognized the high cost of developing inotersen and patisiran and their perceived clinical benefit but felt these treatments should be priced in alignment with what patients can afford. Patients voiced additional uncertainties about potential decisions to end treatment due to cost despite improved disease symptoms and quality of life.

3.4 Summary and Comment

Considering that hATTR is a rare disease, we acknowledge the common limitations of rare disease evidence associated with a small patient population, limited disease-specific clinical measures, clinical trial design challenges, and the lack of long-term safety and efficacy data. In considering the current evidence for inotersen and patisiran, the limitations of inotersen and patisiran clinical evidence include study populations that limit the generalizability of clinical outcomes to all hATTR patients, clinical outcome measures (mNIS+7 and Norfolk-QOL-DN) without defined thresholds for clinical significance, limited functional outcomes such as disease stage progression, and limited data on patients with cardiac involvement, especially among cardiac-dominant patients who are at a higher risk for mortality than patients with neuropathy-predominant hATTR. For both medications, we were limited in interpreting the clinical relevance of changes in polyneuropathy measured by the mNIS+7 and neuropathy-related quality of life (Norfolk-QOL-DN) without established thresholds for meaningful clinical change. Should additional data regarding drug safety and efficacy, or validation studies showing clinically meaningful thresholds, become available, the conclusions of this report may require updating.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Despite these limitations, we found the following in our review of the clinical evidence:

Inotersen

- Both primary efficacy assessments (polyneuropathy [mNIS+7 $_{Ionis}$], and neuropathy-related quality of life [Norfolk-QOL-DN] favored inotersen; on average, inotersen patients' neuropathy remained stable while placebo patients' neuropathy worsened
- 36% of the patients in the inotersen group had an improvement (no increase from baseline) in the mNIS+7 $_{Ionis}$ and 50% had an improvement in the Norfolk QOL-DN score
- Relative to best supportive care, no evidence of improved stabilization of disease progression, as measured by PND score.

- Potential for continued delayed progression of polyneuropathy and declines in neuropathy-related quality of life through nearly two years of inotersen treatment.
- Potential safety signals including thrombocytopenia and glomerulonephritis. One of five deaths among inotersen patients in NEURO-TTR is considered possibly drug-related.

Relative to placebo patients, inotersen patients had more favorable outcomes on the mNIS+7 and Norfolk QOL-DN measures. However, on average, inotersen patients did not experience improvement from baseline in neuropathy symptoms, as measured by the mNIS+7, but rather a slowing in worsening of neuropathy relative to placebo. Regarding safety, there remains some uncertainty given that:

1. All deaths in the Phase III trial occurred in the inotersen arm, one of which was considered possibly-drug related;
2. Other antisense oligonucleotides (nusinersen, volanesorsen) have demonstrated similar risks of thrombocytopenia; and
3. Anti-inotersen antibodies were reported in 30.4% of NEURO-TTR patients, the long-term significance of which is unknown at this point.

The enhanced monitoring protocol added to the trial provides some reassurance that thrombocytopenia risks can be managed. However, the long-term implications of the other safety and antibody concerns are currently unknown. In summary, we have moderate certainty of a comparable, small, or substantial net health benefit relative to best supportive care, with high certainty of at least a comparable net health benefit, and therefore rate the clinical evidence for inotersen to be comparable or better (C+) (Figure 3.1; note that ICER does not change its approach to rating evidence for ultra-rare conditions).

Patisiran

- Mean improvement in polyneuropathy (mNIS+7), and neuropathy-related quality of life (Norfolk-QOL-DN), with statistically significant differences compared to best supportive care (placebo).
- Baseline imbalances in TTR genotype and clinically relevant differences in disease severity (based on NIS) between patisiran and placebo groups, which may impact study validity and generalizability.
- Exploratory endpoint of neuropathy stage stable or improved compared to best supportive care (placebo).
- Statistically significant evidence of lowered cardiac biomarker (NT-proBNP) with unclear clinical relevance.

- Post-hoc evidence of a statistically significant reduction in the composite rate of all-cause hospitalization and mortality compared to best supportive care among patients with cardiac involvement.
- In general, a decreased frequency of AEs compared to best supportive care; no differences in mortality between treatment arms, but all deaths in the patisiran arm were cardiovascular in nature, a phenomenon that has not been otherwise explained. Potential safety signal of complete heart block, though heart block can be observed with cardiac involvement in hATTR.

On average, patients on patisiran demonstrated improvement in neuropathy symptoms, as measured by the mNIS+7. Regarding safety, we deemed the risk of concomitant steroid administration to be low-moderate risk, depending on patient characteristics, based on analogous steroid use in other therapeutic areas. While the rate of death did not differ between the treated and placebo groups, the finding that all deaths in the patisiran group were cardiovascular-related is an additional uncertainty related to use of patisiran, and there has been little explication of this phenomenon in the trial publication or other materials. Four cases of heart block were observed among patisiran patients, and while this finding represents a potential safety signal, it could also represent disease progression. However, no cases of heart block were observed among placebo patients. In summary, we have moderate certainty of a substantial net health benefit with high certainty of at least a small net health benefit compared to best supportive care, and therefore rate the clinical evidence for patisiran to be incremental or better ("B+").

4. Long-Term Cost Effectiveness

4.1 Overview

The objective of the model for inotersen and the model for patisiran is to estimate the cost-effectiveness of each new treatment versus best supportive care (BSC). The trial for inotersen versus placebo (NEURO-TTR) featured a different group of patients compared to the trial for patisiran versus placebo (APOLLO). Differences in the primary outcome measures (i.e., different modifications of mNIS+7) and trial population (e.g., race, geographic region, disease severity) precluded direct comparison using the trial data. As a result, we developed separate Markov models for each treatment compared to BSC. Both models use life-years (LYs) and quality-adjusted life years (QALYs) as the outcomes of interest. In keeping with ICER's value framework for ultra-rare conditions, two separate base cases were conducted. The first base case analysis takes a health care sector perspective (i.e., focusing on direct medical care costs only), and a lifetime horizon using a 3% discount rate for both costs and outcomes. Productivity losses are included in a modified societal perspective analysis for a separate base case. Results are reported for inotersen versus BSC, followed by results for patisiran versus BSC.

For ultra-rare diseases, it should be noted that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations. However, this section focuses only on the cost-effectiveness of the new treatments. This provides only one element to be added to a richer discussion of value.

4.2 Long-Term Cost Effectiveness of Inotersen

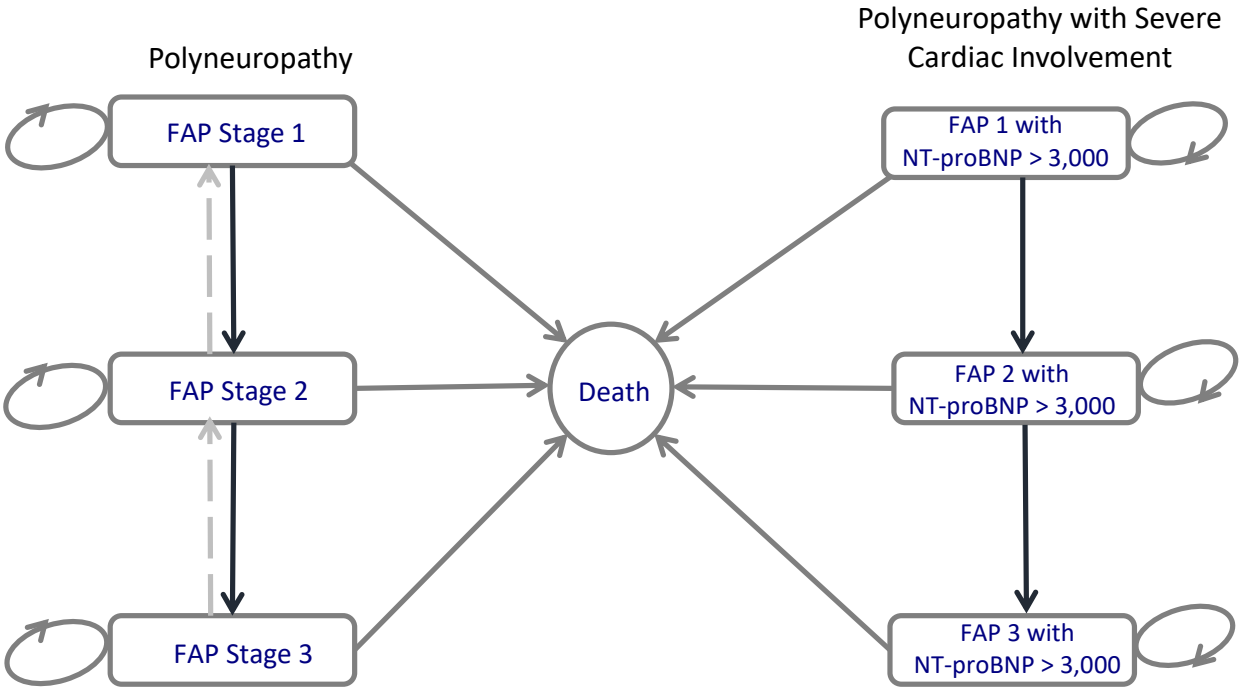
Methods

Figure 4.1 depicts the analytic framework for the economic evaluation of inotersen developed in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA).

Model Structure

The model uses one-month cycle lengths over a lifetime horizon.

Figure 4.1. Model Framework for Inotersen



Severe cardiac involvement (NT-proBNP > 3,000) is estimated based on its prevalence as a baseline characteristic in the available clinical evidence; therefore, patients are assumed to have such involvement at the start of the analysis, and it is not developed or resolved through the course of the disease. This is depicted in the Model Framework figure by the absence of any arrows directly connecting the "Polyneuropathy" states (on the left) with the "Severe Cardiac Involvement" states (on the right). The dashed lines pointing upward illustrate that inotersen has the potential for FAP Stage regression (i.e., improving functioning as indicated by transitioning from a higher FAP Stage to a lower FAP Stage). Previous economic evaluations of treatments for hATTR have used models featuring FAP disease stages[34]. Research reporting a high mortality hazard ratio for patients with NT-proBNP > 3,000 motivated introducing a separate set of disease states to keep track of the increased cost, decreased quality of life and elevated mortality associated with elevated levels of this biomarker. We explored the impact of potential treatment-induced reductions in the number of individuals with severe cardiac involvement in both sensitivity and scenario analyses.

Target Population

Since differences in the primary outcome measures and trial populations (e.g., disease severity) precluded direct comparison of the NEURO-TTR and APOLLO trials, there are two separate cohorts for the base case models—one for each drug, with characteristics based on each trial's baseline population.

The target population for the first economic evaluation was adults with hATTR with an indication for treatment with inotersen. Table 4.1 reports base case population characteristics for the inotersen model. Note that the proportion with severe cardiac involvement was available in APOLLO but not in NEURO-TTR, so an estimate was calculated based on the ratio of prevalence of any cardiac involvement in both trials (see detailed calculation below).

Table 4.1. Base Case Model Cohort Characteristics for Inotersen

For the Inotersen Model:		
	Value	Primary Source
Mean Age	59	Benson et al.[8]
Female	31%	Benson et al.[8]
FAP Stage 1	67%	Benson et al.[8]
FAP Stage 2	33%	Benson et al.[8]
Severe Cardiac Involvement (NT-proBNP > 3,000)	14.2%	Proportional assumption based on relative frequency of general cardiac sub-populations in main trials for inotersen (75/112 or 67.0%) and patisiran (90/148 or 60.8%), yielding 12.9% x 1.1 = 14.2%

Treatment Strategies

The treatment strategies evaluated included:

- Inotersen (once-weekly 300 mg subcutaneous injections)

Comparators

The comparator in the NEURO-TTR clinical trial was placebo, which we use to reflect best supportive care (BSC). Both diflunisal and tafamidis were excluded from consideration, as neither has received FDA approval for the treatment of hATTR amyloidosis, and indirect comparisons with diflunisal were infeasible due to differences in trial design, outcome measure, and study populations.

Key Model Characteristics and Assumptions

Key assumptions made for the economic model of inotersen are listed in Table 4.2.

Table 4.2. Key Model Assumptions for the Inotersen Model

Assumption	Rationale
The disease can be modeled similarly regardless of the genetic variant.	There are not sufficient data to make separate models for each genetic variant.
Disease heterogeneity can be separated into FAP stage progression and severe cardiac involvement (defined as NT-proBNP > 3,000).	Clinically, patients have the potential to experience both polyneuropathy and cardiac symptoms. Separate disease states are needed to capture the differing costs, quality of life, and mortality impacts when NT-proBNP increases above 3,000.
Mortality by FAP stage can be approximated by data outside of the trials (e.g., Adams, 2013[91] and Swiecicki et al. 2015)[32].	There are no trial data on mortality by FAP stage. This was approximated based on mortality data for patients with any or advanced neuropathy.
AEs are not modeled separately.	Any events with an apparent excess risk (e.g., thrombocytopenia) would be unlikely to materially affect model findings.
Patients do not undergo liver transplantation.	There is no clear clinical consensus that this procedure is a common treatment for these patients.
Severe cardiac involvement (NT-proBNP > 3,000) leads to a 10% decrement in the quality of life utility for each FAP stage.	This estimate is based on the 10% decrement for heart failure reported in Sullivan and Ghushchyan, 2006.[35]
There is some quality of life utility benefit for new treatments, even within the same FAP stage.	The trial data show a majority of patients experience "No Change" in their FAP level but statistically significant improvements in their Norfolk QOL.
Drug discontinuation was set equal to that seen in the NEURO-TTR trial.	Drug discontinuation was assumed to be at least this large.
Patients stay on treatment until death.	This assumption is varied in scenario analyses.

Model Inputs

Clinical Inputs

The clinical inputs for inotersen are from diverse sources (e.g., published papers and conference abstracts). As a result, it is necessary to calibrate the resulting transition probabilities (e.g., so that all probabilities sum to one). Transition to the death state is due to either background (other cause) mortality, or amyloidosis-related mortality from polyneuropathy or severe cardiac involvement (NT-proBNP > 3,000). The rates reported in the literature are then converted into probabilities that match the model's one-month cycle length. More details about this process are provided in Appendix D.

The annual transition probabilities for BSC patients are reported below in two tables for patients in each FAP stage with (NT-proBNP > 3,000) and without severe cardiac involvement (NT-proBNP ≤ 3,000). These estimates are conditional on surviving other-cause mortality. The first table is for BSC patients without severe cardiac involvement (NT-proBNP ≤ 3,000). Note that transition

probabilities are generally lower in patients with severe cardiac involvement, owing to excess mortality risk from such involvement.

Table 4.3. Annual Transition Probabilities for Best Supportive Care when NT-proBNP ≤ 3,000

From \ To	FAP Stage 1	FAP Stage 2	FAP Stage 3	Death
FAP Stage 1	0.87	0.10	0.02	0.01
FAP Stage 2	0.00	0.65	0.30	0.05
FAP Stage 3	0.00	0.00	0.74	0.26

Note: probabilities may not sum to one because of rounding.

The second table is for BSC patients with severe cardiac involvement (NT-proBNP > 3,000).

Table 4.4. Annual Transition Probabilities for Best Supportive Care when NT-proBNP > 3,000

From \ To	FAP Stage 1	FAP Stage 2	FAP Stage 3	Death
FAP Stage 1	0.84	0.10	0.01	0.05
FAP Stage 2	0.00	0.61	0.06	0.33
FAP Stage 3	0.00	0.00	0.01	0.99

Note: probabilities may not sum to one because of rounding.

The next set of annual transition probabilities are for patients taking inotersen and are described further below.

Clinical Probabilities/Response to Treatment

Annual transition probabilities for inotersen were not directly available and had to be created by mapping the polyneuropathy disability score (PND) to FAP stage. The same method was used for both inotersen and patisiran when converting PND to FAP stage. For inotersen, the distribution of the PND scores was taken from Page 63 of the Assessment Report by the Committee for Medicinal Products for Human Use (CHMP).[85] The transition probabilities were computed after results were categorized into 1) Improved, 2) No change, 3) Worsened, 4) Missing and 5) Dead for both PND and FAP measures. Patients from the Missing category were redistributed into categories 1), 2) and 3) based on the empirical distribution of the non-missing data. More information about our calculations can be found in Appendix D. The next table reports the model's annual transition probabilities for inotersen patients both with severe cardiac involvement (NT-proBNP > 3,000) and without (NT-proBNP ≤ 3,000). As above, these estimates are conditional on surviving other cause mortality.

Table 4.5. Annual Transition Probabilities for Inotersen by Severe Cardiac Involvement (NT-proBNP) Status, Per Stage

To / From	FAP Stage 1 (NT-proBNP > 3,000)	FAP Stage 2 (NT-proBNP > 3,000)	FAP Stage 3 (NT-proBNP > 3,000)	Death
FAP Stage 1 (with NT-proBNP > 3,000)	0.88 (0.85)	0.10 (0.09)	0.02 (0.01)	0.00 (0.05)
FAP Stage 2 (with NT-proBNP > 3,000)	0.13 (0.12)	0.56 (0.52)	0.26 (0.05)	0.05 (0.31)
FAP Stage 3 (with NT-proBNP > 3,000)	0.01 (0.00)	0.06 (0.01)	0.69 (0.00)	0.25 (0.98)

Note: probabilities may not sum to one because of rounding. Estimates for patients with severe cardiac involvement presented in parentheses.

Mortality

The sex-weighted, age-specific death rate for the inotersen model comes from the United States life tables produced by the National Center for Health Statistics at the Centers for Disease Control and Prevention.[92] The weights for the weighted average of female and male mortality rates come from the NEURO-TTR trial. The death rate from polyneuropathy depends on FAP stage. Mortality for FAP stages 1, 2 and 3 are approximated by the "without neuropathy" curve, the "with neuropathy" curve, and the "with weight loss" curve, respectively, from a natural history study published by Swiecicki et al.[32] The death rate related to severe cardiac involvement (NT-proBNP > 3,000) is estimated based on the trial-based data from Slama et al.[18]

Utilities

Health state utility weights assigned to each FAP stage for inotersen were adjusted by a quality of life decrement to serve as a "toll" for severe cardiac involvement (NT-proBNP > 3,000). The utilities for FAP stages 1 and 2 are from the trial data reported by Denoncourt et al.[33] The missing FAP stage 3 utility value is taken from the "by stage" estimation of Disease Stage 3 in the tafamidis report produced by the York Economic Review Group (ERG).[34] The crosswalk equations in the York ERG report map the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire scores (abbreviated TQoL in their report) onto EQ-5D utility scores needed for economic evaluations. In the York ERG's analysis, the EQ-5D data come from an analysis using the THAOS (Transthyretin Amyloidosis Outcomes Survey) data collected in a longitudinal, observational survey studying the natural history of patients with hATTR. The utility decrement for severe cardiac involvement (NT-proBNP > 3,000) is assumed to be a 10% disutility, reflecting the 10% decrement estimated for heart failure reported by Sullivan and Ghushchyan, 2006.[35]

The utility parameters for inotersen were varied in both scenario and sensitivity analyses to explore the impact of uncertainty. Additionally, we explored the impact of using different sets of utility values (e.g., those reported by the York Economic Review Group).[34]

Table 4.6. Utility Values for Health States for Inotersen

Health State	Utility Value If NT-proBNP ≤ 3,000	Utility Value If NT-proBNP > 3,000
FAP Stage 1	0.710	0.639
FAP Stage 2	0.570	0.513
FAP Stage 3	0.170	0.153

Patients in the NEURO-TTR trial (taking inotersen) reported improvements in Norfolk QOL-DN compared to placebo. In previous economic evaluation models of hATTR,[34] Norfolk QOL-DN scores have been mapped to EQ-5D quality of life utilities, allowing differences in QoL score to be converted into a utility value. Table 4.7 shows the results of taking the reported differences in QoL scores versus placebo and converting them into utilities using the linear equation: EQ-5D = 0.913991 - 0.005682 * QoL (i.e., each 1-point change in QoL has approximately a 0.006 impact on EQ-5D). In the model, patients accrue utility gains through QoL improvements over the time period for which there is evidence of a QoL benefit (i.e., 15 months for inotersen); after building to the maximum amount, the utility gain plateaus. From this point onward, patients continue to receive the plateau level "bonus" utility for as long as they are on treatment.

Assuming a within-stage quality of life gain may double-count gains accrued from delayed disease progression but may also represent within-stage symptom relief. It is possible that there may be some quality of life utility benefit for inotersen, even within the same FAP stage. If one assumes that this gain in disease-specific quality of life also creates a gain in preference-based utility, then additional utility gains for inotersen might be justified (i.e., benefits beyond those from a preferred FAP Stage profile). The additional utility gains in Table 4.7 provide a means of addressing quality of life impacts from treatment within FAP stages (with these "gains," two patients in the same FAP stage could have different quality of life utilities based on their treatment regimen). For example, for the cycle at month 12 a person with hATTR in FAP Stage 3 taking inotersen would have QALYs = 0.072 + 0.17 = 0.242 but a person receiving BSC would have just 0.17 QALYs. The 42% gain in utility from being on treatment is assumed based on the large variation in Norfolk QoL and the small variation in PND transition profiles. In this way, the model captures quality of life benefits that accrue outside of PND / FAP dimensions. This assumption is varied in the scenario analyses.

Table 4.7. Utility Gains from Inotersen Treatment over the First 12 Months

Health State	Utility Gain If Using Inotersen
FAP Stage 1	0.048
FAP Stage 2	0.072
FAP Stage 3	0.072
Severe Cardiac Involvement (NT-proBNP > 3,000)	0.048 if FAP Stage 1 0.072 if FAP Stage 2 or 3

Adverse Events

Previous cost-effectiveness analyses of hATTR did not include AEs in the base case and including them would be unlikely to change the findings qualitatively.

Treatment Discontinuation

Drug discontinuation was set equal to that seen in the NEURO-TTR trial for patients taking inotersen. Base case values were calculated based on the reported discontinuation rates of 22.3% over 15 months.

Economic Inputs for Inotersen

All costs were adjusted to 2018 US dollars using the Consumer Price Index.[93]

Drug Acquisition Costs

In the absence of an actual drug price for inotersen, the drug is assumed to have a placeholder cost of $345,000 per year, based on investment analyst estimates.[94]

For inotersen, the $345,000 drug cost is *not* accompanied by any induction or monitoring costs (see Administration and Monitoring Costs section). However, for the first year inotersen's treatment cost is assumed to be $345,074.16. The $74.16 represents a one-time training cost for self-injection (CPT code 99213: national non-facility price = $74.16), and subsequent years of inotersen are assumed to be $345,000.

Administration and Monitoring Costs

Patients in the NEURO-TTR took daily vitamin A supplements. This is a negligible cost we chose to exclude.

For inotersen, annual monitoring costs of approximately $830.11 for two weekly assays (CPT code 85025: complete blood count with differential WBC, and CPT code 82565: assay of creatinine) are assumed to be covered by the manufacturer, and thus were not included as a cost in this analysis. Likewise, induction costs are not included in the model. These $0 cost assumptions are based on communications from the manufacturer. While the NEURO-TTR study included a "loading dose" of three subcutaneous injections in the first week of treatment, this is not likely to be included in the product label, and the dose will reduce to a once-weekly sub-cutaneous injection of 300mg. The manufacturer also expressed that they will establish a "free" monitoring program once they have finalization of the product label from the FDA. Based on this information at this point, we calculated the Total Drug Regimen cost below.

The Total Drug Regimen cost for inotersen during the first year is $345,074.16 and $345,000 in subsequent years. This produces a Drug Cost per Dose of $6,617.86 (i.e., $345,074.16 / 52.14285714 1-week doses) the first year and $6,616.44 (i.e., $345,000 / 52.14285714 1-week doses) in subsequent years.

Table 4.8. Drug Cost Inputs for Inotersen

Intervention	Dosing and Route of Administration	Drug Cost per Dose	Annual Drug Cost	Annual Other Drug Costs	Annual Total Drug Cost*
Inotersen	300 mg SC	$6,617.86 the 1st year and $6,616.44 afterward	$345,000	$74.16 the 1st year and $0 afterward	$345,074.16 the 1st year and $345,000 afterward

*Note: Including a 1-time $74.16 training cost for inotersen increases the year 1 annual total drug cost to $345,074.16 for inotersen. After the first year, inotersen's annual cost is assumed to be $345,000.

Other Disease-Related Health Care Utilization Costs

By-stage health care utilization costs for inotersen were not available and had to be assumed; we used data reported for the APOLLO trial. The health care utilization costs for inotersen were computed by taking the quantities from the Schmidt et al. poster,[95] which reported annual service use by patients in the year prior to the APOLLO trial. We applied 2018 costs for the relevant CPT codes. More details are shown in Appendix D. Since there were no data for FAP stage 3 participants, we assumed the costs for FAP stage 3 would be 35% more than for FAP stage 2. The 35% assumption is an average of the percentage increase in FAP stage 3 costs reported in a poster by Inês et al. (37% increase) and the report by the York Economic Review Group (33% increase).[34,96] People with severe cardiac involvement (NT-proBNP > 3000) at baseline were assumed to have $85,964 in additional costs per year, equal to two hospital visits (for DRG 291: heart failure & shock with major complication or comorbidity).[97] Lastly, we included a one-time cost of $41,160 when patients transitioned to death. This estimate is based on the difference between the cost of decedents and the cost of survivors reported in Riley and Lubitz (2010).[98] All costs were adjusted to 2018 US dollars.

Table 4.9. Annual Health Care Utilization Costs by FAP Stage

Health state	Annual Health Care Cost
FAP Stage 1	$8,701.36
FAP Stage 2	$27,798.72
FAP Stage 3	$37,528.28
Additional Cost if NT-proBNP > 3,000	$85,964.00
Additional Cost at Death	$41,160.00

Background Age-Specific Health Care Costs

Lassman et al. found that average annual health care spending increases with age, and we use their estimates (adjusted to 2018 US dollars) to create background age-specific health care costs.[99] These are the background health care costs that accrue to patients by virtue of being alive.

Table 4.10. Annual Background Health Care Utilization Costs for Inotersen, by Age Range

Age Range	Background Age-Specific Health Care
45 – 64 years	$9,657
65 – 84 years	$18,295
85+ years	$40,132

Thus, inotersen costs from a health care sector perspective are the sum of the background age-specific costs, the treatment regimen costs, FAP stage and severe cardiac involvement costs, and the one-time cost of transition to death. The modified societal perspective includes these costs as well as the productivity costs described next.

Productivity Costs

Productivity costs for inotersen were included in a dual base case analysis, as per ICER's Value Framework for Ultra Rare Conditions. Estimates for the lost work hours associated with each FAP stage were only available from the APOLLO trial and were assumed identical for inotersen. These were informed by the posters by Berk et al. and Schmidt et al.[93,98] Given there are no estimates for productivity costs accrued in FAP stage 3, we assumed they were the same as those in FAP stage 2. This assumption was also made by the York ERG in their cost-effectiveness analysis of hATTR treatment.[34] In addition, we used an estimate of hours of informal caregiving attributable to cardiovascular disease from Dunbar et al. to approximate the additional productivity costs of severe cardiac involvement.[101] We assumed a $24.23 per hour average hourly wage (US Bureau of Labor Statistics) to create an "hourly price" for that time. More details are provided in Appendix D.

Table 4.11. Productivity Costs by FAP Stage for Inotersen

Health State	Cost
FAP Stage 1	$26,859.68
FAP Stage 2	$54,247.04
FAP Stage 3	$54,247.04
Severe Cardiac Involvement (NT-proBNP > 3,000)	$2,474.86

Using a modified societal perspective, costs that are incurred due to the differential survival of patients under alternative treatment regiments (e.g., inotersen vs. BSC) must net consumption costs from the measurements of productivity gains.[102] Using the data tables in section 8.4.2.1 of

the book by the Second Panel on Cost-Effectiveness in Health and Medicine, we calculated average annual earnings foregone (due to death) net of non-health expenditures. The table below presents these data inputs for our model by age category.

Table 4.12. Modified Societal Perspective Annual Differential Mortality Costs, by Age Range

Age Range	Differential Age-Specific Mortality Costs (Modified Societal Perspective)
55 – 64 years	$30,606
65 – 74 years	$20,659
75+ years	$20,064

Note: Authors' calculation based on the data tables in section 8.4.2.1 of the book by the Second Panel on Cost-Effectiveness in Health and Medicine.[102]

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes for inotersen, using available measures of parameter uncertainty (e.g., standard errors) or reasonable ranges for each input described in the model inputs section for inotersen above. Values were chosen to make the uncertainty large relative to the mean. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for mean costs, disease progression and treatment effects, and beta distributions for utilities, initial disease stage distribution, and disutilities.

Scenario Analyses

We performed several scenario analyses based on modifying one or more of the base case values for the parameters related to initial FAP stage distribution, QALYs, and costs. Additionally, we performed a threshold analysis by systematically altering treatment price to estimate the maximum price that would correspond to given willingness to pay (WTP) thresholds.

Model Validation

We used several approaches to validate the model for inotersen. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

Results for Inotersen

Base Case Results

The base case results for inotersen are reported in Table 4.13. For the base case focused on the health care sector perspective, undiscounted total costs were $1,709,977 for inotersen and $404,059 for BSC, with corresponding life years of 9.6 years and 8.7 years, respectively. Given the severity of hATTR, this corresponds to 5.44 QALYs for inotersen and 4.56 QALYs for BSC. When discounting both costs and outcomes at 3%, total costs were $1,507,450 for inotersen and $329,858 for BSC, with corresponding life years of 7.9 years and 7.3 years, respectively. Quality adjustment of these life years produces estimates of 4.54 QALYs for inotersen and 3.86 QALYs for BSC.

For the base case focused on the modified societal perspective, undiscounted total costs were $1,843,473 for inotersen and $534,183 for BSC. When discounting both costs and outcomes at 3%, total costs were $1,608,862 for inotersen and $431,261 for BSC.

Table 4.13. Results for the Base Case for Inotersen Compared to Best Supportive Care

	Undiscounted			Discounted		
	Total Costs	Life Years	QALYs	Total Costs	Life Years	QALYs
Health Care Sector Perspective						
Inotersen	$1,709,977	9.6	5.44	$1,507,450	7.9	4.54
Best Supportive Care	$404,059	8.7	4.56	$329,858	7.3	3.86
Modified Societal Perspective						
Inotersen	$1,843,473	9.6	5.44	$1,608,862	7.9	4.54
Best Supportive Care	$534,183	8.7	4.56	$431,261	7.3	3.86

Incremental cost-effectiveness ratios for inotersen are reported in Table 4.14. The model produces incremental cost-effectiveness ratio estimates for inotersen that are above commonly cited thresholds of $50,000 - $150,000, at approximately $1.7 million per QALY gained. On a per life-year basis, the incremental cost-effectiveness ratio was approximately $1.95 million per LY.

Likewise, the results show that the incremental cost-effectiveness ratios computed from a modified societal perspective are also high for inotersen. While not evident because of the rounding, incremental cost-effectiveness ratios calculated from the modified societal perspective are slightly higher than those from the health care sector perspective. This is because valuing the greater productivity in the treatment cohort does not fully cancel out the greater informal costs associated with caring for patients with hATTR, as productivity gains are somewhat limited due to the older age and the infirmity of the cohort

Table 4.14. Incremental Cost-Effectiveness Ratios for Inotersen Compared to Best Supportive Care, Discounted at 3%

INCREMENTAL	Inotersen vs. BSC
Incremental Costs	
Health Care Sector Perspective	$1,177,592
Modified Societal Perspective	$1,177,601
Incremental Outcomes	
Life years (LY)	0.61 years
QALYs	0.68 QALYs
Incremental Cost-Effectiveness Ratios (Life years)*	
Health Care Sector Perspective	$1,950,000
Modified Societal Perspective	$1,950,000
Incremental Cost-Effectiveness Ratios (QALYs)*	
Health Care Sector Perspective	$1,730,000
Modified Societal Perspective	$1,730,000

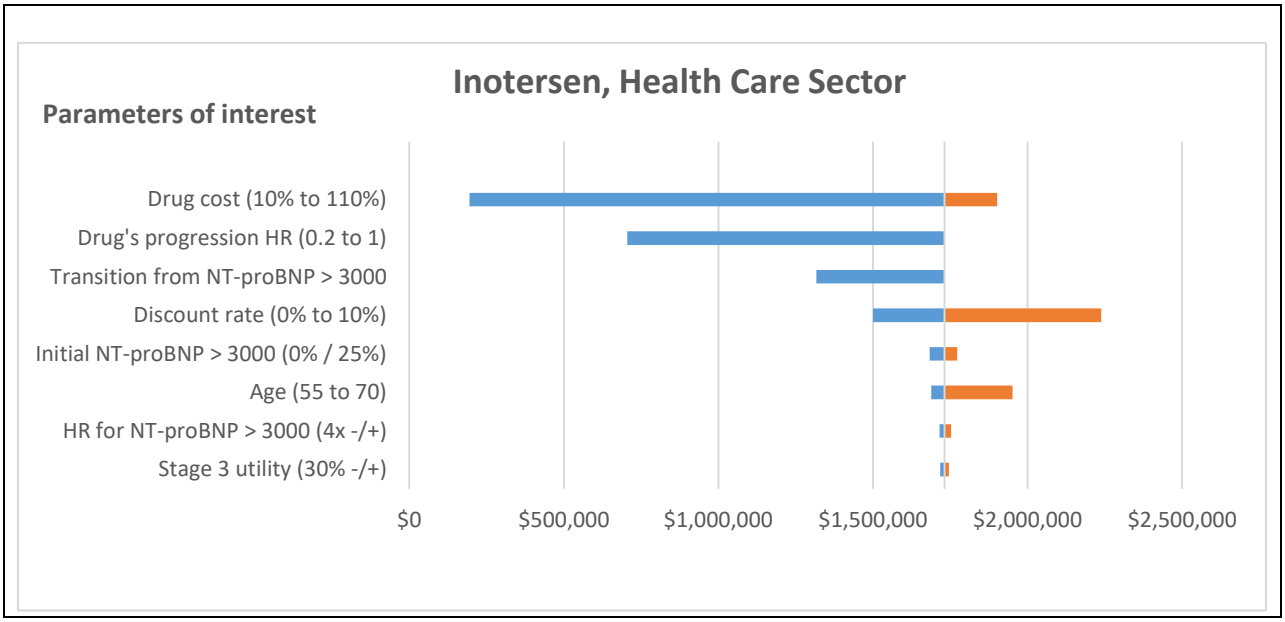
* Note: Incremental cost-effectiveness ratios reported may not be identical to those computed because of rounding.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per QALY. The tornado diagram below shows that inotersen's treatment cost and disease progression are key drivers of the economic results. This finding holds for both the health care sector and the modified societal perspectives. The diagram also shows that there are some unknown parameters that do not appear to affect the incremental cost-effectiveness ratio's magnitude (over the range they were varied). These findings are shown by horizontal bars that have very short lengths.

The tornado diagram below illustrates the parameters of interest, with corresponding values producing a low and high incremental cost-effectiveness estimate. These values are located under the "parameter of interest" column in the figure. The "Transition from NT-proBNP > 3,000" parameter has been set at 50% or 0%. At 50%, the model assumes that 50% of patients with NT-proBNP > 3,000 transition to having NT-proBNP ≤ 3,000. The base case incremental cost-effectiveness ratio was produced by setting the "Transition from NT-proBNP > 3,000" parameter at 0%. This explains why the parameter only has a "low" value (left bar); the "high" value reflects the base case. Results are presented for the health care sector perspective below. Diagrams for the modified societal perspective are available in Appendix D.

Figure 4.2. Tornado Diagram for One-Way Sensitivity Analyses of Incremental Cost-Effectiveness Ratios for Inotersen versus Best Supportive Care from the Health Care Sector Perspective



Using a health care sector perspective, the results from the probabilistic sensitivity analysis strongly suggest that inotersen does not achieve cost-effectiveness results consistent with conventional levels of willingness to pay. The results in the table below show that probability of inotersen being cost-effective is less than 1% across the range of thresholds from $50,000 to $250,000.

Table 4.15. Probabilistic Sensitivity Analysis Results: Inotersen versus Best Supportive Care, Health Care Sector Perspective

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
Inotersen	< 1%	< 1%	< 1%	< 1%	< 1%

In the cost-effectiveness acceptability curves (CEACs) presented in Appendix D, we explore the probability of cost-effectiveness by varying willingness to pay thresholds up to $1 million per QALY gained.

Scenario Analyses Results

The scenario analyses change multiple variables at once to consider different scenarios. The rows of the table describe which variables have been changed from their base case values.

Assumptions about quality of life utility values can increase the incremental cost-effectiveness ratio by over $100,000. For example, by using the base case values found in the York ERG's report, the model's incremental cost-effectiveness ratio approaches $1,950,000. A "worst-case" scenario built

on the findings in Stewart et al. also produces an incremental cost-effectiveness ratio that is more than $200,000 greater than the model's base case estimate.[103] In addition, the model is sensitive to other utility assumptions.

We assumed that the difference in QOL-DN by FAP stage by treatment could be represented by a difference in quality of life utility scores (i.e., patients in the same FAP stage could have different QALY utility scores due to treatment). The scenario analysis "Differential Utility by Treatment" explores the effect of this assumption by varying the size of the benefit and the time over which the benefit accrues. The results show that our base case assumptions are consequential; without them the incremental cost-effectiveness ratio is more than $2.4 million. In contrast, health care costs appear inconsequential. Varying the "disease-specific direct medical costs" did not change the incremental cost-effectiveness ratio by much, given the drug's high cost.

Table 4.16. Scenario Analysis Results: Inotersen versus Best Supportive Care, Health Care Sector Perspective

Scenarios	Incremental Costs (ΔC)	Incremental QALYs (ΔQALY)	ICER* (ΔC/ΔQALY)
Base Case	$1,177,592	0.68	$1,730,000
1. Different FAP Stage Utilities			
York ERG Report (Stage 1 = 0.636; Stage 2 = 0.501; Stage 3 = 0.375)	$1,177,592	0.61	$1,950,000
Stewart et al.[103] worst-case scenario (Stage 1 = 0.570; Stage 2 = 0.410; Stage 3 = 0.050)	$1,177,592	0.59	$1,980,000
2. Differential Utility by Treatment			
No Utility Gain from TQoL Gain	$1,177,592	0.48	$2,430,000
3. Disease-Specific Direct Medical Costs			
Half All Health Care Costs	$1,173,874	0.68	$1,730,000
Double All Health Care Costs	$1,185,028	0.68	$1,740,000

* Note: ICERs reported may not be identical to those computed because of rounding.

Threshold Analysis Results

The table below reports the dose price or "unit price" to achieve incremental cost-effectiveness ratio thresholds. These results suggest that significant discounts from the assumed price are required to achieve commonly-cited thresholds. For example, an annual drug cost of approximately $96,103 would be required to achieve a threshold of $500,000 per QALY for inotersen, below the assumed price of $345,000. The same magnitude of reduction is needed when considering annual drug cost from a modified societal perspective.

Table 4.17. Threshold Analysis Results, Per Inotersen Dose (Only Drug Cost)

Perspective	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $250,000 per QALY	Unit Price to Achieve $500,000 per QALY
Health Care	$99	$293	$487	$874	$1,843
Modified Societal	$99	$293	$487	$874	$1,843

The small difference in required annual drug costs between the health care system and the modified societal perspectives is imperceptible when looking at the (unit) dose cost (i.e., after dividing the annual costs by 52.14286 weekly doses in a year). This is the reason the numbers in the two rows in the table above look the same.

4.3 Long-Term Cost-Effectiveness for Patisiran

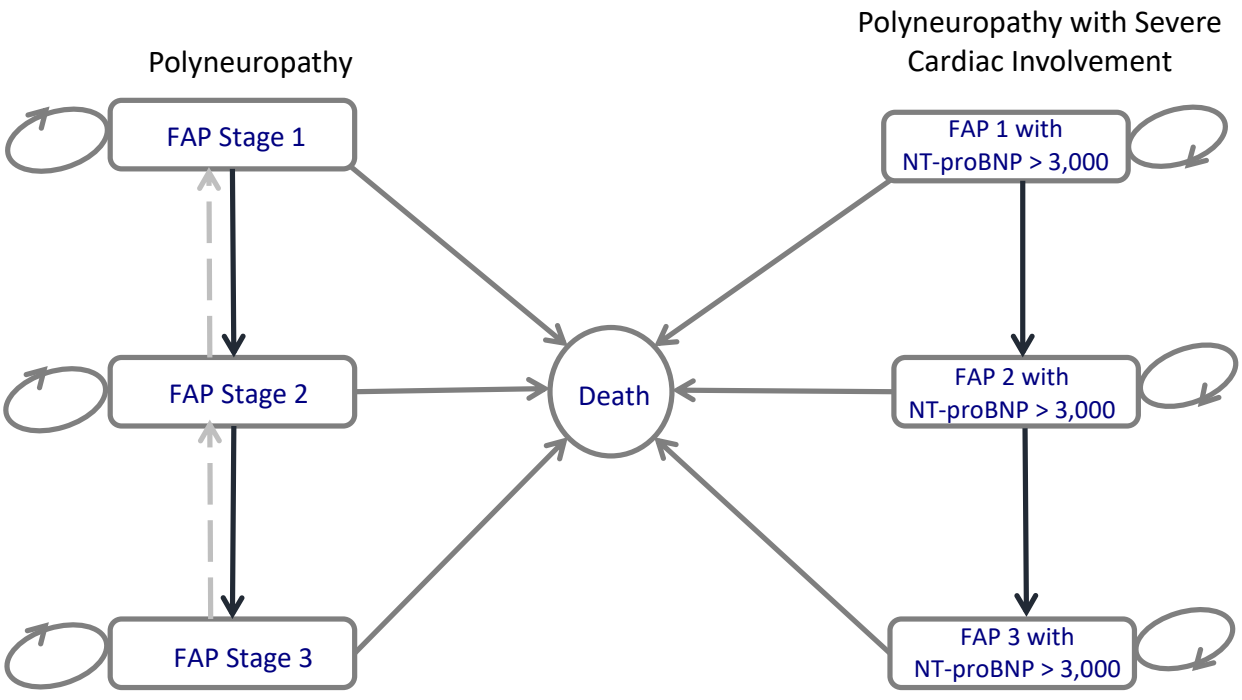
Methods

Figure 4.3 depicts the analytic framework for the economic evaluation of patisiran developed in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA).

Model Structure

The model uses one-month cycle lengths over a lifetime horizon.

Figure 4.3. Model Framework for Patisiran



Severe cardiac involvement (NT-proBNP > 3,000) is estimated based on its prevalence as a baseline characteristic in the available clinical evidence; therefore, patients are assumed to have such involvement at the start of the analysis, and it is not developed or resolved through the course of the disease. This is depicted in the Model Framework figure by the absence of any arrows directly connecting the "Polyneuropathy" states (on the left) with the "Severe Cardiac Involvement" states (on the right). The dashed lines pointing upward illustrate that patisiran has the potential for FAP Stage regression (i.e., improving functioning as indicated by transitioning from a higher FAP Stage to a lower FAP Stage). Previous economic evaluations of treatments for hATTR have used models featuring FAP disease stages. Research reporting a high mortality hazard ratio for patients with NT-proBNP > 3,000 motivated introducing a separate set of disease states to keep track of the increased cost, decreased quality of life and elevated mortality associated with elevated levels of this biomarker. We explore the impact of potential treatment-induced reductions in the number of individuals with severe cardiac involvement in both sensitivity and scenario analyses.

Target Population

The target population for the second economic evaluation was adults with hATTR, with an indication for treatment with patisiran. Table 4.18 reports base case population characteristics for the patisiran model. Given the differences between the NEURO-TTR and APOLLO trials, the base case cohort characteristics are different for the models for inotersen and patisiran, reflecting study population heterogeneity.

Table 4.18. Base Case Model Cohort Characteristics

	Value	Primary Source
For the Patisiran Model:		
Mean Age	62	Adams et al.[12]
Female	26%	Adams et al.[12]
FAP Stage 1	46.2%	Adams et al. [12]
FAP Stage 2	53.8%	Adams et al.[12]
Severe Cardiac Involvement (NT-proBNP > 3,000)	12.9%	Slama et al.[18]

Treatment Strategies

The treatment strategies evaluated included:

- Patisiran (0.3 mg/kg infusion every three weeks)

Comparators

The comparator in APOLLO was placebo, reflecting best supportive care (BSC). Similar to the inotersen model, both diflunisal and tafamidis were excluded from consideration, as neither has

received FDA approval for the treatment of hATTR amyloidosis, and indirect comparisons with diflunisal were infeasible due to differences in trial design, outcome measure, and study populations.

Key Model Characteristics and Assumptions

Key assumptions made for the economic model of patisiran are listed in Table 4.19.

Table 4.19. Key Model Assumptions for Patisiran

Assumption	Rationale
The disease can be modeled similarly regardless of the genetic variant.	There are not sufficient data to make separate models for each genetic variant.
Disease heterogeneity can be separated into FAP stage progression and severe cardiac involvement (defined as NT-proBNP > 3,000).	Clinically, patients have the potential to experience both polyneuropathy and cardiac symptoms. Separate disease states are needed to capture the differing costs, quality of life, and mortality impacts when NT-proBNP increases above 3,000.
Mortality by FAP stage can be approximated by data outside of the trials (e.g., Adams, 2013[91] and Swiecicki et al. 2015)[32].	There are no trial data on mortality by FAP stage. This was approximated based on mortality data for patients with any or advanced neuropathy.
AEs are not modeled separately.	Any events with an apparent excess risk (e.g., thrombocytopenia) would be unlikely to materially affect model findings.
Patients do not undergo liver transplantation.	There is no clear clinical consensus that this procedure is a common treatment for these patients.
Severe cardiac involvement (NT-proBNP > 3,000) leads to a 10% decrement in the quality of life utility for each FAP stage.	This estimate is based on the 10% decrement for heart failure reported in Sullivan and Ghushchyan, 2006.[35]
There is some quality of life utility benefit for new treatments, even within the same FAP stage.	The trial data show a majority of patients experience "No Change" in their FAP level but statistically significant improvements in their Norfolk QOL.
Drug discontinuation was set equal to that seen in the APOLLO trial.	Drug discontinuation was assumed to be at least this large.
Patients stay on treatment until death.	This assumption is varied in scenario analyses.

Model Inputs

Clinical Inputs

The clinical inputs for patisiran are from diverse sources (e.g., published papers and conference abstracts). As a result, it is necessary to calibrate the resulting transition probabilities (e.g., so that all probabilities sum to one). Transition to the death state is due to either background (other cause) mortality, or amyloidosis-related mortality from polyneuropathy or severe cardiac involvement (NT-proBNP > 3,000). The rates reported in the literature are then converted into probabilities that

match the model's one-month cycle length. More details about this process are provided in Appendix D.

The annual transition probabilities for BSC patients are reported below in two tables for patients in each FAP stage with (NT-proBNP > 3,000) and without severe cardiac involvement (NT-proBNP ≤ 3,000). These estimates are conditional on surviving other-cause mortality. The first table is for BSC patients without severe cardiac involvement (NT-proBNP ≤ 3,000). Note that transition probabilities are generally lower in patients with severe cardiac involvement, owing to excess mortality risk from such involvement.

Table 4.20. Annual Transition Probabilities for Best Supportive Care when NT-proBNP ≤ 3,000

From \ To	FAP Stage 1	FAP Stage 2	FAP Stage 3	Death
FAP Stage 1	0.87	0.10	0.02	0.01
FAP Stage 2	0.00	0.65	0.30	0.05
FAP Stage 3	0.00	0.00	0.74	0.26

Note: probabilities may not sum to one because of rounding.

Table 4.21. Annual Transition Probabilities for Best Supportive Care when NT-proBNP > 3,000

From \ To	FAP Stage 1	FAP Stage 2	FAP Stage 3	Death
FAP Stage 1	0.84	0.10	0.01	0.05
FAP Stage 2	0.00	0.61	0.06	0.33
FAP Stage 3	0.00	0.00	0.01	0.99

Note: probabilities may not sum to one because of rounding.

Clinical Probabilities/Response to Treatment

The transition probabilities between FAP stages for patisiran were derived from a poster analyzing APOLLO trial data by Gonzalez-Duarte et al.[20] The transition probabilities were computed after results were categorized into 1) Improved, 2) No change, 3) Worsened, 4) Missing and 5) Dead for both PND and FAP measures. Patients from the Missing category were redistributed into categories 1), 2) and 3) based on the empirical distribution of the non-missing data. More information about our calculations can be found in Appendix D. The next table reports the model's annual transition probabilities for inotersen patients both with severe cardiac involvement (NT-proBNP > 3,000) and without (NT-proBNP ≤ 3,000). As above, these estimates are conditional on surviving other cause mortality.

Table 4.22. Annual Transition Probabilities for Patisiran by Severe Cardiac Involvement (NT-proBNP) Status, Per Stage

To / From	FAP Stage 1 (NT-proBNP > 3,000)	FAP Stage 2 (NT-proBNP > 3,000)	FAP Stage 3 (NT-proBNP > 3,000)	Death
FAP Stage 1 (with NT-proBNP > 3,000)	0.97 (0.93)	0.03 (0.03)	0.00 (0.00)	0.00 (0.04)
FAP Stage 2 (with NT-proBNP > 3,000)	0.05 (0.05)	0.85 (0.79)	0.08 (0.02)	0.02 (0.14)
FAP Stage 3 (with NT-proBNP > 3,000)	0.00 (0.00)	0.02 (0.00)	0.72 (0.00)	0.26 (0.99)

Note: probabilities may not sum to one because of rounding. Estimates for patients with severe cardiac involvement presented in parentheses.

Mortality

The sex-weighted, age-specific death rate for the patisiran model comes from the United States life tables produced by the National Center for Health Statistics at the Centers for Disease Control and Prevention.[92] The weights for the weighted average of female and male mortality rates come from the APOLLO trial. The death rate from polyneuropathy depends on FAP stage. Mortality for FAP stages 1, 2 and 3 are approximated by the "without neuropathy" curve, the "with neuropathy" curve, and the "with weight loss" curve, respectively, from a natural history study published by Swiecicki et al.[32] The death rate related to severe cardiac involvement (NT-proBNP > 3,000) is estimated based on the trial-based curve from the APOLLO study.[18]

Utilities

Health state utility weights assigned to each FAP stage for patisiran were adjusted by a quality of life decrement to serve as a "toll" for severe cardiac involvement (NT-proBNP > 3,000). The utilities for FAP stages 1 and 2 are from the trial data reported by Denoncourt et al.[33] The missing FAP stage 3 utility value is taken from the "by stage" estimation of Disease Stage 3 in the tafamidis report produced by the York Economic Review Group (ERG).[34] The crosswalk equations map the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire scores (abbreviated TQoL in their report) onto the EQ-5D utility scores needed for economic evaluations. In the York ERG's analysis, the EQ-5D data come from an analysis using the THAOS (Transthyretin Amyloidosis Outcomes Survey) data collected in a longitudinal, observational survey studying the natural history of patients with hATTR. The utility decrement for severe cardiac involvement (NT-proBNP > 3,000) is assumed to be a 10% disutility, reflecting the 10% decrement estimated for heart failure reported by Sullivan and Ghushchyan, 2006.[35]

The utility parameters for patisiran were varied in both scenario and sensitivity analyses to explore the impact of uncertainty. Additionally, we explored the impact of using different sets of utility values (e.g., those reported by the York Economic Review Group).[34]

Table 4.23. Utility Values for Health States

Health State	Utility Value If NT-proBNP ≤ 3,000	Utility Value If NT-proBNP > 3,000
FAP Stage 1	0.710	0.639
FAP Stage 2	0.570	0.513
FAP Stage 3	0.170	0.153

Patients in the APOLLO trial (taking patisiran) reported improvements in Norfolk QOL-DN compared to placebo. In previous economic evaluation models of hATTR,[34] Norfolk QOL-DN scores have been mapped to EQ-5D quality of life utilities, allowing differences in QoL score to be converted into a utility value. Table 4.7 shows the results of taking the reported differences in QoL scores versus placebo and converting them into utilities using the linear equation: EQ-5D = 0.913991 - 0.005682 * QoL (i.e., each 1-point change in QoL has approximately a 0.006 impact on EQ-5D). In the model, patients accrue utility gains through QoL improvements over the time period for which there is evidence of a QoL benefit (i.e., 18 months for patisiran); after building to the maximum amount, the utility gain plateaus. From this point onward, patients continue to receive the plateau level "bonus" utility for as long as they are on treatment.

If one assumes that better QoL scores reflect a slower FAP stage progression, then also assuming a "within FAP Stage" treatment gain in QALYs may double count the quality of life gain from treatment. However, nearly 76% of patients in the APOLLO trial did not experience a change in their FAP Stage, despite an average improvement in Norfolk QOL-DN of 21 points in patients receiving patisiran compared to placebo.[12,20] Thus it is possible that there may be some quality of life utility benefit for patisiran, even within the same FAP stage. If one assumes that this gain in disease-specific quality of life also creates a gain in preference-based utility, then additional utility gains might be justified (i.e., any benefits beyond those from a preferred FAP Stage profile). The additional utility gains in Table 4.24 provide a means of addressing quality of life impacts from treatment within FAP stages (with these "gains," two patients in the same FAP stage could have different quality of life utilities based on their treatment regimen). In this way, the model captures quality of life benefits that accrue outside of PND / FAP dimensions. This assumption is varied in the scenario analyses.

Table 4.24. Utility Gains from Patisiran Treatment over the First 12 Months

Health State	Utility Gain If Using Patisiran
FAP Stage 1	0.073
FAP Stage 2	0.097
FAP Stage 3	0.097
Severe Cardiac Involvement (NT-proBNP > 3,000)	0.073 if FAP Stage 1 0.097 if FAP Stage 2, 3

Adverse Events

Previous cost-effectiveness analyses of hATTR did not include AEs in the base case and including them would be unlikely to change the findings qualitatively.

Treatment Discontinuation

Drug discontinuation was set equal to that seen in the APOLLO trial for patients taking patisiran. Base case values were calculated based on the reported discontinuation rates of 6.8% over 18 months.

Economic Inputs

All costs were adjusted to 2018 US dollars using the Consumer Price Index.[93]

Drug Acquisition Costs

Patisiran is assumed to have a cost of $345,000 per year, based on investment analyst estimates.[94] For patisiran infused in-clinic, additional costs of administration and facility mark-up were included (see Administration and Monitoring Costs section).

Administration and Monitoring Costs

For patisiran infused in-clinic, additional costs include:

- 4.3% mark-up to the drug's annual acquisition cost ($345,000 x 4.3% = $14,835);
- $228.11 administration cost per infusion (up to 1 hour + additional infusion time: CPT code 96365 + 96366 = $191.08 + $37.03); and
- $2.90 for pre-infusion drugs at generic WAC prices per infusion (10 mg dexamethasone at $2.70, 500 mg oral acetaminophen at $0.05, 50 mg diphenhydramine at $0.10, and 50 mg ranitidine at $0.05).

Patients in the APOLLO trial also took daily vitamin A supplements. This is a negligible cost we chose to exclude.

We computed the cost per dose by taking the annual total drug cost and dividing by the number of doses in a year. For patisiran, this includes $345,000 (drug cost) + $14,835 (4.3% markup) + $228.11 administration cost per dose * 17.38095 3-week doses / year + $2.90 pre-infusion drugs * 17.38095 3-week doses / year = $363,850 per year. This represents a total drug regimen cost. The drug cost per dose, which includes only the cost of the drug, is $345,000 / 17.38095 3-week doses = $19,849 per dose.

For at-home infusion, we assumed there would be no mark up and no administration cost. This yields an at-home infusion cost of $345,000 (drug cost) + $2.90 pre-infusion drugs * 17.38095 3-week doses / year = $345,050 per year. Assuming a mix of 10% at-home and 90% in-clinic, the weighted average annual total drug regimen cost is $361,970 per year. The drug cost per dose is still $345,000 / 17.38095 3-week doses = $19,849.

Table 4.25. Drug Cost Inputs for Patisiran

Intervention	Dosing and Route of Administration	Drug Cost per Dose	Annual Drug Cost	Annual Other Drug Costs	Annual Total Drug Cost*
Patisiran (Infused 100% In-Clinic)	0.3 mg/kg IV	$19,849.32	$345,000	$18,850.17	$363,850.17

*Note: Assuming a 10%/90% split between at-home and in-clinic infusion, the annual total drug cost is $361,970.

Other Disease-Related Health Care Utilization Costs

By-stage health care utilization costs for patisiran were computed by taking the quantities from the Schmidt et al. poster,[95] which reported annual service use by patients in the year prior to the APOLLO trial. We applied 2018 costs for the relevant CPT codes. More details are shown in Appendix D. Since there were no data for FAP stage 3 participants, we assumed the costs for FAP stage 3 would be 35% more than for FAP stage 2. The 35% assumption is an average of the percentage increase in FAP stage 3 costs reported in a poster by Inês et al. (37% increase) and the report by the York Economic Review Group (33% increase).[34,96] People with severe cardiac involvement (NT-proBNP > 3000) at baseline were assumed to have $85,964 in additional costs per year, equal to two hospital visits (for DRG 291: heart failure & shock with major complication or comorbidity).[97] Lastly, we included a one-time cost of $41,160 when patients transitioned to death. This estimate is based on the difference between the cost of decedents and the cost of survivors reported in Riley and Lubitz (2010).[98] All costs were adjusted to 2018 US dollars.

Table 4.26. Annual Health Care Utilization Costs by FAP Stage

Health state	Annual Health Care Cost
FAP Stage 1	$8,701.36
FAP Stage 2	$27,798.72
FAP Stage 3	$37,528.28
Additional Cost if NT-proBNP > 3,000	$85,964.00
Additional Cost at Death	$41,160.00

Background Age-Specific Health Care Costs

Lassman et al. found that average annual health care spending increases with age, and we use their estimates (adjusted to 2018 US dollars) to create background age-specific health care costs.[99] These are the background health care costs that accrue to patients by virtue of being alive.

Table 4.27. Annual Background Health Care Utilization Costs, by Age Range

Age Range	Background Age-Specific Health Care
45 – 64 years	$9,657
65 – 84 years	$18,295
85+ years	$40,132

Thus, patisiran costs from a health care sector perspective are the sum of the background age-specific costs, the treatment regimen costs, FAP stage and severe cardiac involvement costs, and the one-time cost of transition to death. The modified societal perspective includes these costs as well as the productivity costs described next.

Productivity Costs

Productivity costs for patisiran were included in a dual base case analysis, as per ICER's Value Framework for rare diseases. Estimates for the lost work hours associated with each FAP stage were informed by the posters for the APOLLO trial by Berk et al. and Schmidt et al.[93,98] Given there are no estimates for productivity costs accrued in FAP stage 3, we assumed they were the same as those in FAP stage 2. This assumption was also made by the York ERG in their cost-effectiveness analysis of hATTR treatment.[34] In addition, we used an estimate of hours of informal caregiving attributable to cardiovascular disease from Dunbar et al. to approximate the additional productivity costs of severe cardiac involvement.[101] We assumed a $24.23 per hour average hourly wage (US Bureau of Labor Statistics) to create an "hourly price" for that time. We also included an annual caregiver cost of $3,375 for treatment days. More details are provided in Appendix D.

Table 4.28. Productivity Costs by FAP Stage for Patisiran

Health State	Cost
FAP Stage 1	$26,859.68
FAP Stage 2	$54,247.04
FAP Stage 3	$54,247.04
Severe Cardiac Involvement (NT-proBNP > 3,000)	$2,474.86

Using a modified societal perspective, costs that are incurred due to the differential survival of patients under alternative treatment regiments (e.g., patisiran vs. BSC) must net consumption costs from the measurements of productivity gains.[102] Using the data tables in section 8.4.2.1 of the

book by the Second Panel on Cost-Effectiveness in Health and Medicine, we calculated average annual earnings foregone (due to death) net of non-health expenditures. The table below presents these data inputs for our model by age category.

Table 4.29. Modified Societal Perspective Annual Differential Mortality Costs, by Age Range

Age Range	Differential Age-Specific Mortality Costs (Modified Societal Perspective)
55 – 64 years	$30,606
65 – 74 years	$20,659
75+ years	$20,064

Note: Authors' calculation based on the data tables in section 8.4.2.1 of the book by the Second Panel on Cost-Effectiveness in Health and Medicine.[102]

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes for patisiran, using available measures of parameter uncertainty (e.g., standard errors) or reasonable ranges for each input described in the model inputs section for patisiran above. Values were chosen to make the uncertainty large relative to the mean. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for mean costs, disease progression and treatment effects, and beta distributions for utilities, initial disease stage distribution, and disutilities.

Scenario Analyses

We performed several scenario analyses based on modifying one or more of the base case values for the parameters related to initial FAP stage distribution, QALYs, and costs. Additionally, we performed a threshold analysis by systematically altering treatment price to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Model Validation

We used several approaches to validate the model for patisiran. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

Results for Patisiran

Base Case Results

The base case results for patisiran are reported in Table 4.30. For the base case focused on the health care perspective, undiscounted total costs were $3,946,706 for patisiran and $371,946 for BSC, with corresponding life years of 12.3 years and 7.4 years, respectively. These estimates are within the range of what has been reported in the literature. Given the severity of hATTR, this corresponds to 8.31 QALYs for patisiran and 3.62 QALYs for BSC. When discounting both costs and outcomes at 3%, total costs were $3,173,084 for patisiran and $312,062 for BSC, with corresponding life years of 9.7 years and 6.3 years, respectively. Quality adjustment of these life years produces estimates of 6.54 QALYs for patisiran and 3.11 QALYs for BSC.

For the base case focused on the modified societal perspective, undiscounted total costs were $4,182,277 for patisiran and $517,420 for BSC. When discounting both costs and outcomes at 3%, total costs were $3,355,304 for patisiran and $432,031 for BSC.

Table 4.30. Results for the Base Case for Patisiran Compared to Best Supportive Care

	Undiscounted			Discounted		
	Total Costs	Life Years	QALYs	Total Costs	Life Years	QALYs
Health Care Sector Perspective						
Patisiran	$3,946,706	12.3	8.31	$3,173,084	9.7	6.54
Best Supportive Care	$371,946	7.4	3.62	$312,062	6.3	3.11
Modified Societal Perspective						
Patisiran	$4,182,277	12.3	8.31	$3,355,304	9.7	6.54
Best Supportive Care	$517,420	7.4	3.62	$432,031	6.3	3.11

The model produces incremental cost-effectiveness ratio estimates for patisiran that are above commonly cited thresholds of $50,000 - $150,000, at approximately $835,000 per QALY gained. On a per life-year basis, results were approximately $850,000 for patisiran. The results in Table 4.31 show that the incremental cost-effectiveness ratios computed from a modified societal perspective are also high at approximately $850,000. On a per life-year basis, corresponding results were approximately $870,000.

Table 4.31. Incremental Cost-Effectiveness Ratios for Patisiran Compared to Best Supportive Care, Discounted at 3%

Incremental	Patisiran vs. BSC
Incremental Costs	
Health Care Sector Perspective	$2,861,022
Modified Societal Perspective	$2,923,273
Incremental Outcomes	
Life years (LY)	3.36 years
QALYs	3.43 QALYs
Incremental Cost-Effectiveness Ratios (Life years)*	
Health Care Sector Perspective	$852,000
Modified Societal Perspective	$871,000
Incremental Cost-Effectiveness Ratios (QALYs)*	
Health Care Sector Perspective	$835,000
Modified Societal Perspective	$853,000

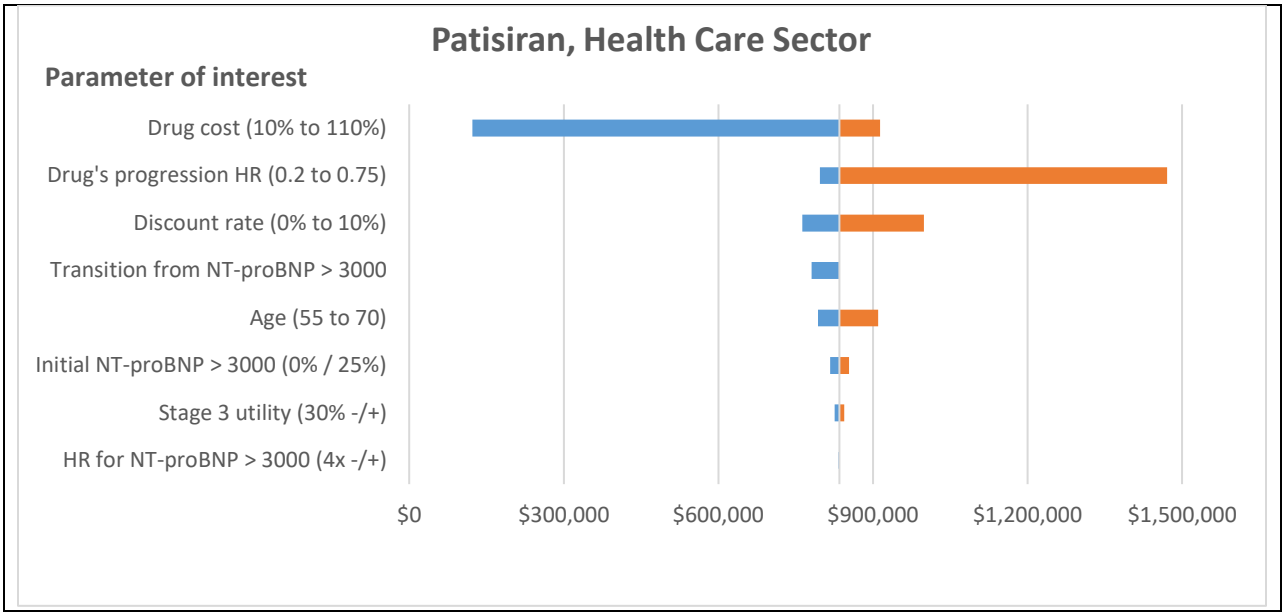
* Note: Incremental cost-effectiveness ratios reported may not be identical to those computed because of rounding.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per QALY. The tornado diagram below shows that patisiran's treatment cost and disease progression are key drivers of the economic results. This finding holds for both the health care sector and the modified societal perspectives. The diagram also shows that there are some unknown parameters that do not appear to affect the incremental cost-effectiveness ratio's magnitude (over the range they were varied). These findings are shown by horizontal bars that have very short lengths.

The tornado diagram below illustrates the parameters of interest, with corresponding values producing a low and high incremental cost-effectiveness estimate. These values are located under the "parameter of interest" column in the figure. The "Transition from NT-proBNP > 3,000" parameter has been set at 50% or 0%. At 50%, the model assumes that 50% of patients with NT-proBNP > 3,000 transition to having NT-proBNP $\leq$ 3,000. The base case incremental cost-effectiveness ratio was produced by setting the "Transition from NT-proBNP > 3,000" parameter at 0%. This explains why the parameter only has a 'low' value (left bar); the 'high' value reflects the base case. Results are presented for the health care sector perspective below. Diagrams for the modified societal perspective are available in Appendix D.

Figure 4.4. Tornado Diagrams for One-Way Sensitivity Analyses of Incremental Cost-Effectiveness Ratios for Patisiran versus Best Supportive Care from the Health Care Sector Perspective



Using a health care sector perspective, the results from the probabilistic sensitivity analysis strongly suggest that patisiran does not achieve cost-effectiveness results consistent with conventional levels of willingness to pay. The results in the table below show that probability of patisiran being cost-effective is less than 1% across the range of thresholds from $50,000 to $250,000.

Table 4.32. Probabilistic Sensitivity Analysis Results: Patisiran versus Best Supportive Care, Health Care Sector Perspective

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
Patisiran	< 1%	< 1%	< 1%	< 1%	< 1%

In the cost-effectiveness acceptability curves (CEACs) presented in Appendix D, we explore the probability of cost-effectiveness by varying willingness to pay up to $1 million per QALY gained.

Scenario Analyses Results

The scenario analyses change variables to consider different scenarios. The rows of the table describe which variables have been changed from their base case values.

Assumptions about quality of life utility values can increase the incremental cost-effectiveness ratio by over $100,000. For example, by using the base case values found in the York ERG's report, the model's incremental cost-effectiveness ratio approaches $960,000. A "worst-case" scenario built on the findings in Stewart et al. also produces an incremental cost-effectiveness ratio that is more

than $100,000 greater than the model's base case estimate.[103] In addition, the model is sensitive to other utility assumptions.

We assumed that the difference in QOL-DN by FAP stage by treatment could be represented by a difference in quality of life utility scores (i.e., patients in the same FAP stage could have different QALY utility scores due to treatment). The scenario analysis "Differential Utility by Treatment" explores the effect of this assumption by varying the size of the benefit and the time over which the benefit accrues. The results show that our base case assumptions are consequential; without them the incremental cost-effectiveness ratio is more than $1.1 million. In contrast, health care costs appear inconsequential. Varying the "disease-specific direct medical costs" did not change the incremental cost-effectiveness ratio by much, given the drug's high cost.

Table 4.33. Scenario Analysis Results: Patisiran versus Best Supportive Care, Health Care Sector Perspective

Scenarios	Incremental Costs (ΔC)	Incremental QALYs (ΔQALY)	ICER* (ΔC/ΔQALY)
Base Case	$2,861,022	3.43	$835,000
1. Different FAP Stage Utilities			
York ERG Report (Stage 1 = 0.636; Stage 2 = 0.501; Stage 3 = 0.375)	$2,861,022	2.98	$961,000
Stewart et al.[103] worst-case scenario (Stage 1 = 0.570; Stage 2 = 0.410; Stage 3 = 0.050)	$2,861,022	2.92	$980,000
2. Differential Utility by Treatment			
No Utility Gain From TQoL Gain	$2,861,022	2.58	$1,110,000
3. Disease-Specific Direct Medical Costs			
Half All Health Care Costs	$2,829,930	3.43	$826,000
Double All Health Care Costs	$2,923,205	3.43	$853,000

* Note: ICERs reported may not be identical to those computed because of rounding.

Threshold Analysis Results

The table below reports the dose price or "unit price" to achieve incremental cost-effectiveness ratio thresholds. When there is no drug price that will achieve a threshold, "None" is reported. These results suggest that significant discounts from the assumed price are required to achieve commonly-cited thresholds. For example, annual drug costs of approximately $200,000 would be required to achieve a threshold of $500,000 per QALY for patisiran, below the assumed price of $345,000. Similar magnitudes of reduction are needed when considering annual drug cost from a societal perspective.

Table 4.34. Threshold Analysis Results, Per Patisiran Dose (Only Drug Cost)

Perspective	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $250,000 per QALY	Unit Price to Achieve $500,000 per QALY
Health Care	$167	$1,421	$2,675	$5,182	$11,450
Modified Societal	None	$966	$2,219	$4,726	$10,994

4.4 Model Validation

Model validation for both models followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Published Evidence on Costs and Cost-Effectiveness

We identified one prior publicly available, UK-based cost-effectiveness analysis of treatment for hATTR amyloidosis (called transthyretin familial polyneuropathy at the time), from the University of York Evidence Review Group assessment of a manufacturer submission for tafamidis.[34] While our current model is similar in structure to this earlier one, there are several important differences, including the treatments and populations analyzed, with the V30M mutation predominant in the tafamidis analysis. Unlike the earlier model, our current analysis accounts for NT-proBNP, excludes the option of liver transplantation, and allows for regression to earlier FAP stage (as well as progression to later stages) and for changes in patients' utility within FAP stage (rather than only between stages). Estimates of mean QALYs from BSC were similar in the two models (2.92 in the York base case and 3.11 and 3.86 in our base case for patisiran and inotersen, respectively). We did not directly compare the other results from this analysis to those from ours, given the differences in treatments evaluated, and in costs and other inputs between the US and UK settings.

4.5 Summary and Comment

The two models produced results suggesting improved quality-adjusted life years accompanied by increased costs from the new treatments for hATTR amyloidosis. We also found that the choice of the modified societal perspective, with its inclusion of productivity costs and losses, increased the total incremental costs for new treatments, and therefore increased cost-effectiveness ratios slightly. In all four of the base cases, the incremental cost-effectiveness ratios were beyond levels normally considered good value for money. Given the high additional treatment cost (i.e., $345,000 each year in drug costs alone), new treatments will need to be accompanied by extremely large corresponding QALY benefits in order to obtain incremental cost-effectiveness ratios below standard thresholds.

The tornado plots provide evidence that the biggest driver of the value of new treatment appears to be the treatment's cost. The disease has profound quality of life impacts, and quality of life utility assumptions do appear to impact the results according to the scenario analysis results. However, the model's optimistic assumptions (compared with those made by others reporting utilities used for QALYs), do not result in incremental cost-effectiveness ratio estimates below $800,000 per QALY.

Limitations

This study had several limitations. First, hATTR amyloidosis is a rare disease and underlying disease models are necessarily built with limited data on natural history and disease-related costs. The economic model estimates the costs and outcomes for populations reflected in the clinical trials, so the fact that approximately 25% of hATTR patients who have diabetes and long-term dexamethasone use may be contraindicated did not affect the calculations. The only cost and QALY data available were reported by FAP stage. This motivated the decision to build a model with costs and QALYs guided by FAP stage. Second, we were limited in measures of effectiveness for hATTR to those measures that were captured in the clinical trials as outcomes (i.e., FAP stage changes), as well as in the types of measures that could be linked to quality of life. In addition, adverse events were not included in this model, which may therefore have overstated cost-effectiveness. Finally, limited available evidence on cardiac parameters, as well as on the benefits of treatment on cardiac outcomes, precluded full estimation of these parameters in the model. Future economic evaluations may have access to more data, providing an evidence base for the claims and assumptions related to the model.

Additionally, costs and quality of life measures have not, to our knowledge, been studied comprehensively for this specific population; therefore, we assumed similarities between this population and people in other studies of hATTR. With a large number of genetic variants, the interplay of neuropathic and cardiac elements of hATTR, and only short-term data, this model relies on several assumptions and extrapolation from our current knowledge.

Conclusions

For ultra-rare diseases, it should be noted that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that may lead to coverage and funding decisions at higher cost-effectiveness ratios. However, at the current assumed prices, neither treatment option is economically attractive at either standard or higher cost-effectiveness thresholds. As a result, substantial price discounts and additional study are indicated.

5. Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements are listed in Table 5.1, and the subsequent text provides detail about the elements that are applicable to the comparison of inotersen and patisiran versus usual care.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving the patient's ability to return to work and/or their overall productivity.
This intervention will have a significant positive impact outside the family, including communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

As of July 2018, treatment options for hATTR patients were limited to an off-label treatment that does not address the underlying cause of disease, or liver transplant for a minority of patients with certain TTR genotypes. Neither treatment effectively targets disease symptoms or progression. According to our stakeholders, the most important factors for treatment relate to the impact a treatment can have on slowing the underlying disease and improving symptoms. While patients would desire significant outcomes, they still highly value what might be perceived as 'modest' improvements in their health condition.

Patisiran and inotersen are the first disease-modifying treatments to be developed for this patient population and for which there have been clinical studies demonstrating benefit. Thus, these treatments offer significant hope to patients and their families. This is especially so given the context of the disease being hereditary, the negative impact it has on patients and caregivers' quality of life, and there being no other approved alternatives available with which to treat the disease.

Inotersen and patisiran also offer reduced complexity that may significantly improve patient outcomes. Both treatments will require patients to consider the potential benefits and risks, including potential side effects as well as treatment frequency and administration.

Because patisiran and inotersen have the potential to slow and/or reverse disease progression, these new treatments may positively impact caregiver and family burden. However, evidence showing impact on caregiver and family burden is not yet available. Stakeholder research with patients and families shows that disease progression has a considerable impact on patients' ability to remain at work. Many patients eventually stop working due to symptoms of the disease, notwithstanding early mortality.[100] Others reduce their working hours, often as an initial step, before stopping work altogether. Drugs which can slow disease progression and reduce symptom burden can therefore potentially have a significant impact on remaining at work, returning to work, and/or overall productivity in the hATTR population. Further, hATTR is a hereditary disease that affects generations of families. It is not unusual for multiple members of an extended family to be living with active disease at any one time and the impact extends to their children both as caregivers and as future patients who may also develop the disease.

Patients also voiced a strong preference for a local or home-based treatment option. Patients and caregivers expressed concern about fatigue and taking time off work should frequent travel be required. As treatments that can stabilize the disease and be administered at home (either as an injectable or as an infusion) as an option, both patisiran and inotersen therefore offer highly valuable potential treatment options to patients and caregivers. However, patients and caregivers also said that a current lack of alternatives means they would be willing to put up with some inconvenience and that efficacy is the most important consideration overall.

Treatments which can slow progression and minimize the effect of symptoms may have multi-faceted benefits – beyond work and productivity-related benefits. One patient eloquently described how her father was only able to attend one football game for his oldest grandson. "*He was in a wheelchair, bundled to keep the cold away. He was unable to stay for the whole game, as exhaustion set in. He was 56 years old at that time. Dad loved football and waited each week for his grandson to tell him about the details of the game. He was never able to attend after that partial game. The disease robbed him of being the grandfather he longed and wanted to be*." New treatments have the potential to enable patients with hATTR to derive greater enjoyment of family life. These therapies also have the potential to reduce health disparities in the future. The V122I mutation disproportionately affects African Americans in the US, causing a cardiomyopathy-predominant presentation. If these therapies are able to improve cardiac outcomes, this could lead to a reduction in racial disparities in heart failure-related morbidity and mortality. Yet if the cost of treatment is significant, those with limited financial resources may find it difficult to afford treatment. Many patients with hATTR expressed concern about affordability of these new medications.

5.2 Contextual Considerations

Patisiran and inotersen represent the first new treatments to address the underlying cause of symptoms and that have the potential to reverse the damage already caused by amyloid deposits. The arrival of any new treatment option is seen as a positive in a disease with no known cure.

Patisiran and inotersen are intended for a patient population with a particularly high lifetime burden of illness and a severe impact on length of life and/or quality of life. Given that hATTR is a hereditary illness, patients often are caregivers for sick family members prior to, or during, their own illness. Notably, patisiran and inotersen have the potential to be novel treatments approved in the US for patients with this condition. When compared with usual care, however, there is significant uncertainty about the long-term risk of side effects with both treatments, given the identified safety concerns with inotersen (e.g., thrombocytopenia and glomerulonephritis) and potential risks associated with long-term steroid use that may be anticipated with patisiran.

6. Value-Based Price Benchmarks

Our annual value-based price benchmarks for inotersen's and patisiran's use in adults with hereditary ATTR (hATTR) amyloidosis are presented in Table 6.1. As noted in the ICER methods document (https://icer-review.org/material/final-vaf-2017-2019/), the value-based benchmark price for a therapy is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For inotersen, price discounts of 94% to 97% from the assumed placeholder list price would be required to reach the $100,000 to $150,000 per QALY threshold prices. For patisiran, price discounts of 90% to 95% from the list price would be required to reach the $100,000 to $150,000 per QALY threshold prices.

Table 6.1. Value-Based Benchmark Prices for Inotersen and Patisiran

	List Price	Net Price	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Discount from List Price to Reach Threshold Prices
Inotersen	$450,000*	$345,000*	$15,275	$25,379	94% to 97%
Patisiran	$450,000	$345,000	$24,700	$46,488	90% to 95%

QALY: quality-adjusted life year

*Assumed placeholder price for inotersen

7. Potential Budget Impact

7.1 Overview

We used results from the same model employed for the cost-effectiveness analyses to estimate the total potential budgetary impact of inotersen and patisiran in adults with hereditary ATTR (hATTR) amyloidosis. We used the estimated placeholder price of $300,000 for each drug, and the cost-effectiveness threshold prices at $50,000, $100,000, and $150,000 per QALY in our estimates of budget impact. Note that the placeholder price is simply an estimate that may not reflect the actual prices at launch, and therefore the actual budget impact of these drugs may differ.

7.2 Methods

Potential budget impact was defined as the total differential cost of using inotersen or patisiran plus best supportive care, rather than best supportive care alone for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate population eligible for treatment: adults with hATTR amyloidosis. To estimate the size of the potential candidate population for treatment, we used an estimate of 1 per 100,000 in the US, which would put the US prevalence at approximately 3,250 individuals.[37] We assumed equal uptake over each of the five years, meaning 650 patients would initiate treatment each year.

ICER's methods for estimating potential budget impact are described in detail here and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, we assumed that inotersen and patisiran would each be added to best supportive care rather than replacing best supportive care in the eligible patients being treated.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in

ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2018-19, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2018 (est.) +1%	3.5%	World Bank, 2018
2	Total health care spending, 2017 ($)	$2.88 trillion	CMS NHE, 2018
3	Contribution of drug spending to total health care spending (%)	17.0%	CMS National Health Expenditures (NHE), 2018; Altarum Institute, 2017
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$481 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$16.8 billion	Calculation
6	Average annual number of new molecular entity approvals, 2016-2017	34	FDA, 2018
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$495.3 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$991 million	Calculation

7.3 Results

Table 7.2 illustrates the per-patient budget impact calculations for inotersen in adults with hATTR amyloidosis, compared to best supportive care. Potential budget impact is presented based on the placeholder list price ($450,000 per year), the placeholder net price ($345,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($25,379, $15,275, and $5,171 per year, respectively).

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Inotersen Treatment of Adults with hATTR Amyloidosis

	Average Annual Per Patient Budget Impact				
	Placeholder List Price	Placeholder Net Price	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Inotersen + Best Supportive Care	$359,655	$284,129	$54,230	$46,962	$39,694
Best Supportive Care	$36,741				
Difference	$322,914	$247,388	$17,489	$10,221	$2,953

QALY: quality-adjusted life year

The average potential budgetary impact when using the placeholder list price for inotersen ($450,000) was an additional per-patient cost of approximately $322,900 and was approximately $247,400 when using the placeholder net price ($345,000). At the three cost-effectiveness threshold prices (at $50,000, $100,000, and $150,000 per QALY), average potential budget impact would range from approximately $17,500 per patient using the annual price ($25,379) to achieve $150,000 per QALY to approximately $3,000 using the annual price ($5,171) to achieve a $50,000 per QALY cost-effectiveness threshold.

Table 7.3 illustrates the per-patient budget impact calculations for patisiran in adults with hATTR amyloidosis, compared to best supportive care. Potential budget impact is presented based on the announced average list price ($450,000 per year), the expected average net price ($345,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($46,488, $24,700, and $2,911 per year, respectively).

Table 7.3. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Patisiran Treatment of Adults with hATTR Amyloidosis

	Average Annual Per Patient Budget Impact				
	List Price	Net Price	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Patisiran + Best Supportive Care	$458,772	$361,574	$85,243	$65,074	$44,903
Best Supportive Care	$39,300				
Difference	$419,472	$322,274	$45,943	$25,774	$5,603

QALY: quality-adjusted life year

The average potential budgetary impact when using the list price for patisiran ($450,000) was an additional per-patient cost of approximately $419,500 and was approximately $322,300 when using the net price ($345,000). At the three cost-effectiveness threshold prices (at $50,000, $100,000, and $150,000 per QALY), average potential budget impact would range from approximately $45,900 per patient using the annual price ($46,488) to achieve $150,000 per QALY to approximately $5,600 using the annual price ($2,911) to achieve a $50,000 per QALY cost-effectiveness threshold.

For each of the drugs, the annual potential budgetary impact of treating the entire eligible population over five years did not exceed the $991 million ICER budget impact threshold at any of these prices (Table 7.4), largely due to the relatively small number of patients eligible for treatment. However, the potential budget impact reached 59% of the threshold with inotersen treatment using the estimated placeholder list price of $450,000 per year, and 80% of the threshold with patisiran treatment when using the list price of $450,000 per year, suggesting an outsized impact relative to the number of individuals affected.

Table 7.4. Estimated Annualized Potential Budget Impact (BI) of Inotersen or Patisiran Treatment Using Different Prices Over a Five-Year Time Horizon, Assuming 650 Eligible Patients per Year

	Inotersen: Percent of Threshold	Patisiran: Percent of Threshold
List Price*	59%	80%
Net Price*	45%	62%
$150,000 per QALY Threshold Price	3%	9%
$100,000 per QALY Threshold Price	2%	5%
$50,000 per QALY Threshold Price	1%	1%

QALY: quality-adjusted life year

*Assumed placeholder price for inotersen

7.4 Access and Affordability

As illustrated in these analyses, treating the entire patient population eligible for treatment with inotersen or patisiran plus best supportive care rather than best supportive care alone is not expected to exceed the $991 million ICER budget impact threshold at WAC or lower prices (note that we used an assumed placeholder price for inotersen). As such, ICER is not issuing an access and affordability alert for these treatments.

8. Summary of the Votes and Considerations for Policy

8.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the September 13, 2018 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of inotersen and patisiran for hereditary transthyretin amyloidosis. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 1:20:58), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and other benefits and contextual considerations related to inotersen and patisiran. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

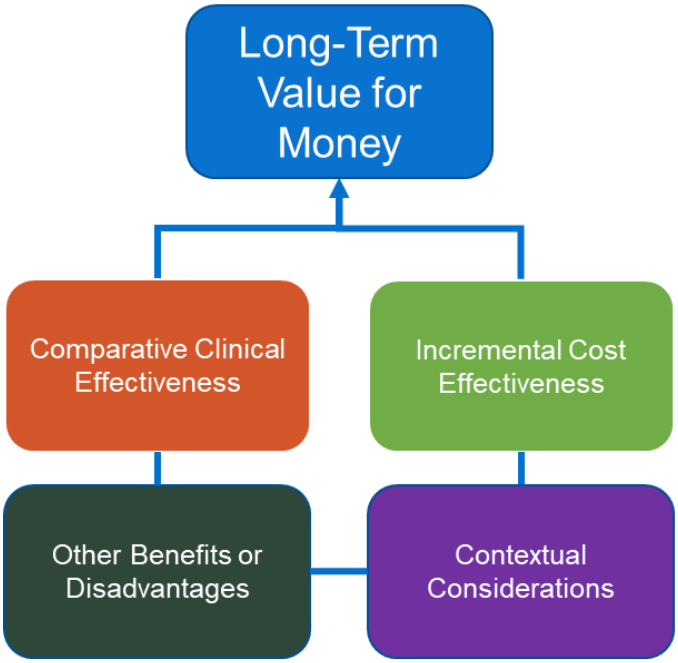
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1 Conceptual Structure of Long-term Value for Money



8.2 Voting Results

1) Is the evidence adequate to demonstrate that the net health benefit of inotersen plus best supportive care is superior to that provided by best supportive care alone?

Yes: 9 votes	**No: 2 votes**

A majority of the panel voted that the evidence was adequate to demonstrate a superior net health benefit of inotersen plus best supportive care to that provided by best supportive care alone. Some panelists in the majority emphasized that their affirmative vote was made cautiously and stated that they were swayed by the input from patients and clinicians. Other panelists in the majority cited the clarity of clinical evidence, the positive difference in result scores, and the large percent change from the baseline. The two panelists that voted in the negative cited safety concerns as the primary justification for their vote.

2) Is the evidence adequate to demonstrate that the net health benefit of patisiran plus best supportive care is superior to that provided by best supportive care alone?

Yes: 10 votes	**No: 1 vote**

A majority of the panel voted that the evidence was adequate to demonstrate a superior net health benefit of patisiran plus best supportive care to that provided by best supportive care alone. The panelists in the majority stated that their reasoning was similar their justifications for an affirmative vote in Question 1. The panelist that voted in the negative argued that the generalizability of the results was problematic, especially combined with the lack of minimum clinically important differences in the outcomes measures used in the trials.

3) Is the evidence adequate to distinguish the net health benefit between inotersen and patisiran when added to best supportive care?

Yes: 1 vote	***No: 10 votes***

A majority of the panel voted that the evidence was inadequate to distinguish the net health benefit between inotersen and patisiran when added to best supportive care. The panel was unable to distinguish between inotersen and patisiran because there were no direct comparisons in the report because the populations and outcome measures were different for the treatments. On average, inotersen patients were younger than patisiran patients, and inotersen patients tended to be in Stage 1, whereas patisiran patients were split between Stages 1 and 2. Additionally, the two modified NIS+7 scores differed in total score and had differences in evaluated domains.

4) When compared to best supportive care alone, does the addition of inotersen or patisiran offer one or more of the following "other benefits"?

Other Benefits	Number of Votes
This intervention offers reduced complexity that will significantly improve patient outcomes.	3/11
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	0/11
This intervention will significantly reduce caregiver or broader family burden.	10/11
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	11/11
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.	8/11
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	3/11
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	4/11
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	4/11

The panel unanimously recognized that the novel mechanism of action was an important other benefit offered by the addition of inotersen or patisiran to best supportive care. A majority also recognized that the new treatments may reduce family and caregiver burden and may improve a patient's ability to return to work. These panelists emphasized that the burden that a hereditary disease places on families cannot be understated, and that these new treatments may also have a positive psychological effect on multiple generations of a family. A number of panelists also argued that the treatments may have a large impact on the entire "infrastructure" of care by slowing disease progression, increasing the likelihood of early detection and treatment, and contributing to better awareness of the disease.

A few panelists offered additional important benefits, including the potential for local or home-based therapy, a reduction in travel time to a treatment center, and a potential decrease in anxiety and depression. Other panelists noted that the long-term financial implications are substantial and noted that many patients with amyloidosis are unable to work and thus have difficulty maintaining health insurance coverage. One panelist argued that the new treatments may exacerbate health disparities due to racism and socioeconomic prejudices in the healthcare system.

5) Are any of the following contextual considerations important in assessing inotersen's or patisiran's long-term value for money in patients?

Contextual Considerations	Number of Votes
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	10/11
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	11/11
This intervention is the first to offer any improvement for patients with this condition.	8/11
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	9/11
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	10/11
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	2/11

The panel unanimously recognized that inotersen and patisiran are intended for the care of individuals with a high lifetime burden of illness, and a near majority also recognized that the treatments are intended for individuals with a particularly high severity of illness. A number of panelists argued that the treatments were the first to offer improvement for patients with amyloidosis. These panelists emphasized that the only other available treatment for the condition is a liver transplant, which isn't available to most patients with the disease.

However, because inotersen and patisiran utilize new technology, many panel members expressed concern regarding the uncertainty about the long-term risks of side effects and the durability or magnitude of long-term benefits. One panelist noted that the development of anti-inotersen antibodies in the trial was concerning, leading to questions about the long-term safety of the treatment. Another panelist expressed some concern regarding long-term safety, but argued that given the progressive nature of the disease, the level of durability shown in the results was sufficient. Two panelists offered an additional contextual consideration, noting that the high cost of treatment should be considered when assessing the long-term value for money.

6) For adults with hereditary transthyretin amyloidosis, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of inotersen plus best supportive care compared with best supportive care alone?

High: 0 votes	Intermediate: 0 votes	*Low: 11 votes*

The panel unanimously judged the long-term value for money to be "low" for treatment with inotersen plus best supportive care versus best supportive care alone. The panel emphasized that their "low" vote was pointed primarily toward the cost of treatment, not necessarily the clinical effectiveness of either intervention. Some panelists noted that even though the treatments offer

substantial utility, the cost is too far above the threshold compared to other treatments for similar diseases. Other panelists argued that even with several large assumptions, the cost per QALY is still too high, which is indicative of just how expensive the treatment is.

7) For adults with hereditary transthyretin amyloidosis, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of patisiran plus best supportive care compared with best supportive care alone?

High: 0 votes	Intermediate: 0 votes	*Low: 11 votes*

The panel unanimously judged the long-term value for money to be "low" for treatment with patisiran plus best supportive care versus best supportive care alone. The panel offered the same rationale as in the previous "low" vote, reiterating that the cost of treatment is too high to justify an "intermediate" or "high" vote, even though the treatment offers clinical benefits. Several panel members also repeated the argument that even with substantial assumptions, the treatment is not cost-effective.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on inotersen and patisiran for hATTR amyloidosis to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, one payer, and two representatives from manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 8.1 Policy Roundtable Members

Name	Title and Affiliation
John Berk, MD	Associate Professor of Medicine, Amyloidosis Center, Boston University
Joel Buxbaum, MD	Consulting Chief Medical Officer, Misfolding Diagnostics; Professor Emeritus, Molecular Medicine, The Scripps Research Institute
Alan Eisenberg, MPP	Vice President, Global Government Relations & Public Policy, Alnylam Pharmaceuticals
Young Fried, PharmD, MSP	Vice President, Pharmacy Plan Services, HealthPartners
Kristen Hsu	Executive Director, Clinical Research, Amyloidosis Research Consortium
Dustin Kaehr	Director, Leadership Development, Lippert Components; Patient Advocate
Michael Pollock	Vice President, Global Market Access, Akcea Therapeutics

The roundtable discussion was facilitated by Dan Ollendorf, PhD, Chief Scientific Officer of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers

1. ***Given that newly approved treatments for hATTR amyloidosis have new mechanisms of action, lack long-term safety and efficacy data, and are very expensive, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments.***

2. ***Payers should negotiate discounts to seek the best value for patients and the health system by bringing the net price of these treatments closer to traditional cost-effectiveness ranges. Savings achieved through these negotiations should be shared with patients to reduce the financial toxicity of long-term treatment.***

3. ***Payers and other policymakers seeking to judge the value of patisiran and inotersen should recognize the heightened responsibility to consider the treatments' broader benefits to patients, caregivers, and society while simultaneously working to maintain affordability of health insurance for all patients now and in the future.***

4. ***Given that clinicians cannot predict which treatment will be most effective for any individual patient, payers may be able to achieve lower prices for the health system and for patients by applying a step therapy policy favoring the less expensive treatment. In considering whether to adopt this approach, however, payers must be aware that the differences in delivery mechanism for these drugs, along with other factors, may lead one drug to be highly preferable for certain patients.***

5. ***Prior authorization criteria should be based on clinical evidence, with input from clinical experts and patient groups. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.***

   <u>Potential patient eligibility criteria:</u>

   i. **Diagnosis.** Given that there are non-genetic forms of amyloidosis, a one-time requirement to confirm the diagnosis of hATTR through genetic testing should be considered. The FDA label for patisiran (and the expected one for inotersen) includes all patients with polyneuropathy caused by hATTR amyloidosis, but cardiomyopathy may be the dominant, or in some cases, the only symptomatic feature of the condition for some patients. Limiting

treatment to patients with demonstrated polyneuropathy is likely to be viewed as unreasonable by clinical experts and patients.

ii. **Severity.** Clinical benefits of treatment have been evaluated only in patients with symptomatic disease. Payers may therefore consider establishing "symptomatic" disease as a criterion for coverage, particularly if genetic testing of asymptomatic patients begins to uncover a much larger population of asymptomatic individuals among whom the penetrance of the genetic abnormality is unclear. However, as a progressive disorder, treatment of asymptomatic patients may be viewed as highly desirable by some patients and clinicians, even though there may be substantial uncertainty regarding the onset and severity of symptoms in asymptomatic individuals.

iii. **Comorbidities.** Patients enrolled in the clinical trials were symptomatic but also had anticipated survival of at least two years and had stable liver function. Perhaps the most difficult coverage issue will be whether patients nearing the need for liver transplantation, or those who have already had liver transplantation, should be eligible for coverage. Patients with prior transplantation were not eligible for the clinical trials, and therefore it is not known whether these patients would benefit from treatment or not. Clinical experts, however, believe these patients should be considered eligible for a trial of therapy.

iv. **Prior treatment course.** A prominent clinical expert at the CEPAC meeting argued that it is reasonable to treat many patients immediately after diagnosis with an oral stabilizer medication (diflunisal) first, and if symptoms worsen begin treatment with patisiran or inotersen. There is no official endorsement of this clinical algorithm from specialty societies or consensus groups at the current time, but it is not unreasonable for payers to have a discussion with a clinician writing an initial prescription for patisiran or inotersen to determine whether a trial of diflunisal would be reasonable.

Potential provider criteria:

i. **Specialty designation.** Few clinicians will see a single case of hATTR amyloidosis in their career, and there is no single specialty that encompasses the care for patients with this condition. Therefore, it does not seem useful to create a specialty edit in coverage policy. There are numerous centers of excellence (COE) in the care of patients with hATTR scattered across the US that are recognized by patient advocacy groups, but comment at the CEPAC meeting suggested that limiting coverage to specialists at these centers would be too restrictive to provide adequate access, especially given that the care of patients with hATTR amyloidosis is ongoing over many years and a COE approach would require too much travel. One potential approach would be to be limit prescribing to specialists with experience caring for patients with hATTR, or providers who attest that they are working in consultation with such specialists. The Amyloidosis Research Consortium offers a tool to identify treatment centers and includes tailored language about the capabilities of the treatment centers: https://www.myamyloidosispathfinder.org/.

Potential limitations on initial length of coverage/stopping rules:

i. Adequate response to these new treatments may require 9-12 months to determine. Ascertainment of response is particularly challenging because clinical symptoms do not always mirror changes in TTR levels in the blood. Therefore, prior to continuing long-term treatment it is reasonable for payers to seek attestation that patients are realizing some benefit from treatment. A conclusive stopping rule, however, cannot be determined.

Manufacturers

6. ***Manufacturers should bring the price for innovative treatments for hATTR down to a level that aligns fairly with the added benefits for patients. Pricing aligned with clinical value is more likely to provide superior access for patients over the long term, and in the short term would lessen the financial toxicity experienced by patients and families. While the overall cost of treating the 3000-3500 hATTR patients in the US with new therapies may be affordable to the health care system as a whole, the US health care system cannot afford to pay prices far above traditional cost-effectiveness levels for the growing tide of treatments for ultra-rare disorders.***

   All manufacturers should abandon claims that their prices are aligned with benefits to patients without presenting an empirical analysis that can be debated in public. Similarly, manufacturers should not resort to vague arguments that prices are justified by the need to invest in future research.

7. ***The high level of uncertainty regarding the long-term safety and effectiveness of patisiran and inotersen suggests that a reasonable price should be lower at the launch of these drugs and only rise to full value-based levels after more robust demonstration of their overall benefits for patients and families.***

Manufacturers and Payers

8. ***Within their means, patients are willing to pay a reasonable amount for one of the new treatments for hATTR. However, co-insurance with high deductibles and other benefit design features leave patients at high risk for financial toxicity, especially since these treatments do not cure the illness and likely must be taken for life. Payers, manufacturers, and those who design health benefits need to recognize the seriousness of financial toxicity for patients and families and seek new approaches to eliminate this burden.***

   Financial toxicity for patients and their families is an important feature of the hATTR landscape. Although the progress in clinical treatment innovation has been welcomed by

all, the combination of extraordinarily high prices and an insurance structure that often requires significant cost sharing by patients results in financial toxicity that affects families significantly year after year.

Patient Advocacy Organizations

9. ***Patient organizations that have a leading role in funding, organizing, and promoting innovative research on new treatments should demand commitments from manufacturers for reasonable value-based pricing of the products patients helped bring to the market.***

   Patient advocacy groups for hereditary amyloidosis are well organized and active. As the field moves beyond the push to get initial treatments approved in the US, these advocacy groups should recognize and exercise their power to influence pricing in order to improve long-term access and affordability.

10. ***Patient organizations should also work with payers to ensure that they understand how diverse the patient population with hATTR is and how important access to effective treatments will be for individuals and their families.***

Providers

11. ***Specialists involved in the care of hATTR should rapidly convene, in partnership with patients, manufacturers, and payers, to develop evidence-based guidelines for appropriate use of new agents.***

    Payers will look to the clinical community to help define appropriate treatment pathways for patients with hATTR, including options for the appropriate use of new, expensive drug treatments. As part of this effort, clinical experts should help define a core set of validated clinical outcome measures for incorporation into future research and provide guidelines for treatment algorithms that can help specify whether step therapy with TTR stabilizers is appropriate for some or most patients. Consensus measures of treatment response/failure are also needed to help create greater consistency across insurance coverage criteria.

12. ***Professional societies should highlight the impact on their patients of failed pricing and insurance policies and demand to be part of a public process to guide policies that balance the goals of affordability and of ample incentives for investments in future innovation.***

Future Research

13. ***Future research should address the durability of improvements in neurological function, longer-term safety, and cardiac outcomes provided by treatments for hATTR.***

    Cardiac outcomes are highly relevant given that the genetic variations of hATTR amyloidosis believed most prevalent in the US have significant cardiac manifestations.

14. ***Future research is needed to validate modified outcome measures used as the basis for regulatory approval for treatments of hATTR. In particular, research and policy development are needed to specify the absolute or relative point changes in the modified mNIS+7 that represent significant clinical differences.***

This is the first ICER review of inotersen and patisiran for hATTR.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

	#	Checklist item
METHODS		
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

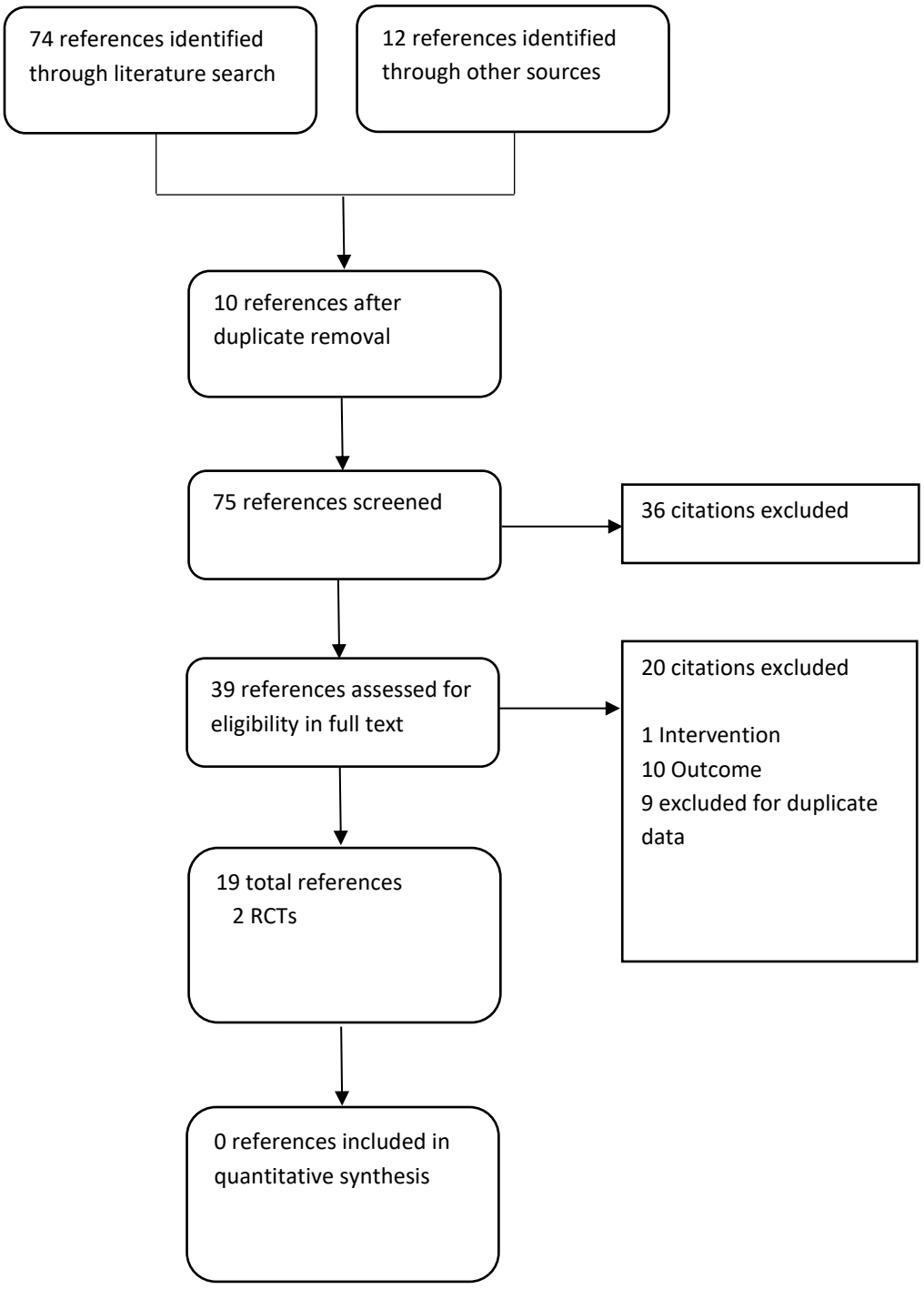
Table A2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	amyloidosis.mp.
2	patisiran.mp.
3	inotersen.mp.
4	ionis ttrrx.mp.
5	isis ttrrx.mp.
6	aln ttr02.mp.
7	rna interference.mp.
8	rnai therapeutics.mp.
9	antisense oligonucleotide.mp.
10	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	1 and 10
12	(animals not (humans and animals)).sh.
13	11 not 12
14	limit 13 to english language
15	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase i or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
16	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.
17	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
18	16 or 17
19	14 not 15
20	18 and 19

Table A3. Search Strategy of EMBASE SEARCH

#1	'amyloidosis'
#2	'patisiran'
#3	'inotersen'
#4	'ionis ttrrx'
#5	'RNA interference'
#6	'RNAi therapeutics'
#7	'antisense oligonucleotide'
#8	#2 or #3 or #4 or #5 or #6 OR #7
#9	#1 AND #8
#10	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#11	'human'/exp
#12	#10 AND #11
#13	#10 NOT #12
#14	#9 NOT #13
#15	#14 AND [english]/lim
#16	#14 AND [medline]/lim
#17	#15 NOT #16
#18	#15 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#19	#17 NOT #18

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Inotersen and Patisiran



Appendix B. Ongoing Studies

Table B1. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Patisiran					
The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of Transthyretin (TTR)-Mediated Amyloidosis in Patients Who Have Already Been Treated With ALN-TTR02 (Patisiran) **Alnylam Pharmaceuticals** **NCT02510261**	Phase III Multicenter, Open-Label, Extension Study Estimated Enrollment: 228	1. Patisiran (ALN-TTR02) administered by intravenous (IV) infusion	Inclusion Criteria • Have completed a patisiran study (i.e., completed the last efficacy visit in the parent study) and tolerated study drug • Be willing and able to comply with the protocol-required visit schedule and visit requirements and provide written informed consent Exclusion Criteria • Any new or uncontrolled condition that could make the patient unsuitable for participation	Primary Outcome Measures • Safety and tolerability of long-term dosing of patisiran as measured by the proportion of subjects with AE leading to discontinuation of study drug [Time Frame: 52 weeks] Secondary Outcome Measures • Change from baseline in Neuropathy Impairment Score (NIS) • Change from baseline in Modified NIS (mNIS +7) composite score • Change from baseline in NIS+7 • Change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire • Change from baseline in EuroQOL (EQ-5D) questionnaire • Change from baseline in nutritional status using modified body mass index (mBMI) • Change from baseline in motor function assessed by NIS-Weakness (NIS-W)	June 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Inotersen					
An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP) Ionis Pharmaceuticals, Inc. NCT02175004	Phase III open-label extension study Estimated enrollment: 135	1. Inotersen - 300 mg IONIS-TTR Rx administered once weekly	Inclusion Criteria • Satisfactory completion of dosing & efficacy assessments in ISIS 420915-CS2 Exclusion Criteria • Any new condition or worsening of existing condition that could make the patient unsuitable for participation, or interfere with the patient participating in and/or completing the study	Primary Outcome Measures • Types of AE that occur during treatment • Change from baseline in blood pressure and heart rate • Change from baseline in QTcF • Change from baseline in number of concomitant medications used • Change from baseline in visual acuity • Change from baseline in light detection ability Secondary Outcome Measures • Change from baseline in the mNIS+7 score • Change from baseline in NIS score • Change from baseline in the Norfolk Quality of Life Diabetic Neuropathy Questionnaire • Change from baseline in mBMI and BMI • Change from baseline in PND score	June 2022

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix C. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also searched for FDA documents related to inotersen and patisiran. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2).[84] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

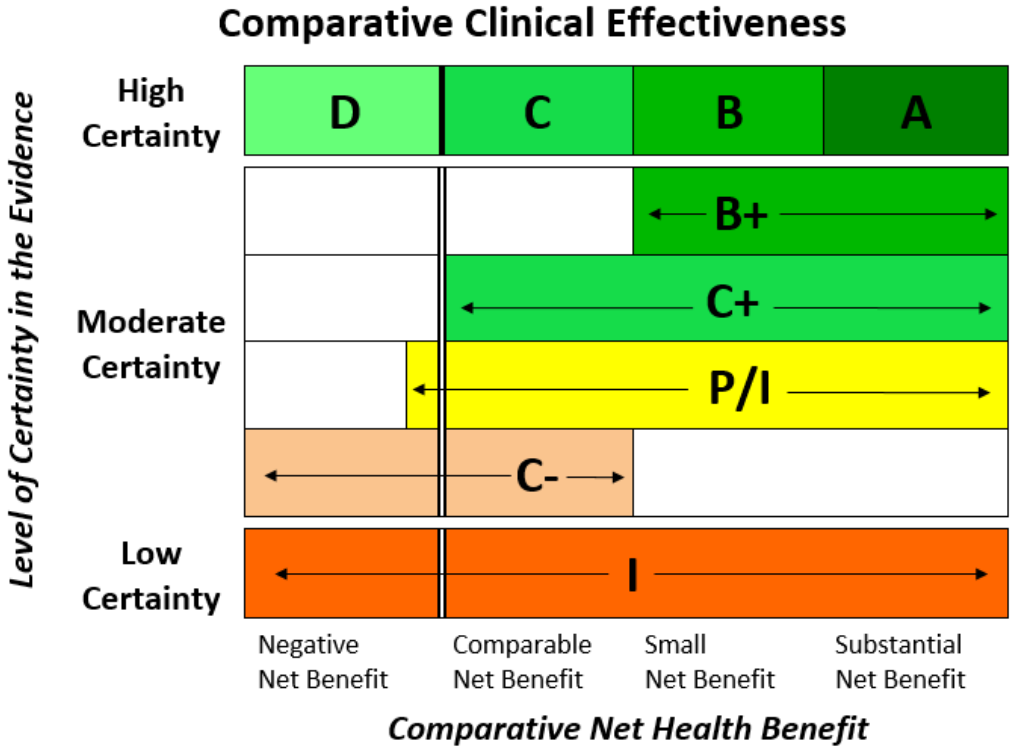
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure C1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[104]

Figure C1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table C1. Evidence Tables

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Inotersen						
Benson et al 2018[8] **NEURO-TTR** **Publication** **Fair quality**	Randomized, double-blind, placebo-controlled phase 3 study 15 months	N= 172 **Study arms** 1. Inotersen: 300 mg weekly subcutaneous doses (n=112) 2. Placebo (n=60)	**Inclusion**: • Adults in FAP Stage 1 or 2 hATTR disease; • NIS Score between 12-130 • Positive amyloid biopsy • TTR variant by genotyping • Ages 18-82. **Exclusion:** • ≥ NYHA 3 • Previous liver transplant	**Age**, years Mean (SD) 1. 59 (12.5) 2. 59.5 (14.0) **Male,** n (%) 1. 77 (69) 2. 41 (68) **Previous use of stabilizers**, n (%) 1. 63 (56) 2. 36 (60) **Cardiomyopathy subset,** n (%) 1. 75 (67) 2. 33 (55) **mNIS+7 score,** mean (SD) 1. 79.2 (37) 2. 74.8 (39) **Norfolk QoL-DN total score,** mean (SD) 1. 48.2 (27.5) 2. 48.7 (26.7) **mBMI**, mean (SD) 1. 101.1 (22.8) 2. 105.0 (22.8)	**Data are LSM change from baseline** **mNIS+7,** score (95% CI) 1. 5.8 (1.6 to 10.0) 2. 25.5 (20.2 to 30.8) Difference: -19.7 (-26.4 to -13.0) **Norfolk QoL-DN,** score (95% CI) 1. 1.0 (-3.2 to 5.2) 2. 12.7 (7.4 to 17.9) Difference: -11.7 (-18.3, -5.1) **mBMI**, LSM (95% CI) 1. -0.3 (-0.61 to 0.02) 2. -0.8 (-1.21 to 0.40) Difference: 0.50 (0.0-1.01) **Difference (inotersen vs. placebo) in LSM change from baseline Norfolk-QOL-DN at 15 months, by domain (95% CI)** Physical	**All data are n (%)** **Any AE** 1. 111 (99) 2. 60 (100) **AE related to trial regimen** 1. 87 (78) 2. 23 (38) **Any SAE** 1. 36 (32) 2. 13 (22) **SAE related to trial regimen** 1. 8 (7) 2. 1(2) **Glomerulonephritis (SAE)** 1. 3 (3) 2. 0 **Thrombocytopenia (SAE)** 1. 3 (3) 2. 0 **Deaths** 1. 5 (4.5) 2. 0

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				FAP Stage 1/Stage 2, (%) 1. 70/30 2. 66/34 **White**, n (%) 1. 105 (94) 2.55 (88) **Black**, n (%) 1. 3 (3) 2. 1 (2) **Asian**, n (%) 1. 1 (<1) 2. 3 (5) **Other or multiple**, n (%) 1. 3 (3) 2. 3 (5) **Europe**, n (%) 1. 37 (33) 2. 23 (38) **N. America**, n (%) 1. 56 (50) 2. 26 (43) **S. America or Australasia**, n (%) 1. 19 (17) 2. 11 (18)	functioning/large fiber neuropathy: -6.33 (-10.03 to -2.62) Symptoms: -2.80 (-3.34 to -1.13) Activities of daily living: -2.10 (-3.34 to -0.85) Small fiber neuropathy: 0.12 (-0.95 to 1.19) Autonomic neuropathy: -0.59 (-1.37 to 0.18 **mNIS+7 subgroup analyses (difference in LSM change from baseline, [95% CI])** Val30Met: -18.9 (-28.1 to -9.6) non-Val30Met: -21.3 (-31.1 to -11.5) Stage 1: -14.2 (-22.5 to -5.9) Stage 2: -29.1 (-40.2 to -18.0) Previous TTR stabilizer	n)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					use: -20.0 (-29.2 to -10.8) No previous TTR stabilizer use: -20.8 (-30.6 to -11.0) With cardiomyopathy: -17.2 (-25.6 to -8.7) Without cardiomyopathy: -25.5 (-36.1 to -14.3) **Norfolk-QOL-DN subgroup analyses (difference in LSM change from baseline)** Val30Met: -12.2 (-21.6 to -3.0) non-Val30Met: -11.1 (-20.9 to -1.4) Stage 1: -9.9 (-18.2 to -1.7) Stage 2: -15.0 (-26.2 to -3.9) Previous TTR stabilizer use: -9.0 (-18.2 to 0.1) p=0.05	

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					No previous TTR stabilizer use: -14.7 (-24.5 to -4.9) With cardiomyopathy: -9.0 (-17.5 to -0.6) Without cardiomyopathy: -16.4 (-27.3 to -5.4) **mBMI**, change from baseline (SE) 1. -0.30 (0.16) 2. -0.80 (0.20) LSM difference: 0.50 (95% CI 0.00 to 1.01) **Following outcomes measured in cardiomyopathy subset** **All data below are treatment difference as LSM (95% CI)** **Global longitudinal strain:** 0.20 (-1.17 to 1.56) **Ejection fraction**: -1.99 (-5.49 to 1.50)	

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					Left ventricular mass: - 2.86 (-22.13 to 16.40)	
Berk 2018[9] **NEURO-TTR** **Conference presentation slides**	**See Benson et al, 2018**	**See Benson et al, 2018**	**See Benson et al, 2018**	**TTR genotype,** n (%) Val30Met 1.56 (50) 2.33 (55) non-Val30Met 1.56 (50) 2.27 (45) **Disease Stage 1/2,** n (%) 1. 74 (66.1)/38 (33.9) 2. 42 (70)/18 (30)	**Data reported are for OLE group*, estimated from graphs** **mNIS+7 Composite score, least squares mean (SE)** Week 52: 1) 31.07 (5.83) 2) 9.05 (1.85) **NorfolkQoL-DN Total score, least squares mean (SE)** Week 52: 1) 11.3 (5.2) 2) 4.52 (2.4) *OLE included patients who switched from 1) placebo to inotersen and patients who 2) continued receiving inotersen for up to 5 years (n=135)	**Discontinuation, %** 1. 22.3 2. 13.3 **Any SAEs, %** 1. 24.1 2. 21.7 **Deaths, n (%)** 1. 5 (4.5) 2. 0
Benson et al 2017[11] **Publication**	Investigator-initiated, open-label study in patients with	N=22 Study arms 1. Inotersen 300mg by weekly subcutaneous	**Inclusion** • Biopsy-proven transthyretin amyloidosis • Signs of chronic	**Data reported are interim; reporting only hATTR, not wild-type** **Age,** years	**Data reported are interim** **NYHA Class,** n (%) Class I: 8 (100)	**Injection site reactions** n (%) 1. 5 (33%) **Platelets >100K*,** n (%)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
	cardiomyopathy Included patients with hATTR and wild-type TTR amyloidosis Data are interim; targeted enrollment reported is 30 and complete study follow-up is 3 years Duration of follow-up: 1 yea	injection weekly	heart failure • Left ventricular wall thickness of ≥ 1.3 cm on transthoracic echocardiogram • Stable renal function and thyroid function **Exclusion** • Not reported	Mean (range) 1. NR (55-72) **Females,** n (%) 1. 0 **NYHA Class,** n (%) Class I: 4 (50) Class II: 4 (50) **Left ventricle mass by ECHO, g** Mean (SEM) 1. 352 (28) **Left ventricle mass by MRI, g** Mean (SEM) 1. 202 (15)	Class II: 0 **Left ventricle mass by ECHO, g** Mean (SEM) 1. 363 (27) **Left ventricle mass by MRI, g** Mean (SEM) 1. 205 (16)	1. 2 (13) *Among all participants, mean platelet decrease of 11%
Coehlo 2018[10] **NEURO-TTR** **Conference presentation**	**See Benson et al, 2018**	**See Benson et al, 2018**	**See Benson et al, 2018**	**See Benson et al, 2018**	**Difference (inotersen vs. placebo) in LSM change from baseline Norfolk-QOL-DN at 15 months (95% CI)** Physical functioning/large fiber neuropathy: -6.33 (-10.03 to -2.62)	**Serious AE, n (%)** 1. 36 (32%) 2. 13 (22%)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					Symptoms: -2.80 (-3.34 to -1.13) Activities of daily living: -2.10 (-3.34 to -0.85) Small fiber neuropathy: 0.12 (-0.95 to 1.19) Autonomic neuropathy: -0.59 (-1.37 to 0.18)	
Patisiran						
Adams et al, 2018[12] **APOLLO** **Publication** **Fair quality**	Phase III randomized, double-blind, placebo-controlled trial 44 international sites, 19 countries Duration of study: 18 months	N=225 <u>Study arms</u> 1. Patisiran, 0.3mg/kg every 3 weeks by infusion (n=148) 2. Matched placebo (n=77)	**Inclusion:** • Ages 18-85 • FAP diagnosis • Neuropathy Impairment Score of 5-130 • Meet Karnofsky performance status requirements • Adequate blood counts and liver function tests • Adequate cardiac function • Negative serology for hepatitis B virus and hepatitis C virus **Exclusion:**	**Age**, years Median (range) 1. 62 (24-83) 2. 63 (34-80) **Males**, n (%) 1. 109 (74) 2. 58 (75) **FAP Stage 1,** n (%) 1. 67 (45) 2. 37 (48) **FAP Stage 2,** n (%) 1. 81 (55) 2. 37 (51) **FAP Stage 3,** n (%) 1. 0	**mNIS+7,** LSM (SE) 1. -6.0 (1.7) 2. 28.0 (2.6) Difference: -31.0 (95% CI -39.9 to -28.1) **Norfolk QoL-DN,** score (SE) 1. -6.7 (1.8) 2. 14.4 (2.7) Difference: -21.1 (-27.2 to-15.0) **Percent reporting improvement in mNIS+7 (vs. baseline)** 1. 56%	**All data reported are n (%)** **Any AE** 1. 143 (97) 2. 75 (97) **Discontinuation due to AE** 1. 7 (5) 2. 11 (14) **Any SAE** 1. 54 (36) 2. 31 (40) **Any severe AE** 1. 42 (28) 2. 28 (36)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
			• Prior or planned liver transplantation • Untreated hypo- or hyperthyroidism • HIV infection • Malignancy in past 2 years, except for basal or squamous cell carcinoma (skin) or carcinoma in situ of cervix that was successfully treated • Recently received investigational device or agent • Currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid	2. 1 (1) **V30M early-onset**, n (%) 1. 13 (9) 2. 10 (13) **V30M, all,** n (%) 1. 56 (38) 2. 40 (52) **non-V30M,** n (%) 1. 92 (62) 2. 37 (48) **PND score I,** n (%) 1. 36 (24.3) 2. 20 (26.0) **PND score II,** n (%) 1. 43 (29.1) 2. 23 (29.9) **PND score IIIa,** n (%) 1. 41 (27.7) 2. 22 (28.6) **PND score IIIb,** n (%) 1. 28 (18.9) 2. 11 (14.3) **PND score IV,** n (%) 1. 0 2. 1 (1.3)	2. 4% **Percent reporting improvement in Norfolk-QOL-DN (vs. baseline)** 1. 51% 2. 10% **PND score change from baseline** Improvement 1. 8% 2. 0 No change 1. 65% 2. 30% **Left ventricular wall thickness** Difference: p=0.02 **Longitudinal strain** Difference: p=0.02 **mBMI**, LSM change from baseline (SD) 1. -3.7 (9.6) 2. -119.4 (14.5) Difference: 115.7 (p<0.001) **mNIS+7 subgroup**	**Deaths** 1. 7 (5) 2. 6 (8)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				mBMI, (kg/m2 x g/L) Mean (95% CI) 1.970 2. 990 **Region,** N (%) **N. America:** 1. 37 (25.0) 2. 10 (13.0) **W. Europe:** 1. 62 (41.9) 2. 35 (46.8**)** **Rest of the world:** 1. 49 (33.1) 2. 31 (40.3)	**analyses (difference in LSM change from baseline, [95% CI])** Val30Met: -37.1 (-44.8 to – 29.4) non-Val30Met: -31.7 (-40.6 to – 22.8) Stage 1: -29.7 (-37.4 to -21.9) Stage 2: -38.2 (-47 to -29.5) Previous TTR stabilizer use: -38.3 (-46.1 to – 30.5) No previous TTR stabilizer use: -29.9 (-39.1 to -20.8) With cardiomyopathy: -37.8 (-46.7 to -28.9) Without cardiomyopathy: -30.7 (-38.3 to -23.0) **Norfolk-QOL-DN subgroup analyses (difference in LSM**	

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					change from baseline) Val30Met: -21.8 (-31.1 to -12.5) non-Val30Met: -20.08 (-30.3 to -11.4) Stage 1: -18.3 (-26.1 to -10.0) Stage 2: -24.2 (-33.6 to -14.7) Previous TTR stabilizer use: -17.6 (-25.7 to -9.4) No previous TTR stabilizer use: -25.9 (-36.2 to 15.6) With cardiomyopathy: -23.0 (-32.0 to -14.0) Without cardiomyopathy: -20.2 (-29.9 to -10.5)	
Adams, 2018[15] **APOLLO** **Conference**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018** in addition to data below **Age,** years Median (IQR) 1. 60 (54-66)		**Any AE,** n (%) 1. 143 (96.6) 2. 75 (97.4) **Discontinuation d/t AE,** n (%)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
presentation				2. 62 (57-72) **mNIS+7 score, points** Mean (SD) 1. 74.6 (37.0) 2. 80.9 (41.5) **NIS score, points** Mean (range) 1. 61 (6.0 to 141.6) 2. 57 (7.0 to 125.5) **Norfolk-QoL-DN score, points** Mean (range) 1. 59.6 (5 to 119) 2. 55.5 (8 to 111)		1. 7 (4.7) 2. 11 (14.3) **SAE,** n (%) 1. 54 (36.5) 2. 31 (40.3)
Gonzalez-Duarte, 2018[20] **APOLLO** **Conference poster**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**Data reported are change from baseline** **Change in PND Score Improved**, n (%): 1. 12 (8.1) 2. 0 **No change,** n (%): 1. 96 (64.9) 2. 23 (29.9) **Worsened,** n (%): 1. 30 (20.3) 2. 32 (41.6) **Missing,** n (%):	**Any adverse event (AE),** n (%) 1. 143 (96.6) 2. 75 (97.4) **Discontinuation d/t AE,** n (%) 1. 7 (4.7) 2. 11 (14.3) **SAE,** n (%) 1. 54 (36.5) 2. 31 (40.3) **Grade 3 or 4 severity SAE, n** (%) 1. NR

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					1. 10 (6.9) 2. 22 (28.6) **Change in FAP Stage Improved,** n (%): 1. 5 (3.4) 2. 0 **No change,** n (%): 1. 112 (75.7) 2. 34 (44.2) **Worsened,** n (%) 1. 21 (14.2) 2. 21 (27.3) **Missing,** n (%): 1. 10 (6.8) 2. 22 (28.6)	2. NR **Deaths,** n (%) 1. 7 (4.7) 2. 6 (7.8) **Infusion-related reaction (IRR),** n (%) 1. NR 2. NR **Flushing,** n (%) 1. NR 2. NR **Renal effects,** n (%) 1. NR 2. NR **Thrombocytopenia,** n (%) 1. NR 2. NR
Adams, 2018[14] **APOLLO** **Conference presentation**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**Difference reported is between-arm difference** **Any hospitalization/death (CI)** HR 0.48 (0.34, 0.69) **Cardiac hospitalization/death (CI)**	

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					HR 0.54 (0.28, 1.01) **Data reported are change from baseline** *Mean mNIS+7 change by NIS quartiles (SE)* **Baseline NIS: ≥6 and <30** 1. -2.76 (2.17) 2. 20 (6.1) **Baseline NIS: ≥30 and <57** 1. -6.73 (2.77) 2. 27.4 (5.3) **Baseline NIS: ≥57 and <84.5** 1. 0.88 (3.57) 2. 31.7 (6.8) **Baseline NIS: ≥84.5 and <141.6** 1. -6.16 (3.53) 2. 32.4 (6.6)	
Slama, 2018[18] **APOLLO** **Conference poster**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018** **Median NT-proBNP, pg/ml** 1. 756.4 2. 845.7 **NT-proBNP ≤3000 ng/L (N=196)** Median NT-proBNP, pg/ml (IQR)	**See Adams et al, 2018** **NT-proBNP >3000 ng/L (N=29)** Risk for mortality (95% CI) 19.3-fold (5.9, 62.8) p-value=8.7	**See Adams et al, 2018**

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				400.1(166.65,924.10) **NT-proBNP >3000 ng/L (N=29)** Median NT-proBNP, pg/ml (IQR) 4257.2(3667.38,5949.67)		
Merlini 2018[21] **APOLLO** **Conference presentation**	Phase III randomized double-blind placebo controlled multicenter trial Duration of study: 18 months	N= 225 <u>Study arms:</u> 1. Patisiran, 0.3mg/kg every 3 weeks by infusion (n=148) 2. Matched placebo (n=77) **Cardiac Subpopulation (N=126)** **1. Placebo (n=36)** **2. Patisiran (n=90)**	**See Adams et al, 2018**	**Cardiac Subpopulation** **Age, years** Median (range) 1. 62 (43-80) 2. 60 (24-79) **Males, n (%)** 1. 30 (83.3) 2. 68 (75.6) **V30M TTR Genotype, n (%)** 1. 12 (33.3) 2. 22 (24.4) **Mean NIS score** 1. 68.7 2. 60.9 **FAP Stage 1/2, n (%)** 1. 13 (36.1)/23 (63.9) 2. 42 (46.7)/48 (53.3) **PND Score, n (%)** 1. I: 7 (19.4)	**Data reported are change from baseline** **Cardiac Subpopulation** **Norfolk QoL-DN** Individual domains **Physical functioning/large fiber** 1. 10.7 2. -0.5 **Activities of daily living** 1. 6.7 2. 0.9 **Symptoms** 1. 3 2. -0.7 **Small fiber** 1. 2.6 2. 0.4 **Autonomic** 1. 0.9 2. -0.3 **LS mean change Norfolk QoL-DN** 1. 20.4 2. -2.6 Treatment difference: -23.0	**See Adams 2018 AAN April 25**

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				II: 12 (33.3) IIIa: 12 (33.3) IIIb: 5 (13.9) 2. I: 24 (6.7) II: 28 (31.1) IIIa: 21 (23.3) IIIb: 17 (18.9) **NYHA Class I/II, n (%)** 1. 16 (44.4)/20 (55.6) 2. 34 (37.8)/56 (62.2)		
Adams, 2017[16] **APOLLO** **Conference presentation slides**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**Difference reported is between-arm difference** **NT-proBNP, ng/L** **Mean change from baseline (95% CI)** 1. −49.9 (NR) 2. 320.4 (NR) Difference: −370.2 (NR; p<0.001)	**See Adams et al, 2018**
Kristen, 2018[19] **APOLLO** **Conference poster**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**Age**, years Median (IQR) 1. 60 (54, 66) 2. 62 (57,72) **TTR genotype** N (%) Val30Met 1. 22 (24.4) 2. 12 (33.3)	**Data reported are change from baseline** **Difference reported is between-arm difference** **Longitudinal strain**, (%) **Worse** 3. 25.3	**Deaths**, n (%) 1. 7 (4.7) 2. 6 (7.8)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				non-Val30Met 1. 68 (75.6) 2. 24 (66.7) **Left ventricle mass** Median (IQR), g 1. 270.9 (216.0 to 322.8) 2. 243.7 (206.2 to 341.0) **Longitudinal strain,** (%) Median (IQR) 1. -15.1 (-17.2 to -12.6) 2. -15.5 (-18 to -12.8) **Ejection fraction**, % Median, SD 1. 60.0 (9.9) 2. 62.2 (8.6)	4. 44 **Improved** 1. 21.3 2. 8 **Stable** 1. 53.4 2. 48 **Longitudinal strain,** (%) LS Mean (SE) 1. 0.08 (0.28) 2. 1.45 (0.48)	
Suhr, 2015[22] **Phase 2** **Publication**	Phase 2 dose-ranging study Duration of follow-up: 208 days	N=29 Study arms (cohorts): 1. Two doses of 0.01 mg/kg by infusion 4 weeks apart (n= 4) 2. Two doses of 0.5 mg/kg by infusion 4 weeks apart (n=3) 3. Two doses of 0.15 mg/kg by infusion 4 weeks apart (n=3)	**Inclusion** • BMI between 17-33km/m^2 • Women of child-bearing potential must have negative pregnancy test • Agree to use appropriate contraceptives • Diagnosis of TTR amyloidosis • Adequate blood counts, liver and	**Age,** years Mean (SD) 1. 65.8 (8.96) 2. 55.7 (24.83) 3. 41.7 (2.52) 4. 58.7 (16.07) 5. 53.8 (15.6**)** **Females,** n (%) 1. 1 (25.0) 2. 0 3. 1 (33.3) 4. 4 (57.1) 5. 3 (25.0**)**	No outcomes of interest reported	**SAE,** n (%) 2 (6.9) **Infusion-related reaction*,** n (%) 3 (10.3) Note: One participant reported three SAE's (nausea, vomiting, and cellulitis) considered related to study drug *Symptoms reported included: tachycardia,

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
		4. Two doses of 0.3 mg/kg by infusion 4 weeks apart (n=7) 5. Two doses of 0.3 mg/kg by infusion 3 weeks apart (n=12)	renal function • Willing to give informed consent and comply with study requirements Exclusion • HIV infection or known or suspected bacterial, viral, parasitic, or fungal infection • Receipt of investigational agent within 30 days prior to first dose • Liver transplant • Poor cardiac function • Considered unfit for study by principal investigator • Employee or family member of the sponsor or clinical study site personnel	**Country,** n (%) W Europe: 27 (93.1) S America: 1 (3.4) US: 1 (3.4) **TTR Genotype,** n (%) Val30Met 1. 2 (50.0) 2. 2 (66.7) 3. 3 (100) 4. 6 (85.7) 5. 9 (75) **non-Val30Met** 1. 2 (50.0) 2. 1 (33.0) 3. 0 4. 1 (14.3) 5. 3 (25.0) **FAP Stage,** n (%) Stage 1: 25 (86.2) Stage 2: 4 (13.8)		decreased oxygen saturation, dizziness, abdominal pain, bronchospasm, erythema, dyspnea, chills, pallor, pyrexia, and tachypnea
Suhr 2018 [26] **Global OLE**	Global, multicenter open label extension	N= 211 Study arms:	**Inclusion**: • Adults with hATTR	**Age**, years Mean (SD)	**Data reported are change from baseline**	**Any adverse event (AE)**, n (%) 1. 119 (86.9)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
(ongoing) **Conference poster**	study Patients who completed the Phase 2 open label extension or Phase 3 APOLLO studies were eligible for enrollment 52 weeks	1. APOLLO Patisiran - 0.3 mg/kg IV every 3 weeks (n=37) 2. APOLLO Placebo IV every 3 weeks (n=49) 3. Patisiran and PBO combined population (n=211) 4. Phase 2 OLE Patisiran - 0.3 mg/kg IV every 3 weeks (n=25)	amyloidosis with polyneuropathy who participated in the Ph 2 OLE or APOLLO study.	1. 61.0 (12.1) 2. 63.5 (11.02) 3. 61.3 (12.28) 4. 58.5 (15.1) **mNIS+7 score**, points Mean (min, max) 1. 75 (8, 199) 2. 101 (22, 190) 3. 77 (3, 199) 4. 46 (3, 128) **TTR genotype** N (%) <u>Val30Met</u> 1. 56 (40.9) 2. 24 (49) 3. 98 (46.4) 4. 18 (72) <u>non-Val30Met</u> 1. 81 (59.1) 2. 25 (51) 3. 113 (53.6) 4. 7 (28) **Concurrent TTR tetramer stabilizer use,** n (%) 1. 0 2. 3 (6.1) 3. 16 (7.6)	**Difference reported is between-arm difference** **Left ventricle mass** Median (IQR), mm 3. 270.9 (216.0- 322.8) 4. 243.7 (206.2- 341.0)	2. 45 (91.8) 3. 189 (89.6) 4. 25 (100) **AE related to study drug,** n (%) 1. 30 (21.9) 2. 22 (44.9) 3. 59 (28) 4. 3 (12) **Discontinuation d/t AE**, n (%) 1. 7 (5.1) 2. 9 (18.4) 3. 16 (7.6) 4. 0 **Severe AE, n** (%) 1. 19 (13.9) 2. 16 (32.7) 3. 38 (18) 4. 3 (12) **Serious AE (SAE)**, n (%) 1. 30 (21.9) 2. 19 (38.8) 3. 55 (26.1) 4. 6 (24) **Deaths**, n (%) 1. 4 (2.9) 2. 7 (14.3) 3. 11 (5.2)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				4. 13 (52) **PND score,** n (%) <u>PND 0/PND I/PND II</u> 1. 1 (0.7)/32 (23.4)/36 (26.3) 2. 0/7 (14.3)/9 (18.4) 3. 1 (0.5)/49 (23.2)/58 (27.5) 4. 0/10 (40.0)/13 (52.0) <u>PND IIIA/PND IIIB</u> 1. 33 (24.1)/27 (19.7) 2. 8 (16.3)/17 (34.7) 3. 42 (19.9)/45 (21.3) 4. 1 (4.0)/1 (4.0) <u>PND IV</u> 1. 8 (5.8) 2. 8 (16.3) 3. 16 (7.6) 4. 0 **FAP Stage 1** No. (%) 1. 58 (42.3) 2. 14 (28.6) 3. 92 (43.6) 4. 20 (80) **FAP Stage 2** No. (%) 1. 71 (51.8) 2. 27 (55.1)		4. 0

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				3. 103 (48.8) 4. 5 (20) **FAP Stage 3** No. (%) 1. 8 (5.8) 2. 8 (16.3 3. 16 (7.6) 4. 0 **NIS score**, points Mean (min,max) 1. 62 (2, 162) 2. 82 (12, 158) 3. 64 (0, 162) 4. 36 (0, 88.6)		
Gillmore, 2018[27] **Global OLE** **Conference abstract**	Global, multicenter open label extension study Patients who completed the Phase 2 open label extension or Phase 3 APOLLO studies were eligible for enrollment Data reported is by previous trial	N= 211 <u>Study arms:</u> 1. APOLLO PBO - 0.3 mg/kg IV every 3 weeks (n=49) 2. APOLLO Patisiran - 0.3 mg/kg IV every 3 weeks (n=137) 3. Ph 2 OLE Patisiran - - 0.3 mg/kg IV every 3 weeks (n=25)	**See Suhr 2018**	**mNIS+7 score**, points Mean (range) 4. 77 (3-199) **NIS score**, points Mean (range) 4. 64 (0-162) **TTR genotype** N (%) <u>Val30Met</u> 4. 46 **PND type,** % 4. PND I, 0.5 PND II, 28 PND IIIA, 20	**Data reported are change from baseline** **Difference reported is between-arm difference** **≥1 dose of patisiran at home,** n (%) 1. 7 (14.3) 2. 15 (10.9) 3. 3 (12.0) 4. 25 (11.8) **Total number of patisiran doses administered at home,**	**Infusion-related reaction (IRR),** n (%) 1. 12 (24.5) 2. 8 (5.8) 3. 2 (8) 4. 22 (10.4)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
	treatment arm 52 weeks	4.Global OLE - Eligible patients from Phase 2 OLE and APOLLO continued receiving patisiran 0.3 mg/kg IV every 3 weeks		PND IIIB, 21 PND IV, 18	n 1. 88 2. 133 3. 48 4. 269 **Number of infusion interruptions d/t IRRs during home infusion,** n 1. 0 2. 0 3. 0 4. 0	
Adams, 2017[24] **Phase 2 OLE** **Conference abstract**	Phase 2 open-label extension study Sub-group analysis by patients on combination therapy of patisiran and stabilizer vs. patients on patisiran monotherapy 24 months	N= 27 Study arms: 1. *Patisiran - 0.3mg/kg IV every 3 weeks for 24 months bbb) ccc) *This arm includes patients with combination therapy (patisiran + stabilizer, n=20) and patients with monotherapy (n=7).	**Inclusion**: • Previously received and tolerated ALN-TTR02 (patisiran) in Study ALN-TTR02-002. • Adequate Karnofsky performance status, liver function, and renal function. **Exclusion:** • Pregnant or nursing. • Has had a liver transplant. • Has a New York Heart Association heart failure	**Age**, years Mean (range) 1. 64 (29-77)	**Data reported are change from baseline** **mNIS+7, score Mean decrease** Combination therapy: 7.0 Monotherapy: 6.7	**SAE,** n Combination therapy: 5/20 Monotherapy: 2/7 **Flushing,** n (%) Combination therapy: 7 (35) Monotherapy: 0 **Infusion-related reaction,** n (%) Combination therapy: 5 (25) Monotherapy:1 (14.3)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
			classification >2 • Has unstable angina. • Has uncontrolled clinically significant cardiac arrhythmia.			
Adams, 2017[25] **Phase 2 OLE** **Conference poster**	Phase II open-label extension Duration of follow-up: up to 2 years	N= 27 Study arm: 1. Patisiran 0.3 mg/kg by infusion every three weeks	**Inclusion:** • Previously received and tolerated patisiran in phase II study • Adequate Karnofsky performance status, liver function, and renal function **Exclusion:** • Pregnant or nursing • Previous liver transplant • NHYA heart failure classification >2 • Unstable angina • Uncontrolled clinically significant cardiac arrhythmia	**Age,** years Mean (range) 1. 64.0 (29-77) **Female,** n (%) 1. 9 (33) **mNIS+7 score, points** Mean (range) 1. 53.0 (2.0-122.5) **NIS score, points** Mean (range) 1. 34.8 (4.0 to 93.4) **mBMI, kg/m2 x albumin (g/dL)** Mean (range) 1. 1030.5 (728.6 to 1379.6) **EQ-5D-5L** Mean (range) 1. 08 (0.3 to 1.0)	**Data reported are change from baseline at 24 months** **mNIS+7 score,** points Mean (SEM) 1. -7.0 (2.0) Median (range) 1. -7.0 (-34.6 to 15.4) **NIS-W score, points** Mean (SEM) 1. 1.2 (1.4) Median (range) 1. 0 (-13.5 to 24.4) **NIS-R score, points** Mean (SEM) 1. -0.5 (0.5**)** Median (range) 1. 0 (-6.0 to 7.0)	**Data reported are no. of patients (%)** **Any SAEs** 1. 7 (25.9) **Deaths** 1. 1 (4) **Flushing*** 1. 7 (25.9) **Infusion related reaction*** 1. 6 (22.2) Other AEs frequently reported: diarrhea, nasopharyngitis, urinary tract infection, vomiting, wound (22.2%); nausea (18.5%); insomnia, neuralgia, pyrexia (14.8%); anemia,

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				TTR Genotype, n (%) **Val30Met** 1. 20 (74) **non-Val30Met** 1. 7 (26) **FAP Stage,** n (%) Stage 1: 24 (89) Stage 2: 3 (11) **PND Score,** n (%) I: 15 II: 9 IIIa: 2 IIIb: 1	**QST** Mean (SEM) 1. -7.4 (2.0) Median (range) 1. -6.0 (-40.0 to 16.0) **NCS Σ5** Mean (SEM) 1. -0.2 (0.2) Median (range) 1. -0.3 (-2.0 to 2.5) **Postural BP** Mean (SEM) 1. -0.1 (0.1) Median (range) 1. 0 (-1.0 to 0.5) **No. with mNIS+7 score unchanged or improved (%)** 1. 20 (77) **mBMI, kg/m2 x albumin (g/dL)** Mean (range) 1. -60.8 (34.9) **EQ-5D-5L** Mean (range)	bronchitis, cataract, infusion site extravasation, edema peripheral, macular degeneration, musculoskeletal pain, and osteoporosis (11.1%) ***Considered drug-related**

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					1. -0.01 (0.02)	
Obici et al, 2018[17] **APOLLO** **Conference presentation slides**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**See Adams et al, 2018**	**Percent with improved mBMI at 18 months** Patisiran: 41.2% Placebo: 6.5%	**See Adams et al, 2018**
Alnylam Pharmaceuticals, 2017[23] **Phase 2 OLE** **Manufacturer slides**	Phase 2 OLE Duration of follow-up: up to 2 years	N= 27 Study arm: 1. Patisiran 0.3 mg/kg by infusion every three weeks	**See Adams 2017**	**See Adams 2017**	**See Adams 2017**	**All data are n (%)** **Deaths**: 1 (3.7) Discontinuations: 1 (3.7) SAEs: 7 (25.9) Severe AEs: 5 (18.5) Infusion-related reactions: 6 (22.2) Flushing: 7 (25.9)
Diflunisal						
Obici, 2015[88] **Conference abstract**	Single arm, open label 24 months	N=24 Study arms: 1. *Diflunisal – 250 mg BID	**Inclusion**: • Late onset FAP patients with moderate to severe neuropathy and cardiomyopathy	**Age**, years Mean (range) 1. 69 (57-82) **Male gender,** n 1. 20 **Disease duration,** months Mean (range) 1. 43 (17-90)	**Progression** PND: Increased by 1 in 8/18 patients Cardiac: Occurred in 2/21 patients	**Discontinuation d/t AE,** n 1. 3 **Increased serum creatinine,** n 1. 3

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				mBMI, (kg/m^2 x g/L) Mean (range) 1. 890 (604-1458) **NT-proBNP** pg/ml Mean (range) 1. 728 (141-5965)		
Berk, 2013[30] **Good**	Investigator initiated international, randomized, double-blind, placebo-controlled study 2 years	N=130 Study arms: 1. *Diflunisal – 250 mg twice daily (n=64) ddd) 2. Placebo (n=66)	**Inclusion**: • 18-75 years, biopsy proven amyloid deposition by Congo Red staining and mutant TTR genopositivity by DNA sequence analysis, signs of peripheral or autonomic neuropathy, and ECOG performance status < 3. **Exclusion:** • Alternative causes of sensorimotor	**Age**, years Mean (SD) 1. 60.3 (11.7) 2. 59.2 (12.2) e) **Male, n (**%) 1. 43 (67.2) 2. 44 (66.7) **TTR genotype** N (%) Val30Met 1. 36 (56.3) 2. 35 (53) non-Val30Met 1. 28 (43.8)	**Data reported are change from baseline** **Difference reported is between-arm difference** **NIS+7 score**, points Mean (95% CI) Month 12 1. 6.2 (2.8, 9.6) 2. 12.5 (8.6, 16.4) Difference: 6.4 (1.2, 11.6)) Month 24 1. 8.2 (2.9, 13.6) 2. 26.3 (20.2, 32.4)	*__Drug-related AEs__, n 1. 4 2. 2 **__Deaths__, n 1. 4 2. 9 *From the diflunisal group the 4 AEs include, gastrointestinal bleed, congestive heart failure, glaucoma, and nausea. From the placebo group the 2 AEs include, headache and renal failure

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
			polyneuropathy, limited survival (<2 years), prior transplantation, severe congestive heart failure (class IV New York Heart Association, (NYHA)) or renal insufficiency (estimated creatinine clearance <30 mL/min), and ongoing anticoagulation	2. 31 (47) **PND,** score Mean, n (%) 1. I – 28 (43.8) II – 18 (28.1) IIIA – 11 (17.2) IIIB – 3 (4.7) IV – 4 (6.3) 2. I – 21 (31.8) II – 23 (34.8) IIIA – 8 (12.1) IIIB – 10 (15.2) IV – 4 (6.1) **NIS+7 score**, points Median (range) 1. 39.3 (3.6-181.6) 2. 42.3 (0-176.1) **NIS score**, points Median (range) 1. 23.5 (0-164.8) 2. 30.8 (0-160.3) **mBMI**, (kg/m^2 x g/L) Mean (SD) 1. 1024 (22.63) 2. 1019 (255) **SF36**, score Mean (SD) **Physical** 1. 35.9 (11.6)	Difference: 18.0 (9.9, 26.2) **NIS score**, points Mean (95% CI) <u>Month 12</u> 1. 4.1 (1.2, 6.9) 2. 10.1 (6.9, 13.3) Difference: 6.0 (1.7, 10.3) <u>Month 24</u> 1. 6.4 (1.6, 11.2) 2. 23.2 (17.8, 28.5) Difference: 16.8 (9.6, 24.0) **mBMI**, (kg/m^2 x g/L) Mean (95% CI) <u>Month 12</u> 1. -18.7 (-51.6 to 14.1) 2. -38.5 (-74.9 to -2.1) Difference: -19.8 (-68.8 to 29.2) <u>Month 24</u> 1. -33.7 (-69.3, to 1.8) 2. -67.9 (-108.1 to -27.7) Difference: -34.1 (-87.8 to 19.5) **SF36**, score Mean (95% CI) <u>Month 12</u>	**12 of the reported 13 deaths occurred off study drug

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				2. 34.8 (11) **Mental** 1. 46.6 (14.1) 2. 46.5 (11.8)	**Physical** 1. 0.7 (-1.1 to 2.5) 2. -1.9 (-3.9 to 0.2) Difference: -2.6 (-5.3 to 0.1) **Mental** 1. 2.5 (0.0 to 5.1) 2. 0.8 (-2 to 3.6) Difference: -1.7 (-5.5 to 2.1) <u>Month 24</u> **Physical** 1. 1.2 (-1.2, 3.7) 2. -4.9 (-7.6, -2.1) Difference: -6.1 (-9.8, -2.5) **Mental** 1. 3.5 (0.4, 6.7) 2. -0.9 (-4.4, 2.5) Difference: -4.5 (-9.2, 0.2)	
Tojo, 2010[105] **Publication**	Single-arm study of Japanese hATTR patients Duration of follow-up: mean 38.0 months (SD: 31.2 months,	N=40* <u>Study arms:</u> 1. Diflunisal 250 mg twice daily† *N analyzable at 12 months = 28; 24 months = 21; 36 months = 16	**Inclusion:** • 20 years or older • Biopsy-proven amyloid deposition by Congo Red staining • Mutant TTR genopositive by DNA sequence analysis • Signs of peripheral	**Age,** years Mean (SD) 1. 60.7 (14.4) **Females,** n (%) 1. 12 (30) **TTR genotype, n (%)** **Val30Met** 1. 30 (75)	**Data reported are mean change per year** **FAP Score, points** Mean (SD) 0.98± 1.39 **mBMI, kg/m2 x albumin** Mean (SD)	**All data are n (%)** **Discontinuation d/t AE:** 13 (32.5) **Discontinuation d/t drug-related AE:** 3 (7.5) **Discontinuation d/t**

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
	range 2-116)	†administered with histamine type-2 receptor agonist or proton pump inhibitor to prevent GI bleeding	or autonomic neuropathy **Exclusion:** • Non-ATTR amyloidosis • Other causes of sensorimotor polyneuropathy • Liver transplantation • Severe congestive heart failure (Class IV NYHA) • Renal insufficiency • Liver dysfunction • Active gastrointestinal bleeding • Thrombocytopenia • NSAID or aspirin hypersensitivity • Pregnancy	**non-Val30Met** 1. 10 (25) **PND Score,** n (%) 1. I: 10 (25) II: 12 (30) IIIA: 8 (20) IIIB: 7 (17.5) IV: 3 (7.5) **mBMI, kg/m2 x albumin** Mean (SD) 1. 838.7 (171.1) **Cardiomyopathy,** n (%) 1. 34 (85) **Ejection fraction (%)** Mean (SD) 1. 68.9 (10.3)	−28.1± 25.6 **Ejection fraction, (%)** Mean (SD) −0.21± 3.76	**thrombocytopenia:** 1 (2.5) **Deaths:** 3 (7.5)
Takahashi, 2014[106] **Publication**	Single arm study in Japanese patients in endemic setting (late onset Val30Met only) Duration of	N= 6 Study arm: 1. Diflunisal 250 mg twice daily	**NR**	**Age,** years Range 45-73 **Mean age at onset, years** Mean (SD) 59.3 (NR) **Mean age at starting**	**mBMI, kg/m2 x albumin** Mean (SD) Year 1: 854.2 ± 120.7 (p = 0.96) **Year 2:** 825.8 ± 102.1 (p = 0.52)	**Data reported are n (%)** **Discontinuations d/t AE** 1 (16.7)

Author & Year of Publication (Trial)	Study Design Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
	follow-up: 5 years			**diflunisal, years** 65.8 **Mean disease duration, years (SD)** 6.5 (5.2) **mBMI, kg/m2 x albumin** Mean (SD) 857.5 ± 67.4 **Ejection fraction (%)** Mean (SD) 71.2 ± 10.9	**Year 3:** 818.7 ± 88.8 (p = 0.31) **Ejection fraction (%)** Mean (SD) **Year 1:** 74.2 ± 6.9 (p = 0.65) **Year 2:** 68.2 ± 5.8 (p = 0.60) **Year 3:** 72.2 ± 6.7 (p = 0.73)	
Sekijima, 2013[107] **Conference abstract**	Single arm, open-label historical control study (Val30Met only) Duration of follow-up: mean 35.0 months (SD: 24.0)	N=45 <u>Study arms:</u> 1. Diflunisal 250 mg twice daily (n=18) 2. Historical controls (n=27)	**Inclusion:** NR **Exclusion:** NR	NR	NR	**Data reported are n (%)** **Discontinuations d/t AEs** 7 (39) **Discontinuations d/t related AEs** 2 (11)

Appendix D. Comparative Value Supplemental Information

Table D1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in Health Care Sector Perspective?	Included in Societal Perspective Analysis?	Notes on Sources, Likely Magnitude & Impact
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	Patisiran's transition probabilities come from a poster by Gonzalez-Duarte et al., 2018. For inotersen, the distribution of the PND scores was taken from Page 63 of the Assessment Report by the Committee for Medicinal Products for Human Use (CHMP). Other transition probabilities are from Adams et al. and Swiecicki et al.
	Health-related quality of life effects	X	X	The utilities for FAP stages 1 and 2 are from Denoncourt et al. The FAP stage 3 utility value is assumed from the York Economic Review Group (ERG). The assumption of a gain in utility within FAP stage is quantified with equations from the ERG report.
	Adverse events	☐	☐	None but likely to make the incremental cost-effectiveness ratio even larger
Medical Costs	Paid by third-party payers	X	X	Medicare costs; Schmidt et al.; Riley and Lubitz; Lassman et al.
	Paid by patients out-of-pocket	☐	X	Considered when doubling the health care costs in the scenario analysis for the Modified Societal perspective.
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	Assumed

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in Health Care Sector Perspective?	Included in Societal Perspective Analysis?	Notes on Sources, Likely Magnitude & Impact
	Unpaid caregiver-time costs	NA	X	Dunbar et al.
	Transportation costs	NA	☐	None but likely to make the incremental cost-effectiveness ratio even larger
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	Berk et al. and Schmidt et al.
	Cost of unpaid lost productivity due to illness	NA	X	Estimates from the 2nd Panel on Cost-Effectiveness[108]
	Cost of uncompensated household production	NA	☐	None, not clear how inclusion would affect the incremental cost-effectiveness ratios
Consumption	Future consumption unrelated to health	NA	X	Estimates from the 2nd Panel on Cost-Effectiveness[108]
Social Services	Cost of social services as part of intervention	NA	☐	Not available
Legal / Criminal Justice	Number of crimes related to intervention	NA	☐	NA
	Cost of crimes related to intervention	NA	☐	NA
Education	Impact of intervention on educational achievement of population	NA	☐	NA
Housing	Cost of home improvements, remediation	NA	☐	None, not clear how inclusion would affect the incremental cost-effectiveness ratios
Environment	Production of	NA	☐	NA

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in Health Care Sector Perspective?	Included in Societal Perspective Analysis?	Notes on Sources, Likely Magnitude & Impact
	toxic waste pollution by intervention			
Other	Other impacts (if relevant)	NA	☐	None but likely to make the incremental cost-effectiveness ratio even larger

NA: not applicable
Adapted from Sanders et al.[108]

Cost-Effectiveness Model Supplemental Information

Model Overview

We developed a model of amyloidosis in which patients progress through three FAP stages of disease in monthly cycles. Patients may also have severe cardiac symptoms defined as NT-proBNP > 3,000. In the base case, we assumed that *without treatment* the disease is purely progressive (e.g., "improvement" transitions from Stage 2 to Stage 1 are not possible). We varied this possibility in sensitivity analysis.

We made two models each to reflect the patient populations in the seminal studies for patisiran and inotersen. In the base case, we assume that individuals could not develop severe cardiac involvement (NT-proBNP > 3,000) because this was not observed in the trial period. Furthermore, we assumed that an individual with severe cardiac involvement could not recover from those symptoms.

Calibration of the Disease Natural History Model

We estimated input parameter values for the disease-specific mortality rate for each stage of disease and stage-specific disease progression rates through calibration. The calibration targets were the 15-month distribution of outcomes from the NEURO-TTR trial, the 18-month distribution of outcomes from the APOLLO trial, the average health state residency times presented in Adams[109], and the survival curves presented in Swiecicki et al. (2015). We assumed disease-specific mortality rates and progression rates to be non-decreasing in disease severity. We hand-tuned parameters to estimate sets of input parameters that fit the calibration targets well on visual inspection. Having identified ranges of parameters which fit the calibration targets well, we randomly generated a set of 100 natural history parameters to be used in probabilistic sensitivity analysis.

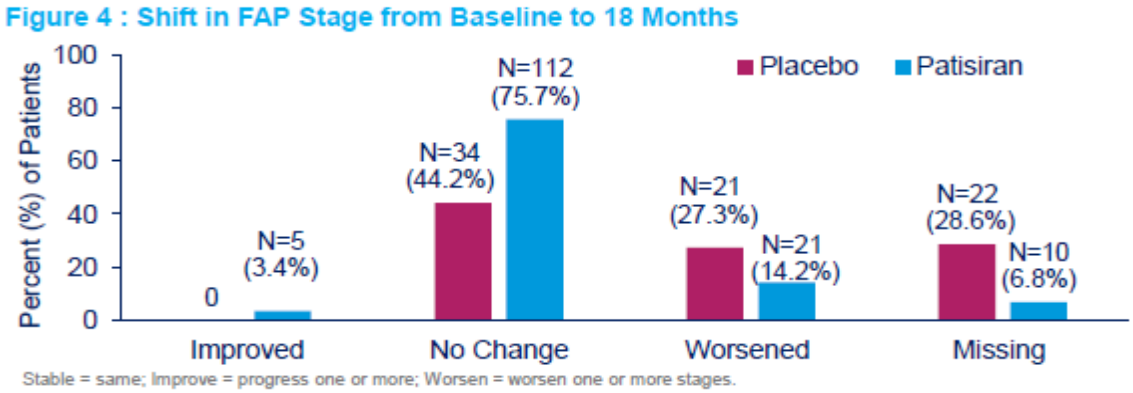
Estimating the Benefits of Treatment

We modelled the benefits of treatment as influencing various disease-specific risks including the rate of transition to an improved health state (from Stage 2 to Stage 1 or from Stage 3 to Stage 2) and the rate of disease progression. We then calculated the rate of transition to an improved health state in order to match the rate observed in each trial. As each trial had few/no individuals in Stage 3 at initiation, we assumed the rate of transition from Stage 3 to Stage 2 was half of the rate from Stage 2 to Stage 1 given the relative severity of the disease states. Finally, we calculated the hazard ratio on disease progression to match the proportion of patients who had an outcome of "No change" or "Worsened" as observed in the trial.

In the base case we assumed a change in quality of life for patients on treatment who remained in the same health state (compared to those receiving usual care) and we assumed that patients discontinued treatment. We varied both of these assumptions in sensitivity analysis.

A key building block of the model involved the findings from the poster by Gonzalez-Duarte et al., 2018, illustrated below.[20]

Figure D1. Figure 4 from "Changes in Neuropathy Stage in Patients with hATTR Following Treatment with Patisiran" by Gonzalez-Duarte et al.[20]



Corresponding data for inotersen became available as well. Consequently, we used the mapping technique developed for our analysis of patisiran data (to map PND to FAP stages). The numbers from page 63 of the Assessment Report by the Committee for Medicinal Products for Human Use (CHMP) show for placebo 2 (3.8%), 37 (71.2%) and 13 (25.0%) Improving, Not Changing and Worsening, respectively; and for inotersen 9 (10.5%), 56 (65.1%) and 21 (24.4%) Improving, Not Changing and Worsening, respectively.[85] For placebo, this represents n = 52 and for inotersen this represents n = 86. The difference between the n that is reported on page 63 of the Assessment Report and the sample size for the trial is assumed to be Dead or Missing. After Dead were deducted from this total, the Missing were allocated according to the empirical distribution of the Improving, Not Changing and Worsening categories.

The additional utility gains from treatment were motivated by the quality of life improvements taken from poster presentations. For inotersen and patisiran, the relevant graphs are copied below. At the end of the NEURO-TTR trial, there was an improvement of 11.68 points. At the end of the APOLLO trial, there was an improvement of 21.1 points. We used this observation to support the assumption that while many patients seemed to experience "No Change" in FAP stage, there also seemed to be an improvement in the Norfolk QoL-DN. For our base case analysis, we assumed a relationship between the Norfolk QoL-DN scores and QALY utilities. We assumed the "crosswalk" reported in the York ERG analysis would apply to this setting as well.

In additional Scenario Analyses, we considered including caregiver burden in the form of additional QALY utility loss. For example, subtracting off -0.05 from each FAP Stage utility (because of the quality of life impact on caregivers) served to increase the incremental cost-effectiveness ratios to approximately $1.8 million per QALY for inotersen and approximately $900,000 per QALY for patisiran. Incorporating a disutility toll of -0.10 for each FAP Stage utility further increased the incremental cost-effectiveness ratios.

Figure D2. Slide 7 from "Safety and Efficacy of Inotersen in Patients with Hereditary Transthyretin Amyloidosis With Polyneuropathy (NEURO-TTR)"

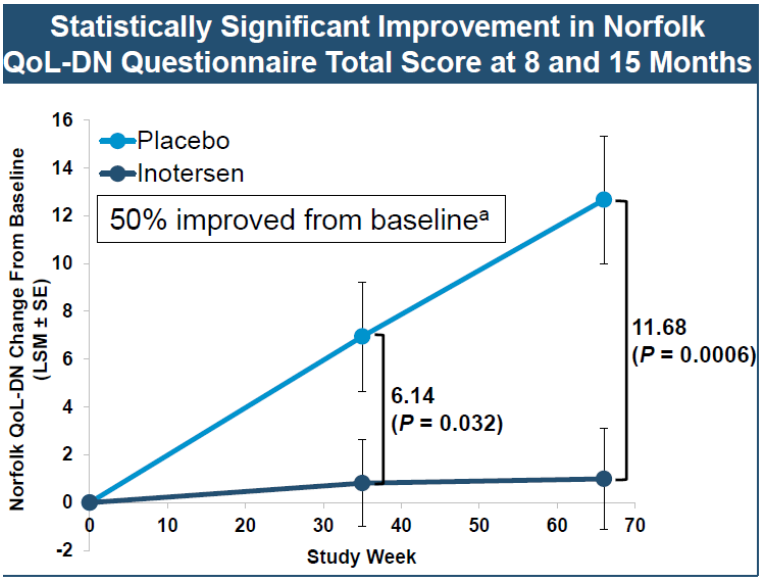


Figure D3. Slide 17 from "Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy: Results from the Phase 3 APOLLO Study"

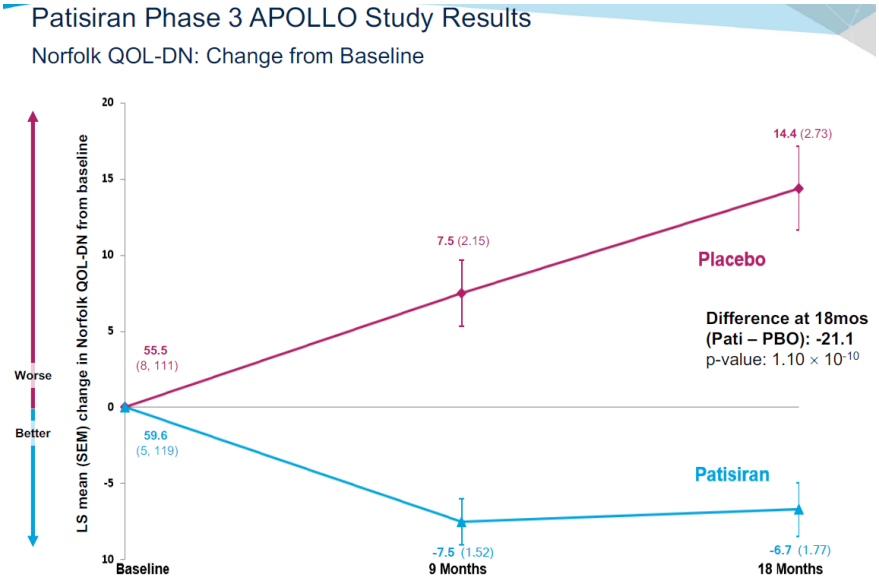


Figure D4. Tornado Diagrams for One-Way Sensitivity Analyses of Incremental Cost-Effectiveness Ratios for Inotersen and Patisiran versus Standard of Care from the Modified Societal Perspective

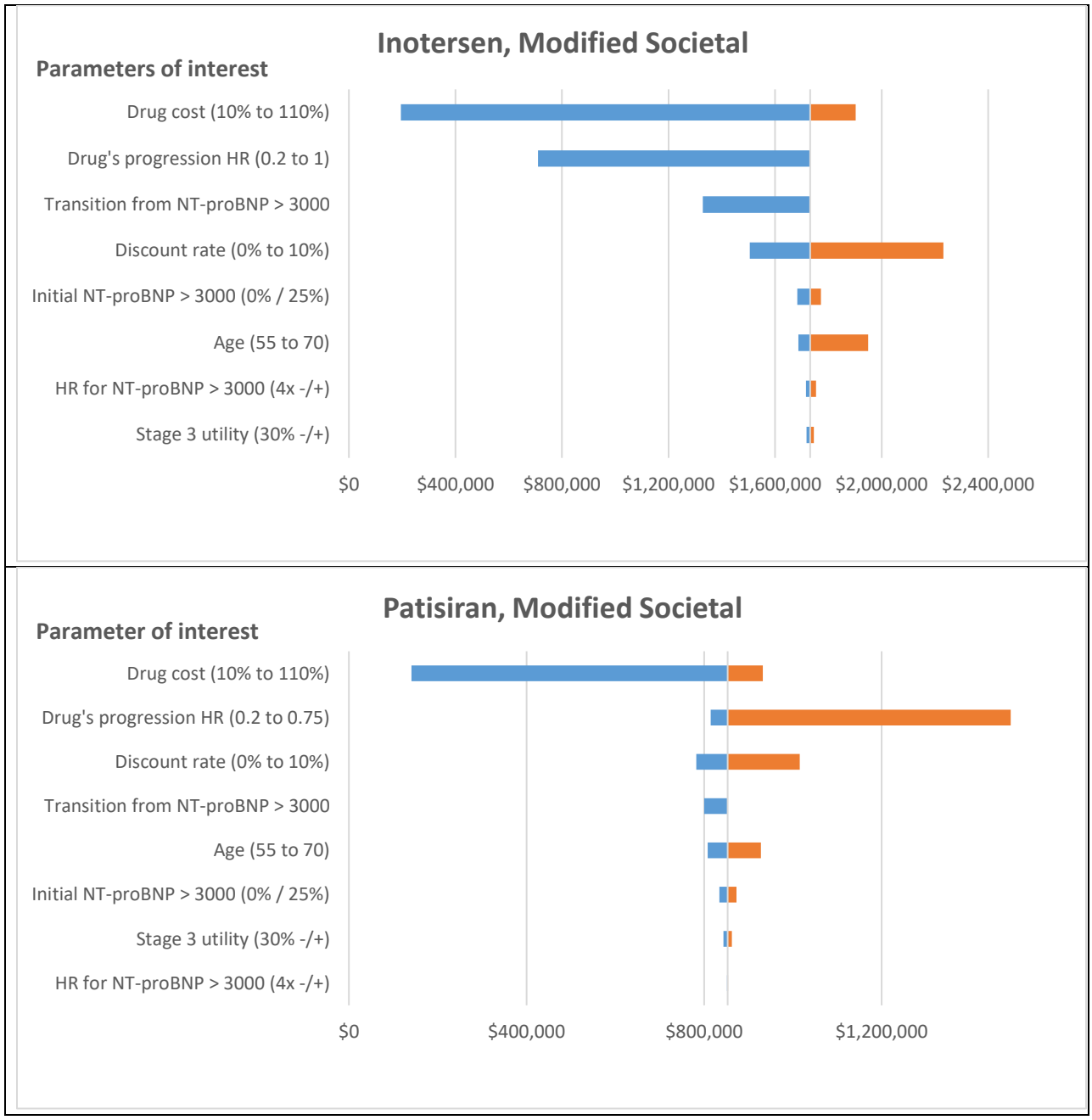


Figure D5. Cost-Effectiveness Acceptability Curve for Inotersen versus Best Supportive Care from the Health Care Sector Perspective

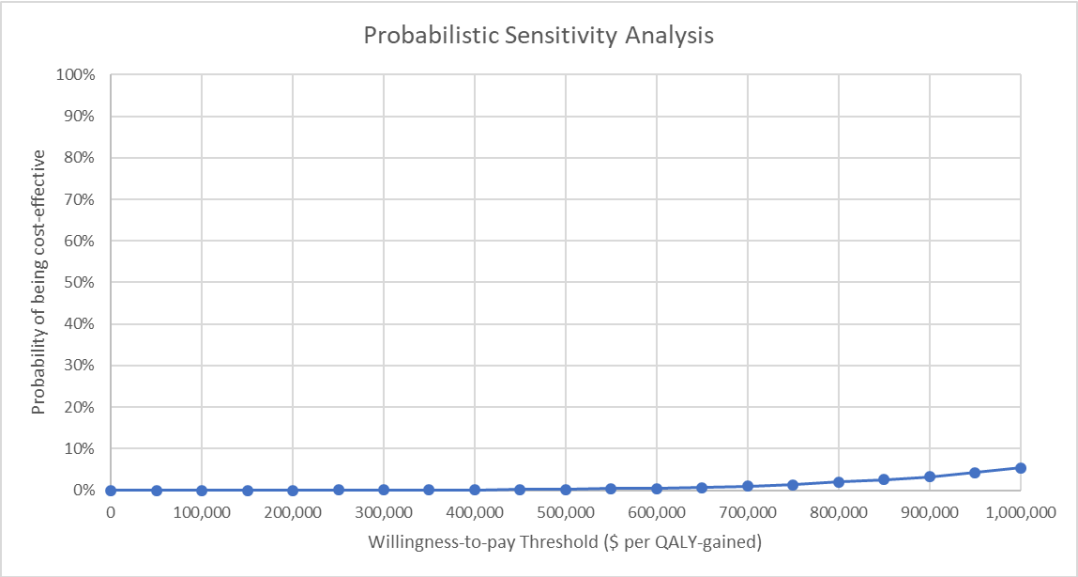


Figure D6. Cost-Effectiveness Acceptability Curve for Patisiran versus Best Supportive Care from the Health Care Sector Perspective

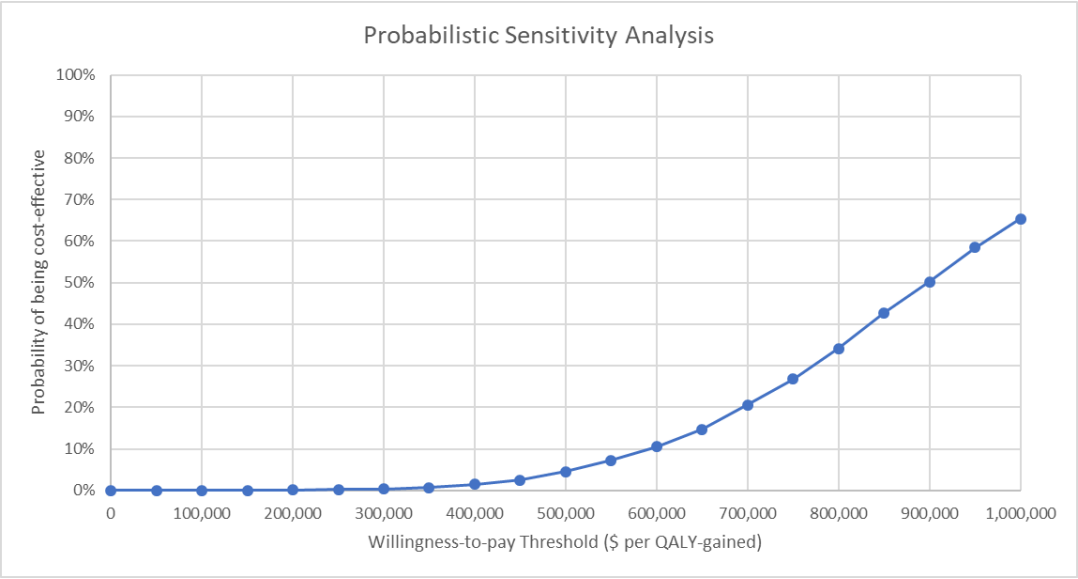


Table D2. Probabilistic Sensitivity Analysis Results: Patisiran versus Best Supportive Care, Modified Societal Perspective

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
Inotersen	< 1%	< 1%	< 1%	< 1%	< 1%
Patisiran	< 1%	< 1%	< 1%	< 1%	< 1%

Figure D7. Cost-Effectiveness Acceptability Curve for Inotersen versus Best Supportive Care from the Modified Societal Perspective

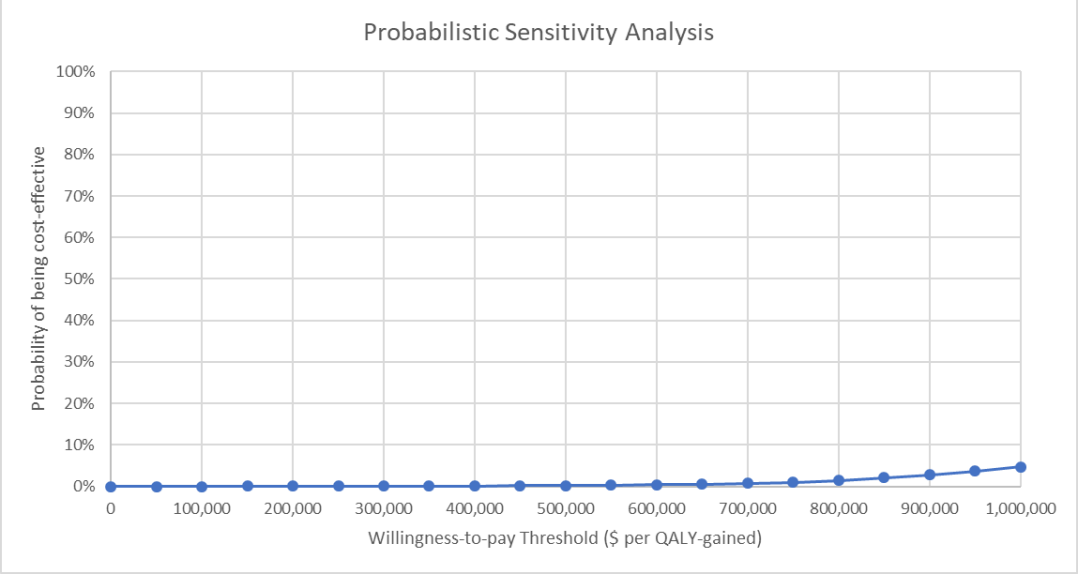
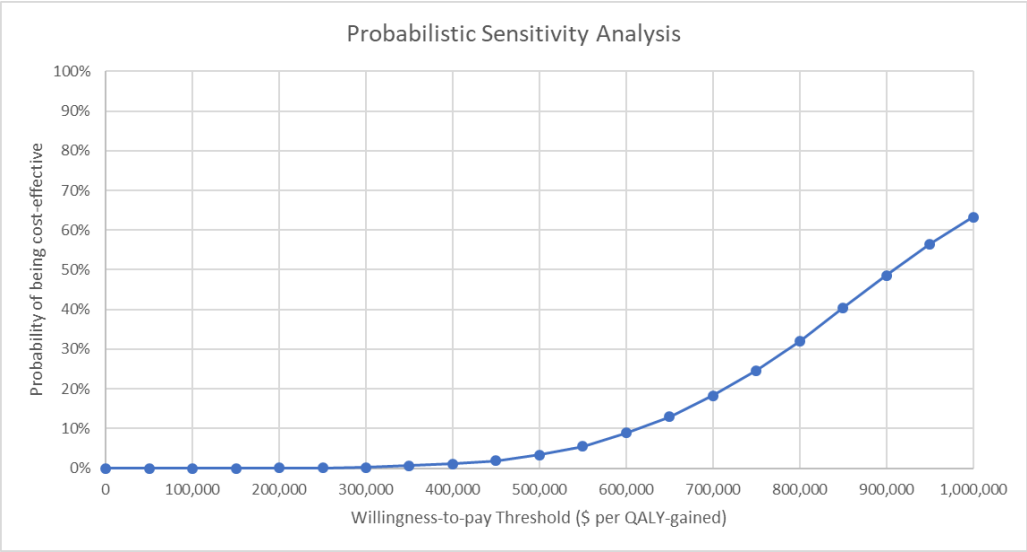


Figure D8. Cost-Effectiveness Acceptability Curve for Patisiran versus Best Supportive Care from the Modified Societal Perspective



Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on September 13, 2018 in Chicago, IL. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Four speakers did not submit summaries of their public comments.

A video recording of all comments can be found here beginning at minute 1:20:58. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Dawn Myers
Patient Advocate

Thank you for the opportunity to share my patient perspective during the CEPAC hATTR meeting. The ability to put into words what many in the room were questioning regarding drug efficacy meant the world to me. Though there were many factors in deciding how both drugs would directly affect a patient's outcome, one many did not fully grasp is the generational impact. The ability for my children, to see me "get better" not worse is truly a paradigm shift in our family. My maternal aunt has seen her mother, sister and brother slowly deteriorate and die from this disease. She now gets to witness disease regression for the first time ever. To have hope that's real, heals the trauma we have all experienced from hATTR.

What concerns me now as the Alnylam EAP program transitions to commercial output is affordability. Currently there are patients that are trying to submit their medication to their insurance and each infusion will be billed at $38,000 per infusion. Many patients will need to pay 20% of that cost through their insurance 18 times per year, not financially possible. The insurance market and Alnylam need to negotiate better price breaks for the patients. Additionally, The Assistance Fund is not the only answer, since some patients are being declined due to income ineligibility. These therapies have provided hope and real disease efficacy. Though they should have a chance to help all hATTR patients, not just those that can afford it.

Conflict of Interest: None declared.

Sonalee Agarwal, PhD
Head, Value & Evidence Strategy, Alnylam

hATTR amyloidosis is an extremely rare, rapidly progressive, multi-system disease that impacts all aspects of life for a U.S. population of about 3,000 diagnosed patients, and generations of families.

Alnylam invested 16 years and more than 2.5 billion dollars translating Nobel Prize-winning technology into a new class of therapies based on RNA interference (RNAi). Alnylam's ONPATTRO is the first and, to date, only product approved by the FDA for hATTR amyloidosis based on its ability to halt progression or reverse neuropathy impairment in a majority of patients.

This offers patients the potential to perform the most basic daily activities—a dramatic shift from the current course of disease as managed through symptomatic or off-label medical treatment.

ICER has recognized the clinical benefit of ONPATTRO and noted that its net price meets affordability thresholds for the U.S. health system.

However, ICER has recommended unrealistic price discounts that do not align with either its rare disease framework or clinical assessments of a breakthrough treatment in rare, debilitating disease such as ONPATTRO.

In addition, ICER's framework inadequately captures broader societal benefits of ONPATTRO, such as lost productivity, and improving emotional well-being.

Alnylam's Patient Access Philosophy helps patients with comprehensive support services, engages insurers in open dialogue about how to pay for value and pledges against arbitrary price increases. At approval, we announced several value-based agreements in principle for ONPATTRO.

Alnylam's focus remains on ensuring patients have access to transformative medicines, and we hope to inspire future value-based collaboration between insurers and developers.

Spencer Guthrie, MPH
Vice President, Global TTR Strategy, Akcea

We appreciate ICER providing us the opportunity to present at your public meeting. While we appreciate your work bringing awareness to amyloidosis, we have serious concerns about the current evidence report. Several experts in amyloidosis treatment as well as patients have pointed out serious inaccuracies with the rating of clinical effectiveness of inotersen in public comments.

We have several significant concerns including ICER's:

- Premature nature of assessment because inotersen is not yet approved and long-term data still being captured

- Lack of consultations with amyloidosis experts in your clinical effectiveness assessments
- Inaccurate classification of inotersen's clinical effectiveness
- Lack of understanding of the clinical meaningfulness of results from the mNIS+7 and Norfolk QOL
- Lack of understanding of utility of the PND and FAP staging
- Lack of understanding of primary mutations in the US, specifically those with neuropathy
- Lack of account for liver or heart transplant in the model
- Unscientific combination of a validated neuropathy staging and a proposed cardiomyopathy staging system.
- Unbalanced assessment of the risk associated with inotersen and patisiran (e.g. lack of inclusion of IV dexamethasone risk in concomitant diabetic patients; no inclusion of the cardiovascular risks associated with patisiran)
- Inappropriate methodology in cost-effectiveness model, including unbalanced and incorrect assignment of two different best supportive care arms in the model

Finally, as Dr Gertz stated in his public comments: ***"we cannot determine if one drug is more effective than the other, so it's hard to understand how you were able to do so. Both drugs are highly effective."***

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the September 13, 2018 Public Meeting of the Midwest CEPAC.

Table G1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Ellie Adair, MPA	ICER	None
Rick Chapman, PhD, MS	ICER	None
Laura Cianciolo, BA	ICER	None
Elise Evers, MSc	ICER	None
Jeffrey S. Hoch, PhD	University of California, Davis	None
Varun Kumar, MBBS, MPH, MSc	ICER	None
Karen E. Lasser, MD, MPH	Boston University School of Medicine	None
Kristin Mickle, MPH	ICER	None
Dan Ollendorf, PhD	ICER	None
Steve Pearson, MD, MSc	ICER	None
Matthew Seidner, BS	ICER	None
Yi Zhang, PhD	University of California, Davis	None

Table G2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD	St. Louis University	*
Ryan Barket, MSW, MPPA	Missouri Foundation for Health	*
Aaron Carroll, MD, MS	Indiana University School of Medicine	*
Rena Conti, PhD	University of Chicago	*
Gregory Curfman, MD	Journal of the American Medical Association (JAMA)	*
Jill Johnson, PharmD	University of Arkansas	*
Timothy McBride, PhD	Washington University in St. Louis	*
Reem Mustafa, MD, MPH, PhD	University of Kansas	*
Harold Pollack, PhD	University of Chicago	*
Timothy Wilt, MD, MPH	Minneapolis VA Center for Chronic Disease Outcomes Research	*
Stuart Winston, DO	St. Joseph Mercy Health System	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participant COI Disclosures

Name	Organization	Disclosures
John Berk, MD	Associate Professor of Medicine, Amyloidosis Center, Boston University	Study site investigator for clinical trials of diflunisal, inotersen, patisiran, and tafamidis.
Joel Buxbaum, MD	Consulting Chief Medical Officer, Misfolding Diagnostics; Professor Emeritus, Molecular Medicine, The Scripps Research Institute	None declared.
Alan Eisenberg, MPP	Vice President, Global Government Relations & Public Policy, Alnylam Pharmaceuticals	Full-time employee of Alnylam Pharmaceuticals.
Young Fried, PharmD, MSP	Vice President, Pharmacy Plan Services, HealthPartners	Full-time employee of HealthPartners.
Kristen Hsu	Executive Director, Clinical Research, Amyloidosis Research Consortium	Full-time employee of Amyloidosis Research Consortium.
Dustin Kaehr	Director, Leadership Development, Lippert Components; Patient Advocate	None declared.
Michael Pollock	Vice President, Global Market Access, Akcea Therapeutics	Full-time employee of Akcea Therapeutics.