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CADTH COMMON DRUG REVIEW

Clinical Review Report

INOTERSEN (TEGSEDI)

(Akcea Therapeutics, Inc.)

Indication: Stage I or II polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis (hATTR)

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Abbreviations

∑5 NCS	sum of five attributes of nerve conduction studies
AE	adverse event
CDR	CADTH Common Drug Review
CI	confidence interval
CM-ECHO	cardiomyopathy-echocardiogram
DB	double blind
FAP	familial amyloidotic polyneuropathy
FAS	full analysis set
hATTR	hereditary transthyretin-mediated amyloidosis
HRQoL	health-related quality of life
LSM	least squares mean
LV	left ventricular
LVEF	left ventricular ejection fraction
mBMI	modified body mass index
MCID	minimal clinically important difference
MCS	mental component summary (SF-36v2)
MMRM	mixed-effect model with repeated measures
mNIS+7$_{Ionis}$	modified Neuropathy Impairment Score + 7 (Ionis version)
mRNA	messenger ribonucleic acid
NIS	Neuropathy Impairment Score
NOC	Notice of Compliance
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy questionnaire
NSC	Neuropathy Symptoms and Change
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PCS	physical component summary (SF-36v2)
PND	polyneuropathy disability
QST	quantitative sensory testing
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SF-36v2	Short Form (36) Health Survey, version 2
TTR	transthyretin

Drug	Inotersen (Tegsedi)
Indication	Stage I or II polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis (hATTR)
Reimbursement Request	As per indication
Dosage Form(s)	Subcutaneous injection
NOC Date	October 3, 2018
Manufacturer	Akcea Therapeutics, Inc.

Executive Summary

Introduction

Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare, progressive, often fatal condition caused by an autosomal dominant mutation in the transthyretin (TTR) gene. TTR is a plasma transport protein for thyroxine and vitamin A that is produced predominantly in the liver.[1] In patients with TTR gene mutations, the protein is destabilized, causing it to disassociate, misfold, and aggregate into amyloid fibrils that are deposited in various tissues in the body. Amyloid accumulation often causes a peripheral neuropathy with involvement of motor, sensory, and autonomic fibres that leads to progressive muscle weakness and disability, pain, and wasting, and may lead to gastrointestinal dysfunction and other autonomic symptoms, such as orthostatic hypotension. Cardiac amyloid deposits lead to cardiac hypertrophy, arrhythmias, and heart failure.[1] Heart failure and sudden cardiac death are common causes of death among those with hATTR.[2] It is estimated that, globally, 10,186 people have hATTR and polyneuropathy (range, 5,526 to 38,468).[3] The prevalence in Canada is not known, but extrapolation from other regions estimates a range of 12 (low) to 53 (mid) to 270 (high) patients with hATTR and polyneuropathy.[3]

Inotersen is an antisense oligonucleotide that comprises 20 nucleotides.[4] The sequence is complementary to a 3' untranslated region of human TTR messenger ribonucleic acid (mRNA). The hybridization of inotersen to TTR mRNA causes the mRNA to degrade.[5] Inotersen is not specific to any particular mutation of hATTR and reduces both mutated and wild-type TTR produced by the liver.[6] The drug is administered as a 300 mg (equivalent to 284 mg parent acid) subcutaneous (SC) injection once weekly.[7] Inotersen received a Health Canada Notice of Compliance (NOC) for stage I or II polyneuropathy in adults with hATTR in October 2018. Based on the Coutinho classification, patients with stage I polyneuropathy are those who do not require assistance with ambulation and patients with stage II polyneuropathy are those who require assistance with ambulation.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of inotersen 189 mg/mL SC injection (administered as a 1.5 mL injection containing 300 mg inotersen sodium or 284 mg parent acid) for the treatment of stage I or stage II polyneuropathy in adults with hATTR.

Results and Interpretation

Included Studies

The NEURO-TTR trial was a phase II/III combined double-blind (DB) randomized controlled trial (RCT) that studied the efficacy and safety of inotersen compared with placebo in 172 patients with hATTR over 65 to 66 weeks. The study was conducted across 10 countries in 24 centres and was completed on March 28, 2017. Patients were randomized in a 2:1 ratio to inotersen 300 mg (N = 112) or placebo (N = 60) and stratified by previous treatment with tafamidis or diflunisal versus treatment-naive, stage I or II polyneuropathy (stage I = patient does not require assistance with ambulation or stage II = patient requires assistance with ambulation), and presence or absence of the V30M mutation. The DB treatment phase lasted for 65 weeks, followed by an end-of-treatment efficacy assessment period of one week. The primary end points were the change in the modified Neuropathy Impairment Score + 7 (Ionis version) (mNIS+7$_{Ionis}$) (range, −22.3 to 346.3, with higher scores indicating poorer function) and the change in the score on the patient-reported Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire (range, −4 to 136, with higher scores indicating poorer quality of life). A decrease in mNIS+7$_{Ionis}$ and Norfolk QoL-DN scores indicated improvement. Other outcomes assessed in the trial were the Short Form (36) Health Survey, version 2 (SF-36v2) for health-related quality of life (HRQoL), the Neuropathy Symptoms and Change (NSC) score, modified body mass index (mBMI), echocardiogram parameters, the cardiac biomarker N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and harms.

The mean age of randomized patients was 59.2 years (range, 27 to 81 years). There were more males (68.6%) than females (31.4%) and the majority of patients were white (91.9%). The diagnosis of hATTR polyneuropathy was made from one month to 25 years previously, with the average time since diagnosis being about three years. A total of 27 different TTR mutations were identified and the most common mutation was V30M (51.7%), followed by Thr60Ala (12.8%). At study entry, about 40% of patients were diagnosed with hATTR cardiomyopathy. Most patients were in New York Heart Association (NYHA) class I (64.5%) and fewer were in NYHA class II (35.5%). About one-third of patients were previously treated with tafamidis (30.8%) or diflunisal (28.5%).

Key limitations of the trial included a larger number of treatment discontinuations in the inotersen group, potential for unblinding due to the much higher frequency of injection-site reactions in the inotersen group, the exclusion of a large proportion of patients from the primary analyses at study end that may have compromised randomization, and the potential for type I error in the secondary and tertiary outcomes due to multiple statistical testing. The trial excluded patients with advanced polyneuropathy who were confined to a wheelchair (i.e., stage III polyneuropathy), patients with a prior liver transplant or on a current TTR stabilizer, and patients in NYHA class III or higher; therefore, the results cannot be applied to those patient populations.

Efficacy

The Norfolk QoL-DN is a self-administrated questionnaire that consists of 35 standardized items, grouped into five domains, and was originally developed to assess patients' perceptions of the symptoms of nerve fibre damage that occur in diabetic neuropathy. It was used in the study to assess the impacts of neuropathy on the functional status of patients with hATTR, given the similarity of the neuropathy pattern between the two

diseases. The five domains are: physical functioning / large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy. The mNIS+7$_{Ionis}$ is a composite outcome of neurological function, with higher scores indicating worse outcomes. It was developed specifically for the monitoring of polyneuropathy in patients with hATTR and has been validated. The Peripheral Nerve Society[8] has proposed a minimal clinically important difference (MCID) of two points in patients with diabetic neuropathy, based on the smallest difference that physicians can detect on the Neuropathy Impairment Score (NIS) component. However, the actual meaningfulness of this difference to patients with hATTR is unclear. The mNIS+7$_{Ionis}$ and Norfolk QoL-DN were tested with a hierarchical strategy to control for multiplicity.

At week 66, the least squares mean (LSM) difference in change from baseline for the Norfolk QoL-DN between inotersen and placebo was −11.68 points (95% confidence interval [CI], −18.29 to −5.06) (statistically significant in favour of inotersen) (Table 1). In a sensitivity analysis that included all randomized patients and conservatively imputed missing data, the LSM difference in change from baseline for the Norfolk QoL-DN remained statistically significant in favour of inotersen (−8.56 points; 95% CI, −15.42 to −1.71). No MCID has been established for the Norfolk QoL-DN, so it is difficult to conclude whether or not the observed difference is clinically meaningful. In subgroup analyses of the Norfolk QoL-DN, none of the treatment by subgroup interactions were statistically significant.

At week 66, the LSM difference in change from baseline for the mNIS+7$_{Ionis}$ between inotersen and placebo was −19.73 points (95% CI, −26.43 to −13.03) (statistically significant in favour of inotersen). In a sensitivity analysis that included all randomized patients and conservatively imputed missing data, the LSM difference in change from baseline remained statistically significant in favour of inotersen (−14.89 points; 95% CI, −22.55 to −7.22). In subgroup analyses of the mNIS+7$_{Ionis}$, the treatment by subgroup interaction was statistically significant for disease stage, with greater improvement among patients with stage II.

All other outcomes, including cardiovascular assessments, were analyzed statistically outside of the hierarchy testing procedure, and the differences between groups for these outcomes are difficult to interpret. No data were available for pain, which was identified as an important outcome by patients, or hospitalizations.

Harms

Nearly all patients experienced an adverse event (AE) (Table 2). More patients who received inotersen discontinued treatment due to an AE than patients who received placebo (14.3% versus 3.3%). [redacted]. In the inotersen group, eight patients withdrew from the study due to thrombocytopenia, congestive cardiac failure, intestinal perforation, cachexia, dementia, intracranial hemorrhage, myoclonus, and acute kidney injury. The inotersen group experienced a much higher incidence of injection-site reactions (erythema [redacted] pain-[redacted], pruritus [redacted]). Thirteen patients (21.7%) who received placebo and 36 patients (32.1%) who received inotersen experienced a serious adverse event (SAE).

[redacted]. More patients receiving inotersen had renal impairment ([redacted]), thrombocytopenia (13.4% versus 1.7%), and decreased platelet count (10.7% versus 0%).

Five deaths occurred in the inotersen group and none in the placebo group. Four of the deaths were attributed to disease progression or complication and one death was due to intracranial hemorrhage associated with a platelet count of about 10×10^9/L.

About one-third of patients in the inotersen group tested positive for anti-drug antibodies, of which the majority were persistent.

[redacted]

Clinical Expert Input[1]

There are significant unmet needs with the currently available therapies for hATTR in Canada. The two main treatments are diflunisal, which is not approved by Health Canada for hATTR, and liver transplantation. These treatments do not reverse the course of disease and, in many, the disease will continue to progress. Patients may not respond to these treatments or may experience intolerable adverse effects. Further, there may be barriers to access.

The upcoming ribonucleic acid (RNA)–targeting treatments for hATTR with polyneuropathy will be considered for first-line use, prior to TTR stabilizers or liver transplant, because they may affect the course of disease and not just the symptoms, they may have fewer risks than liver transplantation, and the level of evidence is higher than the evidence available for diflunisal. The upcoming treatments would be used in patients with a confirmed genetic diagnosis of hATTR who present with clear clinical symptoms and who do not have any contraindications to the drugs, although the criteria for starting RNA-targeting treatment for hATTR is a grey area. The panel discussed the fact that there is no defined threshold for determining when a patient should be considered symptomatic and the situation may be confounded by coexisting conditions, such as occupational carpal tunnel syndrome or diabetic neuropathy. The panel agreed it is difficult to establish an objective guideline of when to start treatment and that this is best left to the expert opinion of the treating physician. The trials recruited patients with earlier stages of polyneuropathy who were not confined to a wheelchair and who had not undergone a liver transplant. The panel discussed that patients with advanced polyneuropathy who are confined to a wheelchair may still have some sensory and motor function in their hands and arms that might be preserved with treatment. More data are required to know if such patients, as well as those with a liver transplant who continue to progress, would benefit from treatment.

The treatments should be administered under the care of specialists, primarily neurologists and cardiologists. An improvement in symptoms or stabilization of neurologic impairment, as assessed clinically, could be considered a clinically meaningful response to treatment. Patients who exhibit a reduced rate of decline may also be responding to treatment, although judging the rate of decrease compared with the natural history of the disease could be challenging, as no clear thresholds are available. There was no consensus among the panel regarding what measure is most suitable to assess response to treatment, and the panel acknowledged that it will be difficult to establish criteria for treatment discontinuation. Continued disease progression may indicate that the patient is not responding to treatment, although disease progression itself is not an indicator of nonresponse. The decision to stop treatment should not be based on only one outcome,

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

such as ambulation, as non-ambulatory individuals may still have function in the upper limbs that is important for maintaining acceptable quality of life (e.g., ability to feed oneself).

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

Conclusions

Inotersen is a new RNA-targeting treatment that slows the progression of neuropathy and loss of HRQoL in patients with stage I or stage II hATTR polyneuropathy and may address certain unmet needs of patients with this condition. However, the clinical significance of the treatment-effect differences between inotersen and placebo is unclear, given the lack of a formally estimated MCID for these outcome measures. As an SC injection that can be self-administered by patients at home after proper training, inotersen potentially offers a more convenient treatment option than patisiran, which requires intravenous infusion. However, there are many questions that remain unanswered, including whether inotersen improves cardiovascular clinical outcomes, is beneficial in patients with a previous liver transplant or in those with advanced (stage III) polyneuropathy, and what the longer-term benefits and harms are. No direct comparative evidence is available to compare inotersen with patisiran or TTR stabilizers. In addition, inotersen appears to be associated with important AEs, particularly thrombocytopenia and glomerulonephritis, requiring regular monitoring, as per the product monograph.

Table 1: Summary of Efficacy Results in Study NEURO-TTR

	n	Mean (SD)	n	Mean (SD)	Change From Baseline, LSM (SE)	LSM Difference: Inotersen Versus Placebo (95% CI)	*P* Value
Norfolk QoL-DN (FAS)	**Baseline**		**Week 66**				
Placebo (N = 59)	[redacted]	[redacted]	52	[redacted]	12.67 (2.67)	−11.68 (−18.29 to −5.06)	0.0006
Inotersen (N = 106)	[redacted]	[redacted]	84	[redacted]	0.99 (2.12)		
SF-36v2 PCS (FAS)	**Baseline**		**Week 65**				
Placebo (N = 59)	[redacted]	[redacted]	51	[redacted]	−3.65 (1.01)	3.59 (1.07 to 6.12)	0.006[b]
Inotersen (N = 106)	[redacted]	[redacted]	85[a]	[redacted]	−0.05 (0.80)		
SF-36v2 MCS (FAS)	**Baseline**		**Week 65**				
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.088[b]

	n	Mean (SD)	n	Mean (SD)	Change From Baseline, LSM (SE)	LSM Difference: Inotersen Versus Placebo (95% CI)	*P* Value
Inotersen (N = 106)	[redacted]	[redacted]	[redacted][a]	[redacted]	[redacted]		
mNIS+7$_{Ionis}$ (FAS)	**Baseline**		**Week 66**				
Placebo (N = 59)	[redacted]	[redacted]	52	[redacted]	25.53 (2.69)	−19.73 (−26.43 to −13.03)	< 0.0001
Inotersen (N = 106)	[redacted]	[redacted]	85	[redacted]	5.80 (2.13)		
NSC Total Score (FAS)	**Baseline**		**Week 66**				
Placebo (N = 59)	[redacted]	[redacted]	52	[redacted]	[redacted]	[redacted]	[redacted][b]
Inotersen (N = 106)	[redacted]	[redacted]	85	[redacted]	[redacted]		
mBMI, kg/m^2 × g/L (FAS)	**Baseline**		**Week 65**				
Placebo (N = 59)	[redacted]	[redacted]	49	[redacted]	[redacted]	[redacted]	[redacted][b]
Inotersen (N = 106)	[redacted]	[redacted]	82	[redacted]	[redacted]		

CI = confidence interval; FAS = full analysis set; LSM = least square mean; mBMI = modified body mass index; MCS = mental component summary; mNIS+7$_{Ionis}$ = modified Neuropathy Impairment Score + 7 (Ionis version); Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NSC = Neuropathy Symptoms and Change; PCS = physical component summary; SD = standard deviation; SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.

[a] Change from baseline was assessed in 84 patients.

[b] Outside of the statistical hierarchy testing strategy.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 2: Summary of Harms

	NEURO-TTR	
	Placebo (N = 60)	**Inotersen (N = 112)**
Patients with > 0 AEs, N (%)	60 (100)	111 (99.1)
Treatment discontinuation due to AEs	[redacted]	16 (14.3)
Patients with > 0 SAEs, N (%)	13 (21.7)	36 (32.1)
WDAE, N (%)	[redacted]	[redacted]
AEs of special interest		
Ocular AEs potentially related to vitamin A deficiency	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Thrombocytopenia	1 (1.7)	15 (13.4)
Platelet count decreased	0 (0)	12 (10.7)
Deaths	0 (0)	5 (4.5)

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report for NEURO-TTR.[7]

Introduction

Disease Prevalence and Incidence

Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare, progressive, often fatal condition caused by an autosomal dominant mutation in the transthyretin (TTR) gene. TTR is a plasma transport protein for thyroxine and vitamin A that is produced predominantly in the liver.[1] In its natural state, TTR exists as a tetramer, but TTR gene mutations can destabilize the protein causing it to disassociate, misfold, and aggregate into amyloid fibrils that are deposited in various tissues in the body. Amyloid accumulation causes a peripheral neuropathy with involvement of motor, sensory, and autonomic fibres that leads to progressive muscle weakness and disability, pain, wasting, gastrointestinal dysfunction, and other autonomic symptoms such as orthostatic hypotension.[1] Cardiac amyloid deposits lead to cardiac hypertrophy, arrhythmias, and heart failure.[1] The leptomeningeal form of TTR amyloidosis is associated with cerebral amyloid angiopathy and ocular amyloidosis.[1] Although patients may be classified as having predominantly neurological or cardiac disease manifestations, these distinctions may be artificial, as neuropathy, cardiomyopathy, vitreous opacities, kidney disease, and meningeal involvement may be present to various degrees in a patient with hATTR.[9] Different classification systems have been used to score disease severity in patients with hATTR (i.e., Coutinho, the familial amyloidotic polyneuropathy [FAP] stage and the polyneuropathy disability [PND] score). These classifications are based largely on ambulation and are described in more detail in Appendix 5. The indication for inotersen is for stage I or II polyneuropathy, which is based on the Coutinho classification. Patients who do not require assistance with ambulation are classified as having stage I polyneuropathy, while those who require assistance with ambulation are classified as stage II.

Neurologic impairment may be rapidly progressive, particularly in the first five years since symptom onset.[10] The patients who provided input to this review rated symptoms of nerve damage (i.e., tingling, numbness, burning pain, carpal tunnel, and weakness) as the most difficult; for many, these symptoms were incapacitating or had a serious impact on their lives. Other symptoms included leg swelling, fatigue, shortness of breath, dizziness, gastrointestinal symptoms, sexual dysfunction, and cardiac symptoms. Walking and activities of daily living become increasingly difficult, leaving patients completely dependent upon caregivers. The input indicated that the deterioration in the patient's quality of life as a result of their condition contributed to emotional distress for patients and their caregivers and led to feelings of uselessness, hopelessness, stress, depression, anxiety, and fear. Progressive heart failure and sudden cardiac death are common causes of death among those with hATTR.[2] Survival estimates reported in the literature vary, ranging from 5 to 15 years after diagnosis.[9,10]

While hATTR is known to be endemic in Portugal, Sweden, and specific regions of Japan, it has been reported in 36 countries worldwide and may be under-diagnosed.[3] It is estimated that, globally, 10,186 people have hATTR and polyneuropathy (range 5,526 to 38,468).[3] Epidemiological studies of hATTR in Canada have not been conducted but when available prevalence estimates are extrapolated to the Canadian population, the estimated number of people with hATTR and polyneuropathy ranges from 12 (low) to 53 (mid) to 270 (high).[3]

More than 100 disease-causing TTR gene mutations have been reported, and the geographic distribution of hATTR mutations is variable.[1,3] Based on the Transthyretin Amyloid Outcome Survey (THAOS), a global longitudinal registry of patients with hATTR,

the most commonly reported mutations among US patients were Val122Ile (n/N = 91/201, 45%) and Thr60Ala (n = 41, 20%), whereas the Val30Met mutation (or V30M) was most common among patients from 16 other countries (n/N = 1,627/2,034, 80%).[11] The phenotype varies among and within various mutations, and the timing, development, and severity of the disease can vary greatly.[12] Thus, some carriers of the gene may live to an advanced age without symptoms, but their children may be clinically affected.[1] For example, in Portugal, penetrance is high, with 80% of V30M carriers showing disease symptoms by age 50.[1] This is in contrast with endemic regions of northern Sweden, where penetrance of the V30M mutation is low (11% by 50 years).[1]

Standards of Therapy

Patients may receive supportive care to manage symptoms of the disease. Disease-modifying treatments include liver transplantation and diflunisal. Liver transplant lowers the production of mutant TTR by approximately 95% and can slow or halt the progression of the disease; it is not curative.[1] However, nerve function may not improve and some patients do not perceive an improvement in their health-related quality of life (HRQoL).[1] Outcomes are generally most favourable if liver transplant, or heart and liver transplant, is performed in young patients with early-stage disease.[1] Access is limited by the availability of donor organs; surgical morbidity is high and transplant patients require life-long immunosuppressant therapy. In the THAOS cohort, 3.3% of symptomatic patients in the US had had a liver transplant compared with 18.6% in the rest of the world.[11] Twenty-year survival after liver transplant was 55.3%, based on data from 1,940 patients with the V30M and other mutations in the Familial Amyloidosis Polyneuropathy World Transplant Registry.[13] Among those with non-V30M mutations, median survival after a liver transplant, or liver and heart transplant, was 7.1 years and 7.8 years, respectively, although survival varied for different mutations.[12] Multivariate analysis showed that modified body mass index (mBMI), early-onset disease (< 50 years of age), disease duration prior to transplant, and V30M versus other mutations were significantly associated with survival following transplantation.[13] Diflunisal is a nonsteroidal anti-inflammatory drug that has been used as a tetramer stabilizer to delay neurological progression in patients with hATTR and polyneuropathy (although not approved for this use by Health Canada).[14] This drug has a number of adverse effects that limit its use, particularly for patients with heart failure or renal impairment, which is common among those with hATTR (Table 3). Moreover, the available evidence to support the use of diflunisal in hATTR is limited to a single randomized controlled trial (RCT) that had a number of methodological issues.[14] The experts who provided input for this review agreed there is a significant unmet need, given the limitations of these therapies for hATTR.

Inotersen is approved in Canada for the treatment of stage I or stage II polyneuropathy in adults with hATTR (Table 3).[15]

Tafamidis, another tetramer stabilizer, is approved in Europe for stage I symptomatic polyneuropathy in patients with hATTR.[16] A phase III trial of tafamidis in patients with hATTR and cardiomyopathy was recently published.[17] The US recently approved tafamidis meglumine and tafamidis for hATTR cardiomyopathy.[18] Tafamidis has not been approved for use in Canada but has been accessible via Health Canada's Special Access Programme.

Drug

Inotersen is an antisense oligonucleotide that comprises 20 nucleotides with five 2'-O-methoxyethyl–modified ribonucleotides at each terminus.[4] The sequence is complementary to a 3' untranslated region of human TTR messenger ribonucleic acid (mRNA).[5] The hybridization of inotersen to TTR mRNA causes degradation of the mRNA by ribonuclease (RNase), and this prevents the production of TTR. Inotersen is not specific to any particular mutation of hATTR and reduces both mutated and wild-type TTR produced by the liver.[6]

The drug is administered as a 300 mg (equivalent to 284 mg parent acid) subcutaneous (SC) injection once weekly.[7] Inotersen received a Health Canada Notice of Compliance (NOC) for stage I or II polyneuropathy in adults with hATTR in October 2018.

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

	Inotersen	Patisiran	Tafamidis	Diflunisal
Mechanism of Action	Antisense oligonucleotide that degrades TTR mRNA	RNA interference (direct sequence-specific degradation of TTR mRNA in the liver)	Stabilizer of TTR	Nonsteroidal anti-inflammatory drug (stabilizer of TTR)
Indication	Health Canada: Stage I or II polyneuropathy in adults with hATTR	Under Health Canada review: hATTR with polyneuropathy in adults	EMA: Treatment of TTR amyloidosis in adult patients with stage I symptomatic polyneuropathy[c] FDA: hATTR cardiomyopathy in adults Currently not approved by Health Canada for hATTR	Not approved by Health Canada for hATTR
Route of Administration	SC	IV	Oral	Oral
Recommended Dose	284 mg SC every week via pre-filled syringe	0.3 mg/kg IV every three weeks, with a maximum dose of 30 mg for patients who weigh 100 kg or more	20 mg capsule once daily	250 mg twice daily
Serious Side Effects / Safety Issues	Thrombocytopenia, glomerulonephritis, reduced vitamin A levels Contraindicated in patients with platelet count < 100 × 10^9/L, urine protein to creatinine ratio ≥ 113 mg/mmol, estimated glomerular filtration rate < 45 mL/L/min/1.73 m^2, severe liver impairment, or hypersensitivity to the product	Infusion-related reactions, reduced vitamin A levels Contraindications: Severe hypersensitivity to product	Urinary tract infections, vaginal infection, diarrhea, upper abdominal pain Contraindications: hypersensitivity to product	Gastrointestinal ulceration and bleeding, altered renal function, renal decompensation, fluid retention, precipitate congestive heart failure Contraindications: hypersensitivity to product or active peptic ulcer

	Inotersen	Patisiran	Tafamidis	Diflunisal
Other	Monitoring of platelet count is required every two weeks for platelet levels > 100 × 10^9/L (increased monitoring and dose adjustments are required for levels < 100 × 10^9/L and drug discontinuation is required for levels < 25 × 10^9/L); vitamin A supplementation is recommended	Must be administered by a health care professional in a supervised setting; premedications are required to minimize the risk of infusion-related reactions (oral acetaminophen, IV corticosteroid, IV histamine-1 blocker, and IV histamine-2 blocker); vitamin A supplementation is recommended	–	Drug not routinely stocked in Canadian pharmacies

EMA = European Medicines Agency; FDA = US Food and Drug Administration; hATTR = hereditary transthyretin-mediated amyloidosis; IV = intravenous; mRNA = messenger ribonucleic acid; RNA = ribonucleic acid; SC = subcutaneous; TTR = transthyretin.

Source: Onpattro draft product monograph;[15] Tegsedi product monograph;[15] Tafamidis summary of product characteristics;[19] Diflunisal product monograph;[20] Berk et al., 2013.[14]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of inotersen 189 mg/mL SC injection for the treatment of stage I or stage II polyneuropathy in adults with hATTR.

Methods

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

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults with hereditary transthyretin-mediated amyloidosis with stage I or stage II polyneuropathy Subgroups: • patients with stage I or stage II polyneuropathy • patients with cardiac manifestations • patients with a previous liver transplant • patients treated previously with a TTR stabilizer • mutation type (V30M versus non-V30M)
Intervention	Inotersen 300 mg SC once weekly
Comparators	• Patisiran • Diflunisal[a] • Tafamidis[b] • Supportive care • Placebo
Outcomes	**Efficacy Outcomes** • Mortality (e.g., cardiovascular or all-cause) • Hospitalizations (e.g., cardiovascular or all-cause) • Health-related quality of life[c] • Cardiovascular morbidity (e.g., NYHA class)[c] • Neurological impairment (including autonomic nervous system)[c] • Neurological symptoms (e.g., pain)[c] • Disability[c] • Functional status[c] • Nutritional status • Cardiac morbidity, biomarkers, or measures of cardiac structure and function (e.g., NT-proBNP, troponin I, LV wall thickness, LV longitudinal strain, LVEF) **Harms Outcomes** AEs, SAEs, WDAEs, injection-related reactions, signs or symptoms of vitamin A deficiency (e.g., night blindness), anti-drug antibodies, thrombocytopenia, glomerulonephritis / renal function decline
Study Design	Published and unpublished phase III and IV RCTs

AE = adverse event; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; TTR = transthyretin; WDAE = withdrawal due to adverse event.

[a] Off-label use in Canada.

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

[c] In the input received by CADTH from patient groups, these outcomes were identified as being of particular importance to patients.

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

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

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

The initial search was completed on March 19, 2019. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 17, 2019. Regular search updates were performed on databases that do not provide alert services.

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

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

Results

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

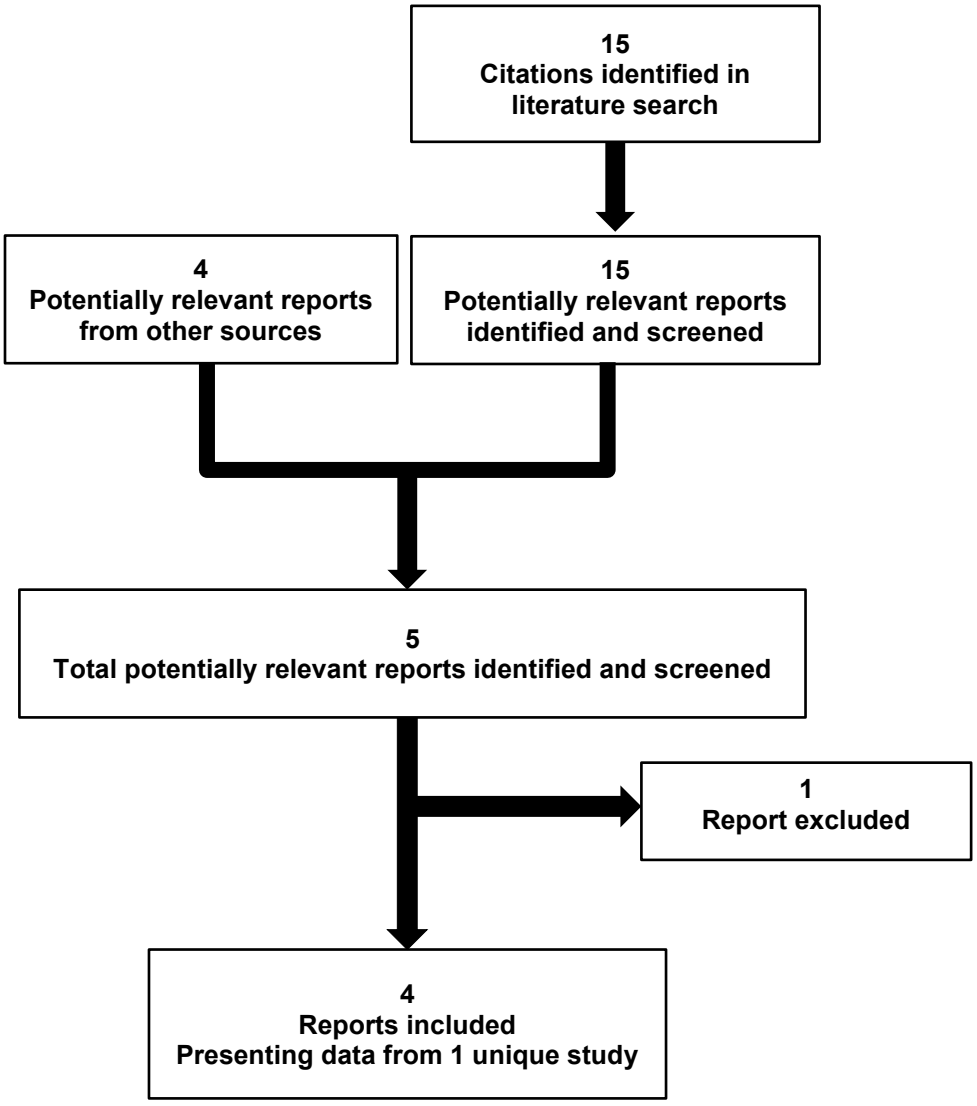

Table 5: Details of Included Studies

		NEURO-TTR
Designs and Populations	**Study Design**	Phase II/III DB RCT
	Locations	24 centres in 10 countries: US, UK, France, Germany, Italy, Portugal, Spain, Argentina, Brazil, and New Zealand
	Randomized (N)	173
	Inclusion Criteria	• 18 to 82 years of age • Stage I or II hATTR polyneuropathy • NIS score ≥ 10 and ≤ 130 • Documented TTR variant by genotyping • Documented amyloid deposit by biopsy
	Exclusion Criteria	• ALT or AST > 1.9 times upper limit of normal • Bilirubin ≥ 1.5 times upper limit of normal • Platelets < 125 × 10^9/L • Positive for protein/blood on urine dipstick • TSH outside normal range • Retinol less than lower limit of normal • Blood pressure > 160/100 mm Hg • Positive for HIV, hepatitis B, or hepatitis C • Karnofsky performance status ≤ 50 • Renal insufficiency (creatinine clearance < 60 mL/min/1.73 m^2) • Type 1 or 2 diabetes • Other causes of sensorimotor or autonomic neuropathy • Treatment with another investigational or biological drug or device within 3 months of screening or 5 half-lives of the study drug • If previously treated with tafamidis, it must have been discontinued for 2 weeks prior to day 1 of study; if previously treated with diflunisal, it must have been discontinued 3 days prior to day 1 of study • Previous treatment with any oligonucleotide or small interfering RNA within 6 months of screening • Prior liver transplant or anticipated liver transplant within one year of screening • NYHA classification ≥ 3 • Acute coronary syndrome or major surgery within 3 months of screening • Known primary amyloidosis • Known leptomeningeal amyloidosis • Anticipated survival < 2 years • Active infection requiring systemic antiviral or antimicrobial therapy • Malignancy within 5 years (except basal or squamous cell carcinoma of skin or carcinoma in situ of cervix that was successfully treated) • Known monoclonal gammopathy or multiple myeloma
Drugs	**Intervention**	Three doses of 300 mg inotersen (equivalent to 284 mg parent acid) SC during week 1, followed by once weekly from weeks 2 to 65
	Comparator(s)	Placebo
Duration	**Phase**	
	Run-in	NA
	Double-blind	65 weeks
	Follow-up	1 week[a]

		NEURO-TTR
Outcomes	**Primary End Point**	• mNIS+7$_{Ionis}$ • Norfolk QoL-DN
	Other End Points	• PND score • NSC score • SF-36v2 • mBMI • NT-proBNP • Echocardiogram parameters (GLS, LVEF, posterior wall thickness) • Harms
Notes	**Publications**	Benson 2018[4]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDR = CADTH Common Drug Review; DB = double blind; GLS = global longitudinal strain; hATTR = hereditary transthyretin-mediated amyloidosis; LVEF = left ventricular ejection fraction; mBMI = modified body mass index; mNIS+7$_{Ionis}$ = modified Neuropathy Impairment Score +7 (Ionis version); NA = not applicable; NIS = Neuropathy Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NSC = Neuropathy Symptoms and Change; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; RCT = randomized controlled trial; RNA = ribonucleic acid; SC = subcutaneous; SF-36v2 = Short Form (36) Health Survey, version 2; TSH = thyroid-stimulating hormone; TTR = transthyretin.

Note: Two additional reports were included (CDR submission[6] and Health Canada review[5]).

[a] This is the one-week period of efficacy evaluation at the end of treatment.

Source: Clinical Study Report for NEURO-TTR.[7]

Included Studies

Description of Studies

One double-blind (DB), parallel-design RCT met the inclusion criteria for the systematic review. The NEURO-TTR trial (NCT01737398) was a phase II/III, combined DB, superiority RCT that compared the efficacy and safety of inotersen 300 mg SC injection weekly with placebo in patients with stage I or II polyneuropathy hATTR. The study was conducted from March 2013 through March 2017 in 24 centres across 10 countries (excluding Canada). A total of 278 patients were screened, of which 173 (62.2%) were randomized in a 2:1 ratio to inotersen (N = 112) or placebo (N = 60) and stratified by previous treatment with tafamidis or diflunisal versus treatment-naive, stage I or II polyneuropathy and the presence or absence of the V30M mutation. The DB treatment phase lasted for 65 weeks followed by an end-of-treatment efficacy assessment period of one week. After completion of the end-of-treatment efficacy assessment, all patients were eligible to enrol in the open-label extension (OLE) study, ISIS 420915-CS3. If patients did not enrol in the OLE, they entered into a six-month post-treatment evaluation period, during which time they received additional visits and a safety assessment. Data for patients in the post-treatment evaluation period are presented in Appendix 6. In Figure 2, the flow of patients in NEURO-TTR from screening to the OLE study or six-month post-treatment evaluation is displayed.

Figure 2: Study Design of NEURO-TTR

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

Extracted from Clinical Study Report for NEURO-TTR.[7]

Populations

Inclusion and Exclusion Criteria

Patients 18 to 82 years of age, with stage I or II hATTR polyneuropathy and a Neuropathy Impairment Score (NIS) ≥ 10 and ≤ 130 were included in the trial. Patients also required a documented TTR genetic variant and presence of amyloid deposit by biopsy. Stages I and II were defined based on ability to ambulate, according to the following:[7]

- Stage I: Does not require assistance with ambulation
- Stage II: Requires assistance with ambulation
- Stage III: Confined to a wheelchair.

Patients with a previous liver transplant, New York Heart Association (NYHA) class ≥ 3, stage III polyneuropathy, and an anticipated survival of less than two years were excluded. If patients were previously treated with tafamidis or diflunisal, these drugs were to be discontinued two weeks or three days, respectively, prior to the start of the study. Patients were eligible to enter the cardiomyopathy-echocardiogram (CM-ECHO) subgroup if they were diagnosed with hATTR cardiomyopathy at study entry or were eligible to participate in the echocardiogram subgroup (i.e., patients with the following at study entry: left ventricular (LV) wall thickness ≥ 13 mm, no history of persistent hypertension ≥ 150 mm Hg within 12 months of screening, and an evaluable baseline echocardiogram as assessed by the central reader). Most patients were enrolled from sites in North America (47.7%) and Europe (34.9%), and the remainder were from South America or Australasia (17.4%).[7]

Baseline Characteristics

Table 6 provides the baseline characteristics of patients in the placebo and inotersen arms of NEURO-TTR. The mean age of randomized patients (N = 172) in both arms combined was 59.2 years (range, [redacted] years). There were more males (68.6%) than females (31.4%) and the majority of patients were white (91.9%). [redacted] The baseline modified Neuropathy Impairment Score + 7 (Ionis version) (mNIS+7$_{Ionis}$) (see outcomes section for definition) was higher in the inotersen group compared with placebo (79.16 versus 74.75). [redacted].[7] More patients in the inotersen group were also in PND stage II or higher (71.4% versus 61.7%). A total of 27 different TTR mutations were identified and the most common mutation was V30M (51.7%), followed by [redacted]. Among the least common mutations were [redacted].[7]

At study entry, about [redacted] of patients were diagnosed with hATTR cardiomyopathy (based on cardiac biopsy, echocardiogram result, or other), and was slightly higher in the inotersen group compared with placebo ([redacted]).[7] Also, more patients in the inotersen group were recruited into the CM-ECHO subgroup than patients in the placebo group (66.4% versus 55.0%). Patients in the inotersen group may have had more severe cardiomyopathy

than patients who received placebo (baseline N-terminal prohormone of brain natriuretic peptide [NT-proBNP], 121.6 pmol/L versus 82.0 pmol/L; global longitudinal strain, −15.9% versus −16.5%; and LV mass, 223.7 g versus 195.8 g).[7] Overall, patients in NYHA class I and II were balanced between the groups, although slightly more patients in the inotersen group were in NYHA class II (36.6% versus 33.3%).

[redacted]

Table 6: Summary of Baseline Characteristics

Characteristic	NEURO-TTR	
	Placebo (N = 60)	Inotersen (N = 112)
Mean age (SD), years	59.5 (14.0)	59.0 (12.5)
Age range, years	[redacted]	[redacted]
Male, n (%)	41 (68.3)	77 (68.8)
Race, n (%)		
White	53 (88.3)	105 (93.8)
Black	1 (1.7)	3 (2.7)
Asian	3 (5.0)	1 (0.9)
Other	3 (5.0)	3 (2.7)
Years since hATTR polyneuropathy diagnosis, mean (range)	3.3 (0.08 to 13.3)	3.5 (0.17 to 24.8)
Stage I, mean (SD)	3.8 (3.6)	3.6 (4.0)
Stage II, mean (SD)	2.1 (2.4)	3.4 (4.8)
mNIS+7$_{Ionis}$, mean (SD)	74.75 (39.00)	79.16 (36.96)
Norfolk QoL-DN, mean (SD)	48.68 (26.75)	48.22 (27.50)
Disease stage		
Stage I	42 (70.0)	74 (66.1)
Stage II	18 (30.0)	38 (33.9)
PND score by stage, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
V	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	24.21 (4.86)	23.99 (4.90)
mBMI (kg/m^2 × g/dL), mean (SD)	105.0 (22.8)	101.1 (22.8)
Genotype, n (%)		
V30M	33 (55.0)	56 (50.0)
Non-V30M	27 (45.0)	56 (50.0)
Diagnosed with hATTR cardiomyopathy[a]		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
NYHA class, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]

Characteristic	NEURO-TTR	
Previous tetramer stabilizer use, n (%)	[redacted]	[redacted]
Tafamidis	[redacted]	[redacted]
Diflunisal	[redacted]	[redacted]

BMI = body mass index; hATTR = hereditary transthyretin-mediated amyloidosis; mBMI = modified body mass index; mNIS+7$_{Ionis}$ = modified Neuropathy Impairment Score + 7 (Ionis version); Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NYHA = New York Heart Association; PND = polyneuropathy disability; SD = standard deviation.

[a] Diagnosed based on cardiac biopsy, echocardiogram result, or other.

Source: Clinical Study Report for NEURO-TTR;[7] Benson, 2018.[4]

Interventions

Inotersen 300 mg (284 mg parent acid) was administered subcutaneously as a single 1.5 mL injection three times as a loading dose on alternate days during the first week, followed by once weekly thereafter from weeks 2 to 65 for a total of 67 doses. If the treatment day coincided with a clinic visit, the injection was administered at the clinic. Otherwise, the injection was administered by study centre personnel or at home by the patient or a caregiver who was trained in administration procedures. The placebo was also administered as a 1.5 mL solution SC injection.

[redacted]

All patients were required to take daily oral supplemental doses of the recommended daily allowance of vitamin A, which was about 3,000 IU. The supplemental dose was provided as a single supplement of commercially available vitamin A or as part of a multivitamin.

Outcomes

The co-primary outcomes were change from baseline to week 66 in the mNIS+7$_{Ionis}$ total score and the Norfolk Quality of Life-Diabetic Neuropathy questionnaire (Norfolk QoL-DN) total score. The mNIS+7$_{Ionis}$ assessment was conducted two times at baseline less than seven days apart (the baseline reading was the average of the two measurements at the sub-component level before the total score was calculated), within 14 days of the first dose of the study drug, at week 35, and two times at week 66 (the week 66 reading was the average of the two measurements at the sub-component level before the total score was calculated). The mNIS+7$_{Ionis}$ assessors were specially trained and prequalified by a central reader. The Norfolk QoL-DN was administered once at baseline, at week 35, and at week 66.

The secondary objectives were to evaluate change from baseline to week 65 in the Norfolk QoL-DN symptoms domain score in stage I and physical functioning / large-fibre neuropathy domain score in stage II, mBMI, and global longitudinal strain by

echocardiogram in the CM-ECHO subgroup. A transthoracic echocardiogram was performed at baseline and at week 65.

Tertiary objectives were to evaluate change from baseline to week 65 in the Short Form (36) Health Survey, version 2 (SF-36v2), individual components of the mNIS+7$_{\text{lonis}}$, and the individual domain scores of the Norfolk QoL-DN questionnaire. Exploratory outcomes were other echocardiogram parameters in the CM-ECHO subgroup, plasma NT-proBNP, PND score, and Neuropathy Symptoms and Change (NSC) score.

Appendix 5 provides details about the outcome measures.

- The Norfolk QoL-DN is a self-administered patient-reported instrument to assess the impact of neuropathy on functional status. It is a disease-specific HRQoL instrument. The domains of the Norfolk QoL-DN are physical function / large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy. The instrument was originally developed for patients with diabetic neuropathy and has been validated in patients with hATTR. A minimal clinically important difference (MCID) for the Norfolk QoL-DN has not been identified.
- The SF-36v2 is a generic HRQoL measure that consists of two composite scores, the physical component summary (PCS) score and the mental component summary (MCS) score, and the following eight domain scores: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Each of the eight domains is scored on a domain-specific scale, where higher scores correspond with better health. Based on anchor data, the developer of the SF-36v2 proposed the following minimal mean group differences for the individual domain scores: physical function, 3; role physical, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3. In general, a change of two points on the PCS and three points on the MCS of the SF-36v2 indicates a clinically meaningful improvement as determined by the patient. The reliability and validity of the SF-36v2 have been demonstrated in various conditions, however, not in patients with hATTR.
- The mNIS+7$_{\text{lonis}}$ is a composite outcome of neurological function, with higher scores indicating worse outcomes. The mNIS+7$_{\text{lonis}}$ was developed specifically for the monitoring of polyneuropathy in patients with hATTR and has been validated, although no anchor-based MCID has been identified. The Peripheral Nerve Society[8] has proposed an MCID of two points in patients with diabetic neuropathy, based on the smallest difference that physicians can detect on the NIS component. The actual meaningfulness of this difference to patients with hATTR is unclear. The mNIS+7$_{\text{lonis}}$ consists of the NIS composite score (maximum of 244 points) and the modified +7 composite score (maximum of 102.32 points). The normal deviates for heart rate response to deep breathing and nerve conduction were used in calculating the total mNIS+7$_{\text{lonis}}$ score in NEURO-TTR. Table 7 provides the components and scoring of the mNIS+7$_{\text{lonis}}$.

Table 7: Components of the Modified Neuropathy Impairment Score (Ionis Version)

Component	Scoring (Points)
NIS Composite	
Cranial nerves	0 to 40
Muscle weakness	0 to 152
Reflexes	0 to 20
Sensation	0 to 32
Modified +7 Composite	
Autonomic nerve assessment: HRDB	−3.72 to 3.72
Peripheral nerve assessment of lower and upper limbs: ∑5 NCS	−18.6 to 18.6
Sensory nerve assessment: touch pressure	0 to 40
Sensory nerve assessment: heat pain	0 to 40

∑5 NCS = sum of five attributes of nerve conduction studies; CDR = CADTH Common Drug Review; HRDB = heart rate to deep breathing; NC = nerve conduction; NIS = Neuropathy Impairment Score.

Source: CDR submission.[6]

The mNIS+7$_{Ionis}$ differs from the mNIS+7 used in the APOLLO trial for patisiran[21] in that it includes NIS-sensation and assesses autonomic dysfunction by measuring heart rate decrease with deep breathing rather than postural blood pressure. A comparison of the mNIS+7, mNIS+7$_{Ionis}$, and the NIS is presented in Appendix 5, Table 30.

- The NSC is a patient questionnaire that consists of five symptom domains (muscle weakness; sensory – hypo/loss of sensation; sensory – paresthesia/hypersensation; autonomic – gastrointestinal and urinary incontinence; and autonomic – non-gastrointestinal or urinary incontinence) and 38 questions. The score ranges from 0 to a maximum of 108 for women and 114 for men, with higher scores representing more severe disease. Components of the NSC were found to correlate with the Norfolk QoL-DN and mNIS+7$_{Ionis}$ in patients with hATTR. No information was available on the reliability, responsiveness, or MCID of the NSC in patients with hATTR or other neurological conditions.
- The PND score is used by physicians to classify hATTR and is primarily based on ambulation, according to the following stages:
  - Stage 0: No symptoms
  - Stage I: Sensory disturbances but preserved walking capability
  - Stage II: Impaired walking capacity but ability to walk without a stick or crutches
  - Stage IIIA: Walking with the help of one stick or crutch
  - Stage IIIB: Walking with the help of two sticks or crutches
  - Stage IV: Confined to a wheelchair or bedridden.
- The nutritional status of patients was evaluated using the mBMI, which is calculated as the product of body mass index (weight in kilograms divided by the square of the height in metres) and serum albumin (g/L). The mBMI corrects for hypoalbuminemia and edema and may reflect nutritional status more accurately than body mass index in conditions such as hATTR that are affected by wasting.
- Cardiac structure and function were assessed with echocardiogram (i.e., global longitudinal strain, left ventricular ejection fraction [LVEF] and LV wall thickness) and measurement of NT-proBNP, a biomarker of cardiac function.

Harms included adverse events (AEs), serious adverse events (SAEs), and immunogenicity. Harms were reported during the on-study period, which was the time

during which treatment was administered until the patient's last contact date in the study. AEs of special interest were those that were identified as important medical risks and included ocular AEs related to vitamin A deficiency, thrombocytopenia, and renal impairment. Platelets were monitored weekly throughout the treatment period and for at least six weeks after the last dose of study drug. If the platelet count was less than 75,000/mm,[3] further doses of the study drug were held until the count increased to at least 100,000/mm.[3] If the platelet count fell below 50,000/mm,[3] then monitoring occurred daily until two successive values showed improvement.

For efficacy outcomes (except for mBMI), the on-treatment assessment period was defined as the time during which the study treatment was administered until 52 days after the last dose of medication. For mBMI, the on-treatment assessment period was the time during which the study treatment was administered until 28 days after the last dose of medication.

Statistical Analysis

Sample Size

The planned sample size was 135 patients, based on a 2:1 ratio of randomization and estimates for changes from baseline in the mNIS+7$_{Ionis}$ and the Norfolk QoL-DN. The estimates were from the published results of a placebo-controlled phase III trial of diflunisal, a retrospective multinational natural history study in 283 patients with hATTR polyneuropathy and uncontrolled data for another TTR mRNA oligonucleotide.[7] The mNIS+7$_{Ionis}$ was estimated to increase by 16 points from baseline to month 15 in the placebo group and by 6.4 points in the treatment group, with a standard deviation (SD) of 14 for the change from baseline in each group.[7] The Norfolk QoL-DN was estimated to increase by 13.3 points from baseline to month 15 in the placebo group and by 2.6 points in the treatment group, with an SD of 18 for the change from baseline in each group.[7] A sample size of 135 provided at least 90% power to detect a 9.6 point difference in the mNIS+7$_{Ionis}$ mean change from baseline between placebo and treatment, and 80% power to detect a 10.7 point difference in the Norfolk QoL-DN, with a two-sided alpha level of 5% and a dropout rate of 25%.[7]

Analyses

The primary analysis was an end-of-treatment efficacy assessment at week 66 in the full analysis set (FAS) using a mixed-effect model with repeated measures (MMRM) at different visits. The MMRM adjusts for categorical effects of treatment (two levels), time (two levels), treatment by time interaction, and each randomization stratification factor (i.e., previous treatment with tafamidis or diflunisal, stage I or II disease, and V30M mutation or non-V30M mutation). The baseline and baseline by time interaction were fixed covariates in the model. The outcomes that were analyzed with the MMRM method were all primary, secondary, and tertiary end points, and exploratory outcomes of echocardiogram parameters, NSC, and NT-proBNP (log-transformed). The difference in change from baseline, between inotersen and placebo, was presented as the least squares mean (LSM) difference with 95% confidence interval (CI).

Missing Data

The mNIS+7$_{Ionis}$ and Norfolk QoL-DN total scores, as well as their components, were considered missing if a patient missed a visit, the visit was performed outside of the analysis window, or the assessment was not conducted at a visit. Missing data in the

primary analyses were handled using the MMRM modelling approach. The modelling strategy assumes that missing data were missing at random.

[redacted]

Adjustment for Multiplicity

The two primary outcomes (i.e., mNIS+7$_{lonis}$ and Norfolk QoL-DN) were tested with a hierarchical ranking strategy to control for multiplicity. The mNIS+7$_{lonis}$ change from baseline to week 66 between inotersen and placebo was tested first with a two-sided alpha level of 0.05. If the null hypothesis for mNIS+7$_{lonis}$ was rejected, then the null hypothesis for the Norfolk QoL-DN was tested with a two-sided alpha level of 0.05. However, if the null hypothesis for mNIS+7$_{lonis}$ was not rejected, then the Norfolk QoL-DN was considered exploratory.

All other secondary, tertiary, and exploratory outcomes were not adjusted for multiplicity.

Sensitivity Analyses

Several sensitivity analyses were conducted to evaluate different methods for imputing missing data, different analysis sets, and different methods for assessing the mNIS+7$_{lonis}$ and Norfolk QoL-DN. The following sensitivity estimates are presented in this review:

- The multiple imputation assuming missing at random method uses means and variances–covariances, after withdrawal, that are based on the patients' treatment group.
- The jump-to-reference method imputes missing placebo data using a missing-at-random assumption and imputes missing inotersen data with the mean response of the placebo group.
- The per-protocol sensitivity analysis is based on the per-protocol set.
- For the mNIS+7$_{lonis}$, scoring heart rate response to deep breathing and nerve conductions using points rather than normal deviates and excluding NIS-sensation.
- For the mNIS+7$_{lonis}$, excluding the domain of heart rate response to deep breathing, for which many observations were missing.

Subgroup Analyses

The following pre-specified subgroup analyses that were relevant for this review were conducted for the mNIS+7$_{lonis}$ and the Norfolk QoL-DN: disease stage (stage I or stage II), patients in the CM-ECHO group (representing patients with cardiac manifestations), V30M mutation and non-V30M mutation, and previous treatment with tafamidis or diflunisal.

Analysis Populations

The randomized set included all patients who were screened and who received a randomization assignment.

The FAS was the primary population for efficacy analysis. This set included all randomized patients who received at least one injection of placebo or inotersen and who had a baseline and at least one post-baseline assessment of the mNIS+7$_{\text{Ionis}}$ total score or Norfolk QoL-DN total score. The results were presented according to randomized treatment.

The per-protocol set included a subset of patients from the FAS who received at least 80% of the prescribed doses of placebo or inotersen and who had no major protocol violations. The per-protocol set was examined in sensitivity analyses for the mNIS+7$_{\text{Ionis}}$ and the Norfolk QoL-DN. The results were presented according to actual treatment received.

The CM-ECHO set included patients who were randomized and who met at least one of the following criteria: diagnosis of TTR cardiomyopathy at study entry or eligible to participate in the echocardiogram subgroup (patients were eligible for the echocardiogram subgroup if they satisfied the following entry criteria: LV wall thickness ≥ 13 mm on transthoracic echocardiogram, no known history of persistent hypertension ≥ 150 mm Hg within 12 months prior to screening, and baseline echocardiogram was evaluable). The results were presented according to randomized treatment.

The safety set included all randomized patients who received at least one injection of placebo or inotersen. The results were presented according to actual treatment received.

The primary and secondary outcomes, except for global longitudinal strain, were assessed in the FAS. Global longitudinal strain and other echocardiogram outcomes were assessed in the all-randomized set and the CM-ECHO set. Tertiary outcomes were assessed in the FAS and safety was assessed in the safety set.

Patient Disposition

Table 8 provides the patient disposition for the placebo and inotersen groups of NEURO-TTR. Of the 173 patients randomized, 172 (60 placebo and 112 inotersen) received at least one dose of study treatment and were included in the safety set. One patient in the inotersen group was randomized in error and did not receive study treatment. More patients (23.0%) in the inotersen group discontinued treatment than the placebo group (13.3%). The primary reason for discontinuation was an AE, which occurred more frequently in patients who received inotersen (14.2% versus 1.7%). The FAS used in the primary efficacy analyses included 165 patients (95.9%), with the proportion included in the inotersen group (N = 106, 94.6%) slightly lower than the placebo group (N = 59, 98.3%). At study entry, 62.8% of patients (55% placebo and 67% inotersen) were diagnosed with cardiomyopathy or were eligible to participate in the echocardiogram subgroup and were included in the CM-ECHO set.

Table 8: Patient Disposition

	NEURO-TTR	
	Placebo	**Inotersen**
Screened, N	278	
Randomized, N (%)	173 (62.2)	
	60	113
Received at least one dose of study drug, N (%)	60 (100)	112 (99.1)
Patients who completed treatment, N (%)	52 (86.7)	87 (77.0)
Patients who discontinued treatment, N (%)	8 (13.3)	26 (23.0)
Adverse event	1 (1.7)	16 (14.2)
Stopping rule met[a]	1 (1.7)	2 (1.8)
Voluntary withdrawal	3 (5.0)	2 (1.8)
Ineligibility	0 (0)	1 (0.9)
Liver transplant	0 (0)	1 (0.9)
Disease progression	3 (5.0)	2 (1.8)
Other	0 (0)	2 (1.8)
FAS, N	[redacted]	[redacted]
PP, N	[redacted]	[redacted]
CM-ECHO subgroup, N	33	75
Safety, N	60	112

AE = adverse event; CM-ECHO = cardiomyopathy-echocardiogram; FAS = full analysis set; PP = per-protocol.

[a] Patients were required to permanently discontinue treatment for the following reasons: pregnancy, withdrawal of consent, an AE that required permanent discontinuation of study treatment, laboratory test abnormalities that met any of the protocol-specified stopping rules, or an AE that required unblinding of the investigator to the patient's treatment assignment.

Source: Clinical Study Report for NEURO-TTR.[7]

Exposure to Study Treatments

The mean number of doses received was about [redacted] for placebo (range [redacted]) and [redacted] for inotersen (range [redacted]). [redacted] The main reason for pauses in dosing were [redacted]

Critical Appraisal

Internal Validity

NEURO-TTR included a relatively large number of patients (N = 172, 24 cites across 10 countries) with this rare condition. Although the trial employed proper randomization procedures by using an interactive voice / Web-response system, the baseline differences in neuropathy and cardiomyopathy suggest that randomization or allocation may have been compromised. At baseline, the inotersen group had a higher mNIS+7$_{Ionis}$ total score [redacted], and more patients were in PND stage II

or higher, which suggested that the inotersen group started the study with more severe neuropathy. Patients in the inotersen group may also have had more severe cardiomyopathy than patients in the placebo group based on [redacted], baseline NT-proBNP level, global longitudinal strain, and LV mass. There were also slight imbalances in race, disease stage, and previous TTR stabilizer use. The clinical relevance of these differences is unclear. In clinical trials of rare diseases with small numbers of patients, differences in baseline characteristics may be observed and due to chance alone. In this trial, however, there were consistent differences in measures of neuropathy and cardiomyopathy that suggested that the inotersen group started with more severe disease. These imbalances would have biased treatment response against inotersen; however, despite the imbalance, efficacy estimates favoured inotersen. [redacted]

Patients, sponsors, monitors, and study centre personnel were blinded throughout the study until all patients had completed the treatment period and end-of-treatment efficacy assessments. The NIS component of the mNIS+7$_{Ionis}$ was performed by an independent neurologist who was blinded to treatment allocation and who was not involved in the day-to-day care of patients. Both inotersen and placebo were contained in stoppered glass vials and stored at 2°C to 8°C and administered in a similar manner (1.5 mL solution SC injection). It is unclear if the appearance of the study drugs (e.g., colour, viscosity) were similar.

Although the study was double-blinded, about one-third of patients who received inotersen experienced injection-site erythema and one-fifth experienced injection-site pain, whereas in the placebo group, injection-site reactions were experienced at a much lower incidence. The presence of an injection-site reaction may have led patients or investigators to accurately guess that an active treatment was being administered. If patients of investigators were able to correctly guess treatment, this may have led to bias in the subjectively assessed outcomes of Norfolk QoL-DN, SF-36v2, and NSC score, with the direction of bias in favour of inotersen if patients believed that active treatment would improve their condition.

NEURO-TTR included efficacy outcomes related to neuropathy, HRQoL, nutritional status, and outcomes related to cardiac morbidity. One of the primary outcomes, the Norfolk QoL-DN, has been validated in patients with hATTR. The other primary outcome, mNIS+7$_{Ionis}$, was developed specifically to assess polyneuropathy in patients with hATTR. The mNIS+7$_{Ionis}$ assessors in NEURO-TTR were specially trained and prequalified by a central reader,[4] although details about the type of training received were not provided. Several of the efficacy outcomes (i.e., Norfolk QoL-DN, mNIS+7$_{Ionis}$, SF-36v2, and NSC) include subjective components. These outcomes may be subject to a greater risk of bias due to unblinding than the more objective outcomes of mBMI, PND score, NT-proBNP, and echocardiogram parameters. Any biases resulting from misclassification of patients on stratification factors with the interactive voice / Web-response system appear to be minimal. The manufacturer conducted analyses based on the case report form results and found that statistical significance between inotersen and placebo remained unchanged for most outcomes, except for the Norfolk QoL-DN domain of physical functioning / large-fibre neuropathy, which lost statistical significance.

The number of patients who discontinued from treatment was much higher in the inotersen group than placebo, and primarily because of AEs, which indicates that attrition was not random. In the inotersen group, 23% of patients discontinued treatment, whereas in the placebo group, about 13% of patients discontinued. The exclusion of these patients from analyses may have biased results in favour of inotersen if these patients ended up having worse outcomes.

The primary outcomes (i.e., mNIS+7 and Norfolk QoL-DN) were tested with a hierarchical strategy. All other efficacy outcomes were tested at a two-sided alpha of 0.5 with no adjustment for the performance of multiple statistical tests. The primary efficacy analyses (aside from the echocardiogram parameters) were conducted on the FAS, which included patients who accepted at least one injection of treatment and with at least one post-baseline assessment of the primary outcomes. The FAS excluded one patient randomized to the placebo group and six patients from the inotersen group. In addition, many patients were excluded from statistical analyses of efficacy outcomes at week 65 or week 66; in the placebo group, the percentage of patients included for the analysis at week 65 or week 66 ranged from 83% (mBMI) to 88% (Norfolk QoL-DN, mNIS+7_{lonis}, NSC score, and PND score), and in the inotersen group the percentage ranged from 77% (mBMI) to [redacted]. The percentage of patients included in the 65-week analyses were even lower for some of the cardiac outcomes (e.g., 75% placebo and 69% inotersen for LVEF). This may have further compromised randomization and resulted in biasing outcomes in favour of inotersen because only those patients who tolerated and responded to treatment may have remained in the final analyses. Several sensitivity analyses were performed on the primary outcomes of mNIS+7_{lonis} and Norfolk QoL-DN, including with multiple imputation assuming a jump-to-reference approach, which included all patients randomized to placebo (N = 60) and inotersen (N = 112). The jump-to-reference approach imputed missing inotersen data with the mean response of the placebo group. Other sensitivity analyses were conducted as described in the statistical analysis section. The jump-to-reference analysis is the most informative for addressing bias due to differential attrition rates because it included all randomized patients and assumed that patients in the inotersen group responded in the same way as placebo. The results of the jump-to-reference sensitivity analyses for the Norfolk QoL-DN and mNIS+7_{lonis} continued to favour inotersen, although the point estimates were smaller in magnitude than the primary analyses. Likewise, the Health Canada review indicated that the estimates for the jump-to-reference analyses were preferred to address potential biases in the main analyses.[5]

No sensitivity analyses were performed for all other efficacy outcomes and, therefore, it is unclear if the results of the primary analyses would be the same if all randomized patients were included.

According to the manufacturer's statistical analysis plan, The MMRM model used for efficacy outcomes implicitly accounted for missing data, assuming that data were missing at random. Given the differential attrition rates in the inotersen group, the assumption of data missing at random may not be valid. [redacted].
The pattern of missing data for the other outcomes is unclear.

External Validity

There is limited information and data about the characteristics of patients with hATTR in Canada, and no patients with hATTR in Canada were included; thus, the generalizability of the patient population in NEURO-TTR is unclear. NEURO-TTR did not have any study sites in Canada. Clinical expert input suggested the baseline characteristics of patients in NEURO-TTR were representative of the patients with hATTR polyneuropathy seen in practice. The mean age of patients in NEURO-TTR was 59.2 years ([redacted]), with the majority being male (≈ 69%) and white (≈ 92%). The age of onset for symptoms in hATTR ranges from the second to ninth decade of life, so the age range of patients was appropriate.[1] The most common mutation in the NEURO-TTR population was V30M and, among the least common mutation, was [redacted]. According to one of the clinical experts consulted for this review, most patients in Canada with hATTR have either the V30M mutation (patients of Portuguese or Italian descent) or the Val122Ile mutation (patients of Caribbean descent).

The trial excluded patients with more severe disease, such as stage III polyneuropathy, patients with NIS > 130, NYHA class ≥ 3, and a Karnofsky performance status ≤ 50. The trial also excluded patients with type 1 or 2 diabetes, concurrent use of tafamidis or diflunisal, prior liver transplant, acute coronary syndrome, leptomeningeal amyloidosis, and patients with an anticipated survival of less than two years. The results, therefore, cannot be generalized to these patients. In addition, since the trial included patients with stage I or II polyneuropathy, the results cannot be extrapolated to patients with advanced polyneuropathy who are confined to a wheelchair. It is also unclear if the results would apply to patients with hATTR who present with predominant cardiomyopathy, as these patients were not included in the trial.

Inotersen was administered as a loading dose of three injections of 300 mg during the first week, followed by once weekly thereafter, and was supplied in stoppered glass vials. The Health Canada product monograph indicates no loading dose is needed during the first week. In the Health Canada review, it is mentioned that a loading dose may increase the risk of adverse effects and is not required when treatment is administered for an extended time period.[5,15] Patients were required to take daily oral supplemental doses of the recommended daily allowance of vitamin A, which was about 3,000 IU, which is also recommended in the product monograph.[15]

Inotersen was compared with placebo while, in clinical practice, patients may be treated with liver transplant, a TTR stabilizer (i.e., tafamidis, which is available in Canada through the Health Canada Special Access Programme, or diflunisal, which is used off-label for hATTR), or the ribonucleic acid interference drug, patisiran, which is anticipated to receive a Health Canada NOC. However, no data were available to assess the efficacy and safety of inotersen in patients with liver transplantation or its use as an add-on to TTR stabilizers. Therefore, the generalizability of the findings to real-world clinical practice is limited.

The primary outcomes of neuropathy, the mNIS+7$_{\text{Ionis}}$ and Norfolk QoL-DN scores, are validated measures in patients with hATTR. The clinical experts consulted for this review indicated that the mNIS+7 is not routinely applied in its entirety in clinical practice and is resource-intensive to administer. Patients were followed for up to 66 weeks, which may be an adequate length of time for a clinical trial on this rare and progressive condition; however, it is not reflective of clinical practice because patients will likely stay on this

medication for extended periods. The extension of NEURO-TTR is following patients for up to five years and provides data for longer-term treatment.

Efficacy

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

Recall that only the change from baseline to week 66 for the primary outcomes, the Norfolk QoL-DN and total mNIS+7$_{\text{Ionis}}$ scores, were adjusted for multiplicity based on the statistical analysis plan for NEURO-TTR. Interpretations of the 95% CIs and *P* values (two-sided alpha 0.05) for all other comparisons should take into consideration the potential for inflated type I error.

Mortality

Mortality data are presented in detail in the harms section. There were five deaths in the inotersen group and none in the placebo group.

Hospitalizations

No data were available for hospitalizations.

Health-Related Quality of Life

Table 9 presents score data for the disease-specific HRQoL instrument, the Norfolk QoL-DN, at baseline, week 66, and the LSM difference in change from baseline. At week 66, [redacted]. The LSM difference in change from baseline for inotersen compared with placebo was −11.68 points (95% CI, −18.29 to −5.06). Figure 3 shows [redacted]. In sensitivity analyses (Table 19 in Appendix 4), the LSM differences in change from baseline for the Norfolk QoL-DN supported the primary analysis.

Figure 3: Norfolk Quality of Life-Diabetic Neuropathy Least Squares Mean Change From Baseline (Full Analysis Set)

Figure 3 contained confidential information and was redacted at the request of the manufacturer.

Source: Extracted from the Clinical Study Report for NEURO-TTR (p.104).[7]

Table 20 in Appendix 4 provides data for the individual domains of the Norfolk QoL-DN in the FAS. The LSM differences favoured inotersen versus placebo for physical functioning / large-fibre neuropathy (LSM difference, −6.33; 95% CI, −10.03 to −2.62), symptoms score (LSM difference, −2.80; 95% CI, −4.47 to −1.13), and activities of daily living (LSM difference, −2.10; 95% CI, −3.34 to −0.85).

In subgroup analyses (Table 21 in Appendix 4), the treatment by subgroup interactions were not statistically significant for disease stage (stage I or II), the CM-ECHO set, V30M or non-V30M mutation, and previous treatment or no treatment with a TTR stabilizer. Treatment effects were statistically significant in favour of inotersen for all subgroups of interest except for previous treatment with TTR stabilizer, which was not statistically significant.

Table 9: Disease-Specific Health-Related Quality of Life

	Baseline		Week 66			LSM Difference: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)	Change, LSM (SE)		
Norfolk QoL-DN (FAS)							
Placebo (N = 59)	[redacted]	[redacted]	52 (88.1)	[redacted]	12.67 (2.67)	−11.68 (−18.29 to −5.06)	0.0006
Inotersen (N = 106)	[redacted]	[redacted]	84 (79.2)	[redacted]	0.99 (2.12)		

CI = confidence interval; FAS = full analysis set; LSM = least squares mean; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; SD = standard deviation; SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.

Note: Table 10 presents results for the SF-36v2, which is a generic health-related quality-of-life instrument. The SF-36v2 was not part of the statistical hierarchy testing strategy.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 10: Generic Health-Related Quality of Life

	Baseline		Week 65			LSM Difference: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)	Change, LSM (SE)		
SF-36v2 PCS (FAS)							
Placebo (N = 59)	[redacted]	[redacted]	51 (86.4)	[redacted]	−3.65 (1.01)	3.59 (1.07 to 6.12)	0.006[b]
Inotersen (N = 106)	[redacted]	[redacted]	85[a] (80.2)	[redacted]	−0.05 (0.80)		
SF-36v2 MCS (FAS)							
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.088[b]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted][a]	[redacted]	[redacted]		

CI = confidence interval; FAS = full analysis set; LSM = least squares mean; MCS = mental component summary; PCS = physical component summary; SD = standard deviation; SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.

[a] Change from baseline was assessed in 84 patients.

[b] SF-36v2 was outside of the statistical hierarchy testing strategy.

Source: Clinical Study Report for NEURO-TTR.[7]

Neurologic Impairment

Table 11 presents data for the total mNIS+7$_{\text{lonis}}$ score. At week 66, the mean (SD) of the mNIS+7$_{\text{lonis}}$ was [redacted] points in the inotersen group and [redacted] points in the placebo group. The LSM difference in change from baseline favoured inotersen (−19.73; 95% CI, −26.43 to −13.03). Figure 4 [redacted].

Figure 4: Modified Neuropathy Impairment Score + 7 (Ionis Definition) Least Squares Mean Change From Baseline (Full Analysis Set)

Figure 4 contained confidential information and was redacted at the request of the manufacturer.

Source: Clinical Study Report for NEURO-TTR (p. 81).[7]

Table 22 in Appendix 4 presents the sensitivity estimates for mNIS+7$_{Ionis}$. These estimates were also in favour of inotersen and supported the primary analysis for the mNIS+7$_{Ionis}$.

In subgroup analyses (Table 23 in Appendix 4), the treatment by subgroup interaction was statistically significant for disease stage (stage I and stage II) only. Patients in stage II had a larger effect estimate than patients in stage I (LSM, −29.12; 95% CI, −40.22 to −18.02 for stage II and LSM, −14.20; 95% CI, −22.50 to −5.91 for stage I). For other subgroups of interest (i.e., CM-ECHO set, V30M or non-V30M mutation, and previous treatment with a TTR stabilizer), effect estimates were statistically significant in favour of inotersen.

The changes in baseline for the domains of NIS-weakness, NIS-reflexes, and NIS-sensation (Table 24 in Appendix 4) suggested benefit with inotersen compared with placebo. Change from baseline scores were also in favour of inotersen as compared with placebo on the modified +7 composite score (LSM difference in change from baseline, −6.49; 95% CI, −10.32 to −2.66) and the individual nerve conduction and heat pain sensory domain scores (Table 25 in Appendix 4). The domain of heart rate response to deep breathing had many missing observations (36.5% for placebo and 41.2% for inotersen) because it could not be assessed in patients with active pacing or atrial fibrillation.

The NSC score (Table 11) was [redacted], with an LSM difference in change from baseline of [redacted]. The individual NSC domain scores are shown in Table 26 (Appendix 4). Scores for the muscle weakness, sensory (paresthesia, hypersensation), and autonomic (other than gastrointestinal and urinary incontinence) domains also appeared to be in favour of inotersen.

Table 11: Neurologic Impairment

	Baseline		Week 66			LSM Difference: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)	Change, LSM (SE)		
mNIS+7$_{Ionis}$ (FAS)							
Placebo (N = 59)	[redacted]	[redacted]	52 (88.1)	[redacted]	25.53 (2.69)	−19.73 (−26.43 to −13.03)	< 0.0001
Inotersen (N = 106)	[redacted]	[redacted]	85 (80.2)	[redacted]	5.80 (2.13)		
NSC Total Score (FAS)							
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][a]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; FAS = full analysis set; LSM = least squares mean; mNIS+7$_{Ionis}$ = modified Neuropathy Impairment Score + 7 (Ionis version); NSC = Neuropathy Symptoms and Change; SD = standard deviation; SE = standard error.

[a] The NSC was outside of the statistical hierarchy testing strategy.

Source: Clinical Study Report for NEURO-TTR.[7]

Pain

No specific pain outcomes were measured.

Disability and Functional Status

The number of patients whose PND score improved, had no change, or worsened is shown in Table 12. At week 65, PND scores were available for [redacted] in the placebo group and [redacted] in the inotersen group. [redacted]

Table 12: Polyneuropathy Disability Score

	Change From Baseline to Week 65	
	Placebo (N = 59)	Inotersen (N = 106)
PND Score Change (FAS)		
n (%)	[redacted]	[redacted]
Improved	[redacted]	[redacted]
Not changed	[redacted]	[redacted]
Worsened	[redacted]	[redacted]

FAS = full analysis set; PND = polyneuropathy disability.

Source: Clinical Study Report for NEURO-TTR.[7]

Nutritional Status

The mBMI is presented in Table 13.

Table 13: Nutritional Status

	Baseline		Week 65			LSM Difference: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)	Change, LSM (SE)		
mBMI, kg/m^2 × g/L (FAS)							
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][a]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; FAS = full analysis set; LSM = least squares mean; mBMI = modified body mass index; SD = standard deviation; SE = standard error.

[a] The mBMI was outside of the statistical hierarchy testing strategy.

Source: Clinical Study Report for NEURO-TTR.[7]

Cardiovascular Morbidity and Biomarkers

The echocardiogram parameters of global longitudinal strain, LVEF, and posterior LV wall thickness were not statistically different between inotersen and placebo in the all-randomized set (Table 14), [redacted] (Table 15). The CM-ECHO subset (Table 27 and Table 28 in

Appendix 4) did not demonstrate statistical differences in global longitudinal strain, LVEF, posterior LV wall thickness, or NT-proBNP.

Table 14: Echocardiogram Parameters (All-Randomized Set)

	Baseline		Week 65			LSM Difference: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)	Change, LSM (SE)		
GLS (%)							
Placebo (N = 60)	52 (86.7)	−16.49 (4.05)	46 (76.7)[a]	−16.24 (4.25)	0.55 (0.49)	0.31 (−0.84 to 1.47)	0.594[b]
Inotersen (N = 113)	98 (86.7)	−15.92 (4.30)	80 (70.8)[a]	−15.91 (4.19)	0.86 (0.40)		
LVEF (%)							
Placebo (N = 60)	59 (98.3)	64.78 (8.29)	45 (75.0)	64.63 (7.46)	−0.64 (1.06)	−0.84 (−3.38 to 1.69)	0.511[b]
Inotersen (N = 113)	106 (93.8)	65.35 (7.78)	78 (69.0)[c]	64.43 (10.17)	−1.48 (0.87)		
Posterior LV Wall Thickness (cm)							
Placebo (N = 60)	60 (100)	1.18 (0.34)	48 (80.0)	1.22 (0.35)	0.031 (0.030)	−0.017 (−0.089 to 0.056)	0.654[b]
Inotersen (N = 113)	111 (98.2)	1.34 (0.42)	83 (73.5)[d]	1.32 (0.39)	0.014 (0.024)		

CI = confidence interval; GLS = global longitudinal strain; LSM = least squares mean; LV = left ventricular; LVEF = left ventricular ejection fraction; SD = standard deviation; SE = standard error.

[a] Change from baseline was assessed in 41 patients in placebo group and 72 patients in inotersen group.

[b] The GLS, LVEF, and LV wall thickness were outside of the statistical hierarchy testing strategy.

[c] Change from baseline was assessed in 76 patients in inotersen group.

[d] Change from baseline was assessed in 82 patients in inotersen group.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 15: Cardiac Biomarker N-Terminal Prohormone of Brain Natriuretic Peptide

	Baseline		Week 65			LSM Difference: Inotersen Versus Placebo (95% CI) (Ratio GM)	*P* Value
	n (%)	GM (CV)	n (%)	GM (CV)	Change, LSM (SE), Ratio GM		
pmol/L (FAS)							
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][b]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted][a]	[redacted]	[redacted]		

CI = confidence interval; CV = coefficient of variation; FAS = full analysis set; GM = geometric mean; LSM = least squares mean; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SE = standard error.

[a] Change from baseline was assessed in 82 patients in inotersen group.

[b] NT-proBNP was outside of the statistical hierarchy testing strategy.

Source: Clinical Study Report for NEURO-TTR.[7]

Harms

Only those harms identified in the review protocol (Table 3) are reported.

Anti-Drug Antibodies

Among the 112 patients who received at least one dose of inotersen, 34 patients (30.4%) tested positive for anti-drug antibodies (Table 16). The anti-drug antibodies were [redacted]. The mean mNIS+7$_{Ionis}$ change score from baseline to week 66 was 4.76 points (SD 15.70) for patients in the inotersen group who tested negative for the anti-drug antibody and 2.95 points (SD 5.82) for those who tested positive. The mean Norfolk QoL-DN change score from baseline to week 66 was −0.56 points (SD 20.74) for the patients in the inotersen group who tested negative for the anti-drug antibody and 0.98 points (SD 14.85) for those who tested positive. In patients who tested positive, there was a higher incidence of certain AEs, such as injection-site erythema (35.3% versus 29.9%), thrombocytopenia (17.6% versus 11.7%), and ocular events potentially related to vitamin A deficiency (26.5% versus 16.9%). In patients who tested negative for the anti-drug antibody, there was a higher incidence of injection-site pain (22.1% versus 14.7%), infections and infestations (67.5% versus 47.1%), peripheral edema (20.8% versus 14.7%), decreased platelet count (13.0% versus 5.9%), and renal impairment (22.1% versus 17.6%).

Table 16: Anti-Drug Antibodies

	Placebo (N = 60)	Inotersen (N = 112)
Positive, n (%)	0 (0)	34 (30.4)
Transient[a]	[redacted]	[redacted]
Persistent[b]	[redacted]	[redacted]
Negative, n (%)	60 (100)	77 (68.8)
Unknown, n (%)	[redacted]	[redacted]
Onset, N	[redacted]	[redacted]
Median (days)	[redacted]	[redacted]
Peak titre, N	[redacted]	[redacted]
Median	[redacted]	[redacted]

[a] Transient anti-drug responses were defined as a positive result at one sampling time point, or positive results at two or more sampling time points where the first and last positive samples were separated by < 16 weeks and the last sampling time point was negative.[6]

[b] Persistent anti-drug responses were defined as positive results at two or more sampling time points where the first and last samples were separated by ≥ 16 weeks, or a positive sample detected at the last sampling point or at a sampling time point < 16 weeks before a negative last sample.[6]

Source: Clinical Study Report for NEURO-TTR.[7]

Adverse Events

Almost all patients experienced an AE (100% in the placebo group and 99.1% in inotersen group). The inotersen group experienced a higher incidence of injection-site reactions (erythema [redacted], anemia (13.4% versus 3.3%), thrombocytopenia (13.4% versus 1.7%), decreased platelet count (10.7% versus 0%), nausea (31.3% versus 11.7%), and vomiting (15.2% versus 5.0%). More patients in the inotersen group also experienced headache (23.2% versus 11.7%), pyrexia (19.6% versus 8.3%), chills (17.9% versus 3.3%), myalgia (15.2% versus 10.0%), arthralgia (11.6% versus 8.3%), and peripheral edema (18.8% versus 10.0%).

[redacted] Table 17: [redacted].

Serious Adverse Events

Thirteen patients (21.7%) who received placebo and 36 patients (32.1%) who received inotersen experienced an SAE. Events that occurred in 1% or more patients in either the placebo or inotersen groups are listed in Table 17.

Withdrawals Due to Adverse Events

An AE led to discontinuation of the study treatment among two patients ([redacted]) who received placebo and 16 patients ([redacted]) who received inotersen. In the inotersen group, four patients discontinued treatment due to thrombocytopenia and two patients discontinued treatment due to glomerulonephritis.

One patient in the placebo group withdrew from the study due to hypoesthesia. In the inotersen group, eight patients withdrew due to an AE (thrombocytopenia, congestive cardiac failure, intestinal perforation, cachexia, dementia, intracranial hemorrhage, myoclonus, acute kidney injury, cachexia).

Adverse Events of Special Interest

Ocular AEs potentially related to vitamin A deficiency occurred in about an equal proportion in patients receiving placebo and inotersen ([redacted]). In the CM-ECHO group, ocular AEs potentially related to vitamin A deficiency occurred in [redacted] in the inotersen group and [redacted] in the placebo group. More patients receiving inotersen had renal impairment [redacted], thrombocytopenia (13.4% versus 1.7%), and decreased platelet count (10.7% versus 0%). In the inotersen group, mean decreases in platelet count occurred gradually over a period of several weeks, with an onset within the first 13 weeks of dosing and a nadir of mean values reached three to six months after starting treatment. As mentioned, injection-site reactions occurred at a higher frequency with inotersen than with placebo. Most injection-site reactions were mild in severity, transient, self-resolving, or managed with treatment.

Mortality

Five deaths occurred in the inotersen group and none in the placebo group. Four of the deaths were attributed to disease progression or complication, and one death was due to intracranial hemorrhage associated with a platelet count of about 10×10^9/L.

Table 17: Harms

	NEURO-TTR	
	Placebo (N = 60)	Inotersen (N = 112)
Patients with > 0 AEs, N (%)	60 (100)	111 (99.1)
Most common AEs[a]		
Injection-site erythema	[redacted]	[redacted]
Nausea	7 (11.7)	35 (31.3)
Fatigue	12 (20.0)	28 (25.0)
Diarrhea	12 (20.0)	27 (24.1)
Headache	7 (11.7)	26 (23.2)
Injection-site pain	[redacted]	[redacted]
Pyrexia	5 (8.3)	22 (19.6)
Peripheral edema	6 (10.0)	21 (18.8)
Urinary tract infection	12 (20.0)	21 (18.8)
Chills	2 (3.3)	20 (17.9)
Fall	13 (21.7)	19 (17.0)
Myalgia	6 (10.0)	17 (15.2)
Vomiting	3 (5.0)	17 (15.2)
Anemia	2 (3.3)	15 (13.4)
Constipation	6 (10.0)	15 (13.4)
Thrombocytopenia	1 (1.7)	15 (13.4)
Asthenia	8 (13.3)	14 (12.5)
Arthralgia	5 (8.3)	13 (11.6)
Injection-site pruritus	[redacted]	[redacted]
Dizziness	7 (11.7)	12 (10.7)
Decreased platelet count	0 (0)	12 (10.7)
Muscular weakness	6 (10.0)	11 (9.8)
Pain in extremity	8 (13.3)	10 (8.9)
Cough	8 (13.3)	10 (8.9)
Hypoesthesia	6 (10.0)	10 (8.9)
Nasopharyngitis	6 (10.0)	9 (8.0)
Thermal burn	6 (10.0)	6 (5.4)
Neuralgia	9 (15.0)	3 (2.7)
SAEs		
Patients with > 0 SAEs, N (%)	13 (21.7)	36 (32.1)
Most common SAEs[b]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Thrombocytopenia	0 (0)	2 (1.8)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	NEURO-TTR	
	Placebo (N = 60)	Inotersen (N = 112)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Deep-vein thrombosis	1 (1.7)	1 (0.9)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
WDAEs		
WDAE (discontinue treatment), N (%)	[redacted]	[redacted]
WDAE (discontinue study), N (%)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
AESI		
Ocular AEs potentially related to vitamin A deficiency	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Thrombocytopenia	1 (1.7)	15 (13.4)
Platelet count decreased	0 (0)	12 (10.7)
Deaths		
Number of deaths, N (%)	0 (0)	5 (4.5)
Disease progression/complication (cachexia, intestinal perforation, congestive cardiac failure)	0	4
Intracranial hemorrhage	0	1

AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency ≥ 10%.

[b] Frequency ≥ 1%.

Source: Clinical Study Report for NEURO-TTR.[7]

Clinical Expert Input

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

Unmet Needs with Current Therapies

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

Place in Therapy

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

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

Considerations for Appropriate Use in Clinical Practice

Identification of Symptomatic Hereditary Transthyretin-Mediated Amyloidosis

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

Stage of Polyneuropathy

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

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

Patients With Previous Liver Transplant

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

Patients With Cardiomyopathy

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

Patients Who Are Pre-Symptomatic

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

Patients Who Are Confined to a Bed or Palliative

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

Prescribing Physician and Treatment Setting

Treatments that are given intravenously should be administered under the care of specialists, primarily neurologists and cardiologists, in centres that routinely administer infusions, such as hospitals, university centres, specialty clinics, and private centres.

Assessment of Initial Treatment Response

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

used in clinical practice and may be resource-intensive to administer. Also, the quantitative sensory testing component of the mNIS+7 is not available in all centres. More general measures will be needed if they are to be implemented in clinical practice.

Ongoing Patient Assessments

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

Treatment Discontinuation

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

Additional Considerations

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

Discussion

Summary of Available Evidence

The evidence for inotersen consisted of one phase II/III multi-centre, DB RCT trial in 172 patients with stage I or stage II hATTR polyneuropathy (NEURO-TTR). Patients were randomized in a 2:1 ratio to inotersen 300 mg (N = 112) or placebo (N = 60) SC injection for about 15 months. The primary outcomes were mNIS+7$_{Ionis}$ and Norfolk QoL-DN at week 66, which were the only outcomes tested within a statistical hierarchy strategy. A decrease from baseline in the mNIS+7$_{Ionis}$ total score represents a reduction in neurological impairment, and a decrease from baseline in the Norfolk QoL-DN total score represents improved HRQoL. Key limitations of the trial included larger number of treatment discontinuations in the inotersen group, potential for unblinding due to the much higher frequency of injection-site reactions in the inotersen group, the exclusion of a large proportion of patients from primary analyses at study end that may have compromised randomization, and potential for type I error in the secondary and tertiary outcomes due to multiple statistical testing. The trial excluded patients with advanced polyneuropathy who were confined to a wheelchair, patients with a prior liver transplant or on a current TTR stabilizer, and patients in NYHA class ≥ 3 and, therefore, the study results may not be generalizable to these patient subpopulations.

Interpretation of Results

Efficacy

At week 66, the LSM change from baseline for the Norfolk QoL-DN and mNIS+7$_{Ionis}$ were statistically significant in favour of inotersen compared with placebo: −11.68 points (95% CI, −18.29 to −5.06) and −19.73 (95% CI, −26.43 to −13.03), respectively. However, a larger number of patients in the inotersen group discontinued treatment, primarily due to AEs. This may have resulted in biasing treatment in favour of inotersen if those patients who remained in the trial had better responses than patients who withdrew. As well, a relatively large percentage (> 10%) of patient data were excluded from statistical analyses of efficacy outcomes at week 66; the exclusions were differential between treatment groups. Several sensitivity analyses were conducted, and all confirmed the statistical significance of the primary outcomes. In particular, more conservative sensitivity analyses, that included all randomized patients, continued to demonstrate statistically significant estimates in favour of inotersen for the Norfolk QoL-DN (−8.56; 95% CI, −15.42 to −1.71) and mNIS+7$_{Ionis}$ (−14.89; 95% CI, −22.55 to −7.22), albeit with a smaller magnitude of difference between groups. The Health Canada review also noted these limitations and likewise concluded that the sensitivity analyses confirmed the primary outcomes were achieved in NEURO-TTR.[5] The domain of physical functioning / large-fibre neuropathy appeared to be where most points were contributed to the Norfolk QoL-DN total score. The domains of symptoms and activities of daily living also favoured inotersen, but there were no differences for small-fibre or autonomic neuropathy. The muscle weakness domain drove the mNIS+7$_{Ionis}$ result, and the domains of reflexes and sensory scores, nerve conduction scores, and heat pain sensory score additionally favoured inotersen.

No MCID has been established for the Norfolk QoL-DN, so it is difficult to conclude whether or not the observed difference is clinically meaningful. In primary and sensitivity analyses, the differences between inotersen and placebo in the mNIS+7$_{Ionis}$ exceeded the mean

difference between groups by two points, proposed by the Peripheral Nerve Society as a clinically meaningful difference in patients with diabetic neuropathy.[8] This MCID was based on the smallest degree of change that a physician can detect. Moreover, this was based on the NIS, which does not include the quantitative sensory testing component, nerve conduction studies, or autonomic components of the mNIS+7; thus, it is unclear if the two-point difference can be applied to the mNIS+7$_{Ionis}$. According to a clinical expert consulted for this review, the mNIS tools are not used for patient assessment in clinical practice; however, it was noted that degree of change in the mNIS+7$_{Ionis}$ observed in NEURO-TTR may be clinically relevant. However, since the value of two points was not derived from an anchor-based technique, the actual clinical meaningfulness to patients is unclear. There is no evidence that inotersen stops disease progression or improves symptoms, as the Norfolk QoL-DN and mNIS+7$_{Ionis}$ both exhibited worsening from baseline to week 66.

For other efficacy outcomes, such as SF-36v2 PCS, NSC score, and PND score, the differences appeared to be in favour of inotersen; however, these (and all other non-primary) outcomes were outside of the statistical hierarchy and no sensitivity analyses were conducted to include all randomized patients. The SF-36v2 is a generic HRQoL instrument that has been validated in many conditions, but not in hATTR. A change of two points on the PCS and three points on the MCS of the SF-36v2 indicates clinically meaningful improvements. From baseline to week 65, the inotersen group did not achieve these thresholds for clinical improvement on the PCS or MCS, although the changes were better than placebo. No data were available on the validity, reliability, or MCID of the NSC score, so it is difficult to conclude whether or not the observed difference is clinically meaningful. For cardiac outcomes, there was no clear evidence of benefit in the FAS or in patients in the CM-ECHO subgroup. In manufacturer-provided post hoc analyses that classified patients as having cardiomyopathy based on interventricular septum thickness ≥ 15 mm (rather than LV wall thickness ≥ 13 mm; subgroup N = 51, 35 inotersen and 16 placebo), patients treated with inotersen had improvements in intraventricular septum thickness, LV mass, and posterior wall thickness versus placebo.[22] In an ongoing, open-label study in patients with wild-type or hATTR cardiomyopathy, stabilization of LVEF, strain, and beta-type natriuretic peptide was observed in 11 patients who had completed three years of follow-up.[23] It is difficult to base any firm conclusions of cardiovascular benefit based on these analyses, which were conducted post hoc and in a subgroup of patients.

Hereditary transthyretin-mediated amyloidosis affects many organ systems, with neuropathy and cardiomyopathy as predominant features. NEURO-TTR captured many outcomes that were mentioned by patients as important, such as impairment in the ability to carry out daily activities, neuropathy, autonomic dysfunction, quality of life, and impacts on mental health. However, no data were available specifically for burning pain, fatigue, dizziness, shortness of breath, or leg swelling, which were mentioned by a majority of patients in the input for this submission as severe or incapacitating. There was also no data available to assess whether inotersen reduces hospitalization. The impact of inotersen on prolonging survival is currently unknown and will require more long-term studies. [redacted]. The extension study will be following patients for a total of five years.

The eligibility criteria for NEURO-TTR were restrictive and included patients at earlier stages of disease (i.e., stage I and II polyneuropathy). Therefore, evidence in support of

continuing inotersen once patients progress to stage III polyneuropathy is lacking. According to clinical experts, in practice, patients will likely be on inotersen for extended periods and there are no clear criteria for stopping treatment. Experts also indicated that if a patient becomes bedridden or palliative, it is anticipated that the benefits of treatment would be minimal.

Patients in their input to CADTH for this review noted that existing therapies for hATTR are largely for symptom relief or supportive care, and they perceived existing therapies as being of only limited benefit. At the time of drafting this review, two other drugs are being reviewed by Health Canada for similar indications to inotersen. Patisiran is ribonucleic acid interference drug that reduces the production of TTR mRNA. This drug was evaluated in the APOLLO trial over 18 months in 225 patients with hATTR polyneuropathy of PND score ≤ 3b.[24] In APOLLO, the LSM difference in the mNIS + 7 for patisiran versus placebo was −34 points; 95% CI, −39.9 to −28.1 and the LSM difference in the Norfolk QoL-DN was −21.1 points; 95% CI, −27.2 to −15.0.[24] The other new pharmacological treatment for hATTR is tafamidis. In an 18-month RCT of 128 patients with stage I hATTR polyneuropathy and the V30M mutation, the difference in change from baseline in the Norfolk QoL-DN between tafamidis 20 mg daily versus placebo was −5.2 points; 95% CI, −11.8 to 1.3.[25] Diflunisal is already on the market in Canada, but it is used off-label in the management of hATTR. In an RCT of 130 patients with hATTR and clinically detectable peripheral or autonomic neuropathy followed for two years, diflunisal 250 mg or placebo twice daily were compared.[14] The difference in change from baseline in the NIS+7 between placebo and diflunisal was 16.3 points; 95% CI, 8.1 to 24.5. Mean PCS and MCS of the SF-36v2 increased for diflunisal by 1.5 and 3.7 points, respectively, while they decreased for the placebo group.[14] The primary evidence for the efficacy of inotersen comes from one placebo-controlled trial, NEURO-TTR. Inotersen has not been compared directly to any of these other drugs, and no indirect comparisons were either submitted by the manufacturer or identified in a search of the literature. Therefore, the comparative effects of inotersen are unknown.

Harms

About one-third of patients in the inotersen group tested positive for anti-drug antibodies, of which the majority were persistent. There is not enough data to ascertain the long-term impact, if any, of anti-drug antibodies on the efficacy of inotersen.

Nearly all patients in NEURO-TTR experienced an AE regardless of treatment. More patients who received inotersen discontinued treatment due to an AE than patients who received placebo [redacted]. In the inotersen group, [redacted] withdrew from the study due to thrombocytopenia, congestive cardiac failure, intestinal perforation, cachexia, dementia, intracranial hemorrhage, myoclonus, acute kidney injury, and cachexia.

Thirteen patients (21.7%) who received placebo and 36 patients (32.1%) who received inotersen experienced an SAE. No single SAE was notable for either treatment group.

Of the AEs of special interest for this review, ocular AEs potentially related to vitamin A deficiency occurred in about an equal proportion in patients receiving placebo and inotersen. The inotersen group experienced a higher incidence of injection-site reactions; the reactions were reported as generally mild to moderate in severity and manageable.

More patients receiving inotersen had renal impairment, thrombocytopenia, and decreased platelet count.

Five deaths occurred in the inotersen group and none in placebo. Four of the deaths were attributed to disease progression or complication and one death was due to intracranial hemorrhage in association with a platelet count of about 10×10^9/L, which occurred prior to the implementation of more frequent monitoring and was likely associated with inotersen treatment. Health Canada noted this imbalance in deaths and suggested that it may — partially — reflect the possible imbalance in disease severity between groups at baseline.[5]

[redacted]

Health Canada, the US FDA, and the European Medicines Agency have all noted the increased risk of thrombocytopenia and renal impairment with inotersen and have established mitigation plans to ensure these harms are monitored and that patients and physicians receive the proper education to handle these events.[5,26,27] The Health Canada product monograph for inotersen contains a boxed warning about thrombocytopenia and glomerulonephritis.[15] The monograph indicates that platelets should be monitored every two weeks during treatment and for eight weeks after discontinuation. If platelet counts are above 100×10^9 g/L, then weekly inotersen doses can be administered. However, dosage adjustments and increased monitoring are required if platelet counts fall below this level.[15] If the platelet count falls below 25×10^9 g/L, then it is recommended that inotersen be discontinued and corticosteroids administered to reverse the platelet decline.[15] Monitoring of the urine protein to creatinine ratio and the estimated glomerular filtration rate are indicated to evaluate for glomerulonephritis at a minimum of every three months. Monitoring should be increased to every four weeks if the urine protein to creatinine ratio is equal to or more than twice the upper limit of normal, or if the estimated glomerular filtration rate is less than 60 mL/min.[15] Patient and physician education, close monitoring, and labelling should help mitigate the increased risks of thrombocytopenia and glomerulonephritis associated with inotersen treatment. Patients at even higher risk, such as those taking antiplatelets, anticoagulants, or nephrotoxic medications may require increased monitoring.

As with efficacy, there are no comparative safety data for inotersen versus patisiran, tafamidis, or diflunisal.

Conclusions

Inotersen is a new RNA-targeting treatment that slows the progression of neuropathy and loss of HRQoL in patients with stage I or stage II hATTR polyneuropathy and may address certain unmet needs of patients with this condition. However, the clinical significance of the treatment-effect differences between inotersen and placebo is unclear, given the lack of formally estimated MCID for these outcome measures. As an SC injection that can be self-administered by patients at home after proper training, inotersen potentially offers a more convenient treatment option than patisiran, which requires intravenous infusion. However, there are many questions that remain unanswered, including whether inotersen improves cardiovascular clinical outcomes, whether it is beneficial in patients with a previous liver transplant or in those with advanced (stage III) polyneuropathy, and what its longer-term benefits and harms are. No direct comparative evidence is available to compare inotersen with patisiran or TTR stabilizers. In addition, inotersen appears to be associated with important AEs, particularly thrombocytopenia and glomerulonephritis, requiring regular monitoring, as per the product monograph.

Appendix 1: Patient Input Summary

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

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

One patient group, Hereditary Amyloidosis Canada (HAC) provided input for this submission. HAC's mandate is to provide the hereditary transthyretin-mediated amyloidosis (hATTR) community with access to information about the disease, the pathway to diagnosis and treatment, and up-to-date clinical trial information. HAC also supports the hATTR community to advocate for members' needs. On their conflict-of-interest declaration, HAC stated it worked with Impetus Digital to design the online survey and collect and analyze the results. HAC did not receive help from outside the group to complete the submission and had no financial conflicts to declare.

2. Condition Related Information

Information for this submission was obtained from the results of an online survey that was available in English and French from February 11 to March 1, 2019. The survey was promoted through social media and other online platforms and emailed directly to physicians, patients, and caregivers. The survey was completed by 13 patients with hATTR, 10 caregivers, and two others. Sixteen respondents were from Canada, six were from the US, and three were from other regions. In addition, seven people (six patients, one caregiver) were interviewed by telephone by the author of this submission. All seven respondents, one of whom was from Canada, had experience with Tegsedi.

Hereditary transthyretin-mediated amyloidosis is a progressive, debilitating, and fatal disease. Misdiagnosis is not uncommon, and most people reported that one to five years passed between when they first sought medical care for their symptoms until a diagnosis was obtained.

Most people reported that the disease limited their ability to perform daily tasks such as shopping, meal preparation, eating, housework and maintenance, and personal care / bathing. Some patients reported that their symptoms (neuropathy, severe diarrhea, extreme fatigue) limited their ability to work, and some reported having to leave their jobs. Others reported refraining from participating in leisure activities and social events due to their symptoms. Some also noted that their loved ones ultimately became fully dependent on family members and outside support for their care and survival. The deterioration in patients' quality of life contributed to emotional distress for patients and their caregivers and led to feelings of uselessness, hopelessness, stress, depression, anxiety, and fear.

> *"Quality of life as a patient, suffice to say, I am a shadow of my former self. Anything that requires fine motor skills is a challenge. Any physical activity has become almost impossible. The bathroom issues are another saga. Whenever I am out, the first thing I need to find is the washroom. Due to the autonomic conditions, even a few seconds' delay ends in disaster. Blood pressure tanks. Dizziness upon standing. Uncooperative limbs climbing a flight of stairs or going downstairs. So, quality of life is impaired drastically due to this illness. We desperately need some treatment to assist making us feel somewhat human again."*

Among survey respondents, nerve damage (e.g., tingling, numbness, burning pain, carpal tunnel, weakness) was reported to be severe or incapacitating for 88%, while 60% had severe or incapacitating leg swelling, fatigue, shortness of breath, or dizziness. Approximately half reported severe or incapacitating gastrointestinal symptoms, sexual

dysfunction, or cardiac symptoms (arrhythmia, chest pain). Patients noted they were least affected by symptoms related to kidney dysfunction, brain dysfunction, and eye problems.

3. Current Therapy Related Information

More than half of the people surveyed said they or the patient they cared for had received or were currently receiving treatment specifically for hATTR, and nine said they had not received or were not currently receiving treatment for hATTR. One patient had received a liver transplant and others mentioned supportive care (e.g., for water retention or diarrhea) or revusiran (which has been discontinued). Many patients mentioned diflunisal but only two felt it was effective in slowing their disease progression. Most of those who received diflunisal noted they continued to have symptoms and saw their disease progress, and a few had to discontinue treatment due to adverse effects. Six patients mentioned they had difficulty swallowing diflunisal, with some frequently choking on the pills. The patient responses reflect the significant unmet need for disease-specific treatment options.

Most patients and caregivers mentioned that the most critical need is slowing the progression of or reversing peripheral neuropathy (pain, numbness, and sleep issues) and autonomic neuropathy affecting the gastrointestinal system (diarrhea, vomiting, and choking) and blood pressure.

Some patients noted having “extreme difficulty” accessing treatment in Canada, which they found to be “distressing, tiring, time-consuming, and extremely expensive.” Financial barriers to accessing treatment were mentioned by one-third of respondents, including the cost of travel to the nearest clinic in Canada or the US for treatment, which resulted in time off work. Patients also mentioned that treatments for hATTR that have been approved in the US and Europe are either not approved or not funded in Canada and, therefore, are out of reach due to the high cost of treatment and travel to get them.

4. Expectations About the Drug Being Reviewed

Six patients and one caregiver who had experience with Tegsedi were interviewed by telephone. Two out of the six patients had been on Tegsedi for more than four years, two had been on Tegsedi for approximately nine months, and the two others started Tegsedi in February 2019.

The two patients who had been on Tegsedi for years indicated that their quality of life had improved significantly, and their neuropathy had remained fairly stable or had improved. A third patient noted a slight improvement in gastrointestinal issues and polyneuropathy but felt the weekly injections and lab visits were inconvenient. Five of the six patients interviewed said they experienced brief redness and soreness at the injection site that was easily manageable. The other side effects noted were chills and flu-like symptoms immediately after injection (one person), headaches, and bruising at the injection site.

Most survey respondents (72%) hoped Tegsedi would provide neuropathy symptom relief (primarily from pain). Other common hopes included improved quality of life and slowing the progression of the disease. Overwhelmingly, patients said that access to Tegsedi would provide hope for a better life that, ideally, would mean a normal, active, and long life.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–present) Embase (1974–present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 19, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No publication type filters were applied.
Limits:	Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.ot	Original title (MEDLINE)
.dq	Candidate term word (Embase)
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Line #	Search Strategy
1	(Tegsedi* or inotersen* or ISIS 420915 or ISIS420915 or 0IEO0F56LV or 950736UC77).ti,ab,kf,ot,hw,rn,nm.
2	1 use medall
3	*inotersen/
4	(Tegsedi* or inotersen* or ISIS 420915 or ISIS420915).ti,ab,kw,dq.
5	3 or 4
6	(conference abstract or conference review).pt.
7	5 not 6
8	7 use oemezd
9	2 or 8
10	remove duplicates from 9

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: tegsedi OR inotersen OR ISIS 420915 OR ISIS-420915 OR ISIS420915	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: tegsedi OR inotersen OR ISIS 420915 OR ISIS-420915 OR ISIS420915	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	March 13 to March 15, 2019
Keywords:	tegsedi, inotersen, ISIS 420915, ISIS-420915, ISIS420915
Limits:	Publication years: all

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

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (Free)
- Databases (Subscription-Based)
- Internet Search

Appendix 3: Excluded Studies

Table 18: Excluded Studies

Reference	Reason for Exclusion
1. Clinical Study Report: study number. An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP) [CONFIDENTIAL internal manufacturer's report]	Not an RCT

RCT = randomized controlled trial.

Appendix 4: Detailed Outcome Data

Table 19: Norfolk Quality of Life-Diabetic Neuropathy Sensitivity Analyses

	n (%)	LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI) at Week 66	*P* Value
Multiple Imputation Assuming Missing at Random			
Placebo (N = 60)	59 (98.3)	−10.91 (−17.61 to −4.21)	0.002
Inotersen (N = 112)	111 (99.1)		
Multiple Imputation Assuming Jump to Reference			
Placebo (N = 60)	59 (98.3)	−8.56 (−15.42 to −1.71)	0.015
Inotersen (N = 112)	111 (99.1)		
Per-Protocol			
Placebo (N = 52)	52 (100)	−10.82 (−17.65 to −3.99)	0.002
Inotersen (N = 83)	80 (96.4)		

CI = confidence interval; LSM = least squares mean; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 20: Norfolk Quality of Life-Diabetic Neuropathy Domain Scores

	Baseline		Week 66		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)		
Physical Functioning / Large-Fibre Neuropathy						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Symptoms Score						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Activities of Daily Living						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Small-Fibre Neuropathy						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Autonomic Neuropathy						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; LSM = least squares mean; SD = standard deviation.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 21: Norfolk Quality of Life-Diabetic Neuropathy by Subgroups

	Baseline		Week 66		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n	Mean (SD)	n	Mean (SD)		
Disease Stage I						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Disease Stage II						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment by subgroup interaction *P* value for disease stage = [redacted]						
CM-ECHO Set						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Non–CM-ECHO Set						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment by subgroup interaction *P* value for CM-ECHO set = [redacted]						
V30M Mutation						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
No V30M Mutation						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment by subgroup interaction *P* value for V30M mutation = [redacted]						
Previous Treatment With TTR Stabilizer						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
No Previous Treatment With TTR Stabilizer						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment by subgroup interaction *P* value for previous treatment with TTR stabilizer = [redacted]						

CI = confidence interval; CM-ECHO = cardiomyopathy-echocardiogram; LSM = least squares mean; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; SD = standard deviation; TTR = transthyretin.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 22: Modified Neuropathy Impairment Score (Ionis Version) Sensitivity Analyses

	n (%)	LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI) at Week 66	*P* Value
Multiple Imputation Assuming Missing at Random			
Placebo (N = 60)	[redacted]	[redacted]	[redacted]
Inotersen (N = 112)	[redacted]		
Multiple Imputation Assuming Jump to Reference			
Placebo (N = 60)	[redacted]	[redacted]	[redacted]
Inotersen (N = 112)	[redacted]		
Per-Protocol			
Placebo (N = 52)	[redacted]	[redacted]	[redacted]
Inotersen (N = 83)	[redacted]		
NIS-Sensation Excluded and HRDB / Nerve Conductions Scored Using Points			
Placebo (N = 59)	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]		
HRDB Component Excluded			
Placebo (N = 59)	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]		

CI = confidence interval; HRDB = heart rate deep breathing; LSM = least squares mean; NIS = Neuropathy Impairment Score.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 23: Modified Neuropathy Impairment Score (Ionis Version) by Subgroups

	Baseline		Week 66		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n	Mean (SD)	n	Mean (SD)		
Disease Stage I						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Disease Stage II						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment by subgroup interaction *P* value for disease stage = [redacted]						
CM-ECHO Set						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Non–CM-ECHO Set						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Treatment by subgroup interaction *P* value for CM-ECHO set = [redacted]						
V30M Mutation						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
No V30M Mutation						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Baseline		Week 66		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n	Mean (SD)	n	Mean (SD)		
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment by subgroup interaction *P* value for V30M mutation = [redacted]						
Previous Treatment With TTR Stabilizer						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
No Previous Treatment With TTR Stabilizer						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment by subgroup interaction *P* value for previous treatment with TTR stabilizer = [redacted]						

CI = confidence interval; CM-ECHO = cardiomyopathy-echocardiogram; LSM = least squares mean; SD = standard deviation; TTR = transthyretin.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 24: Neuropathy Impairment Score Domain Scores

	Baseline		Week 66		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)		
Muscle Weakness						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Reflexes Score						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Sensory Score						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; LSM = least squares mean; SD = standard deviation.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 25: Modified +7 Domain Scores

	Baseline		Week 66		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)		
Nerve Conduction Score						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Heat Pain Sensory Score						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Touch Pressure Sensory Score						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
HRDB Score						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; HRDB = heart rate to deep breathing; LSM = least squares mean.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 26: Neuropathy Symptoms and Change Domain Scores

	Baseline		Week 66		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)		
Muscle Weakness						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Sensory (Hypo/Loss of Sensation)						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Sensory (Paresthesia, Hypersensation)						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Autonomic (GI / Urinary Incontinence)						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		
Autonomic (Other Than GI / Urinary Incontinence)						
Placebo (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 106)	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; GI = gastrointestinal; LSM = least squares mean; SD = standard deviation.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 27: Echocardiogram Parameters in Cardiomyopathy-Echocardiogram Set

	Baseline		Week 65		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI)	*P* Value
	n (%)	Mean (SD)	n (%)	Mean (SD)		
GLS (%)						
Placebo (N = 33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 75)	[redacted]	[redacted]	[redacted]	[redacted]		
LVEF (%)						
Placebo (N = 33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 75)	[redacted]	[redacted]	[redacted]	[redacted]		
Posterior LV Wall Thickness (cm)						
Placebo (N = 33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 75)	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; GLS = global longitudinal strain; LSM = least squares mean; LV = left ventricular; LVEF = left ventricular ejection fraction; SD = standard deviation.

Source: Clinical Study Report for NEURO-TTR.[7]

Table 28: Cardiac Biomarker N-Terminal Prohormone of Brain Natriuretic Peptide in Cardiomyopathy-Echocardiogram Set

	Baseline		Week 65		LSM Difference in Change From Baseline: Inotersen Versus Placebo (95% CI) (Ratio GM)	*P* Value
	n (%)	GM (CV)	n (%)	GM (CV)		
NT-proBNP (pmol/L)						
Placebo (N = 33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen (N = 75)	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; CV = coefficient of variation; GM = geometric mean; LSM = least squares mean; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SD = standard deviation.

Source: Clinical Study Report for NEURO-TTR.[7]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN)
- Short Form (36) Health Survey, version 2 (SF-36v2)
- modified Neuropathy Impairment Score + 7 (Ionis version) (mNIS+7$_{Ionis}$)
- Neuropathy Symptoms and Change (NSC) score
- polyneuropathy disability (PND) staging
- familial amyloidotic polyneuropathy (FAP) and Coutinho staging
- modified body mass index (mBMI)
- N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- echocardiogram measures: left ventricular (LV) longitudinal strain, LV wall thickness, left ventricular ejection fraction (LVEF)

Findings

Table 29: Summary of Outcome Measures and Their Measurement Properties

Instrument	Type	Evidence of Validity	MCID	References
HRQoL				
Norfolk QoL-DN	Disease-specific HRQoL measure that evaluates the impact of neuropathy on functional status 35 items, grouped into five domains of physical functioning / large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy	Yes	Unknown	Vinik (2014)[28]
SF-36v2	General health status instrument 36 items in eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health; and two component summaries, the PCS and the MCS	Yes[a]	General use: 2 points on the PCS and 3 points on the MCS	User manual[29]
Neurologic Impairment				
mNIS+7$_{Ionis}$	Measure of neurological impairment with clinical assessments and neurophysiologic tests The measure used in NEURO-TTR was a 346.32-point composite consisting of NIS-cranial, NIS-weakness, NIS-reflexes, NIS-sensation, ∑5 NCS,	Yes	Unknown	Peripheral Nerve Society (1995)[8] Suanprasert (2014)[30] Dyck (2017)[31]

Instrument	Type	Evidence of Validity	MCID	References
	touch-pressure and heat-pain QST, and heart rate to deep breathing			
NSC	Patient questionnaire on the presence of, severity, and change in neurological symptoms Consists of 38 questions with five domains (motor, sensory – hypo/loss, sensory – paresthesia/ hypersensation, autonomic – GI or urinary, autonomic – other)	Yes	Unknown	CSR for NEURO-TTR study[7] Dyck (2017)[31]
Disability and Functional Status				
PND score	Staging of hATTR based on mobility	No	NA	Ando (2013)[1]
FAP stage	Staging of hATTR based on mobility and neuropathy	No	NA	Ando (2013)[1]
Coutinho stage	Staging of hATTR based on mobility and neuropathy	No	NA	Adams (2013)[32]
Nutritional Status				
mBMI	Measure of nutritional status, that takes into consideration hypoalbuminemia mBMI = BMI × albumin	Yes	Unknown	Suhr (1994)[33] Suhr (2005)[34] Franz (2013)[35] Suhr (2014)[36]
Cardiovascular Biomarkers and Echocardiogram				
NT-proBNP	A marker of cardiac stress and injury Cardiac biomarker that is released from the heart into the circulation in response to myocardial wall tension and stress	Yes	Unknown	Sattianayagam (2012)[37] my (2016)[38] Ternacle (2016)[39] Kristen (2017)[40]
LV longitudinal strain	A measure of cardiac function An echocardiogram measure of systolic dysfunction	Yes	Unknown	Stanton (2009)[41] Quarta (2014)[41] Hu (2015)[42] Ternacle (2016)[39] Barros-Gomes (2017)[43] Rocha (2017)[44] Siepen (2018)[45]
LV wall thickness	A measure of cardiac structure An echocardiogram measure to identify structural impairment due to remodelling from amyloid infiltrates	Yes	Unknown	Kristen (2007)[46] Sattianayagam (2012)[37]
LVEF	An echocardiogram measure of systolic dysfunction	Yes	Unknown	Ruberg (2012)[2]

∑5 NCS = sum of five nerve conduction studies; BMI = body mass index; CSR = Clinical Study Report; FAP = familial amyloidotic polyneuropathy; GI = gastrointestinal; hATTR = hereditary transthyretin-mediated amyloidosis; HRQoL = health-related quality of life; LV = left ventricular; LVEF = left ventricular ejection fraction; mBMI = modified body mass index; MCID = minimal clinically important difference; MCS = mental component summary; $mNIS+7_{Ionis}$ = Modified Neuropathy Impairment Score + 7 (Ionis version); NA = not applicable; NIS = Neuropathy Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NSC = Neuropathy Symptoms and Change; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PCS = physical component summary; PND = polyneuropathy disability score; QST = quantitative sensory testing; SF-36v2 = Short Form (36) Health Survey, version 2.

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

Health-Related Quality of Life

Norfolk Quality of Life-Diabetic Neuropathy

The Norfolk QoL-DN is a self-administered patient-reported, disease-specific, quality-of-life instrument that consists of 35 items grouped into five domains that may be used to assess the impacts of neuropathy on functional status.[4] The five domains are: physical functioning / large-fibre neuropathy (15 items), activities of daily living (5 items), symptoms (8 items), small-fibre neuropathy (4 items), and autonomic neuropathy (3 items).[28] In the validated tool, patients are asked to recall symptoms over a four-week period. Part 1 of the questionnaire consists of seven symptom items, which are recorded on a binary scale of present (1) or absent (0).[7] Part 2 of the questionnaire consists of 28 items to assess activities of daily living, with most responses rated on a five-point Likert scale ranging from 0 (not a problem) to 4 (severe problem).[7] Item 31 is rated on a five-point scale of −2 (excellent), −1 (very good), 0 (good), 1 (fair), and 2 (poor). Item 32 is rated on a five-point scale of −2 (much better), −1 (somewhat better), 0 (about the same), 1 (somewhat worse), and 2 (much worse).[7] The domains are aggregated with the integer sum to arrive at a total score, with higher scores representing poorer health status. The total score ranges from −4 (best quality of life) to 136 (worst quality of life).[4] The instrument was originally developed to assess patients' perceptions of the symptoms of the nerve fibre damage that occurs in diabetic neuropathy.[28] The pattern of neuropathy in hereditary transthyretin-mediated amyloidosis (hATTR) is similar to that of diabetic neuropathy.[28]

The Norfolk QoL-DN was validated in 61 patients with hATTR with the V30M mutation and stage I to III disease from a single study centre in Portugal.[28] The questionnaire was translated into Portuguese and validated linguistically. The patients in this study had stage I (independent ambulation, N = 29), stage II (assistance required to walk, N = 16), or stage III (confined to a wheelchair or bedridden, N = 16) hATTR. There were approximately equal proportions of men (50.8%) and women (49.2%) and the average age ranged from 39 years for stage I patients to 55 years for stage III patients. All patients completed the Norfolk QoL-DN at baseline, and stage II and stage III patients completed the questionnaire again at four weeks.[28] According to the clinical experts consulted for this review, the V30M mutation is most common in Canadian patients of Portuguese or Italian descent. The study results will be generalizable to those patients; however, they may be less generalizable to patients with other types of hATTR mutations or who present with predominant cardiomyopathy.

Validity: The Norfolk QoL-DN was correlated with objective measures of neurological function, which included the modified form of Neurological Impairment Score (NIS), NIS–lower limbs domain, and quantitative sensory testing (QST).[28] The correlation with NIS followed a quadratic equation, with an initial increase of 1.02 points per unit in NIS total score. The five domains of the Norfolk QoL-DN correlated strongly with the NIS–lower limb subscales of muscle weakness, reflexes, and sensation (Pearson's r ranged from 0.51 to 0.87).[28] The Norfolk QoL-DN also correlated strongly with small-fibre function as assessed with heat-pain threshold (Pearson's r = 0.65), and correlated moderately with cooling-detection threshold (Pearson's r = 0.42) and with autonomic function, as assessed with heart rate response to deep breathing (Pearson's r = −0.38).[28]

Discriminant validity: Norfolk QoL-DN discriminated between patients with and without disease and between patients with different stages of disease (mean total score [SD]: healthy volunteers = 2.6 [5.0]; stage I = 21.0 [14.5]; stage II = 73.1 [27.5]; stage III = 95.4 [2.7], $P < 0.002$).[28] With duration of disease, the Norfolk QoL-DN followed a

quadratic equation, with an initial increase of 9.12 points per year of symptom duration, and levelling off at about 19 years.[28]

Reliability: The instrument was demonstrated to have test–retest reliability, as there were no statistically significant differences between the baseline and week 4 assessments in patients with stage II or III disease.[28] Aside from small-fibre neuropathy, there were also no statistically significant differences in the individual domains at baseline and week 4.[28]

A minimal clinically important difference (MCID) for the Norfolk QoL-DN was not identified for patients with diabetic neuropathy or hATTR. The instrument may not capture the impact of all the important aspects of the condition on quality of life where peripheral neuropathy is not the predominant symptom. For example, the instrument does not capture the emotional or psychological impacts of the condition. It has three questions related to autonomic function (vomiting diarrhea and dizziness) but does not address other relevant symptoms such as renal and urinary symptoms and sexual dysfunction. It is unclear if it would adequately capture cardiac symptoms.[25]

Short Form (36) Health Survey, Version 2

The SF-36v2 is a 36-item, general health–status instrument that has been used extensively in clinical trials in many disease areas.[29] It was developed in 1996 based on the original SF-36 and required that some substantial changes be made to address the shortcomings of the SF-36.[29] Like the SF-36, the SF-36v2 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[29] Each of the eight domains is scored on a domain-specific scale, where higher scores correspond with better health.[29] A principal components analysis of the eight domains is also used to create two component summaries, the physical component summary (PCS) and the mental component summary (MCS).[29] The scores from the eight domains are each converted to a scale ranging from 0 to 100, which are then transformed into a t score (mean of 50 and standard deviation of 10) that are standardized to the US general population. Thus, a score of 50 on any scale would be at the average or norm of the general US population, and a score 10 points lower (i.e., 40) would be one standard deviation below the norm. The domain scores are then aggregated using a weighted formula to score the summary scores, which are also transformed into a t score.[29]

Based on anchor data, the developer of the SF-36v2 proposed the following minimal mean group differences for the individual domain scores: physical functioning, 3; role physical, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3. It should be noted that these MCID values were determined to be appropriate for groups with mean t score ranges of 30 to 40; for higher t score ranges, MCID values may be higher.[29] As these MCID values were based on clinical and other non–patient-reported outcomes, they do not necessarily identify the smallest difference that patients would consider important. In general, a change of two points on the PCS and three points on the MCS of the SF-36v2 indicates a clinically meaningful improvement, as determined by the patient.[29]

The reliability and validity of the SF-36v2 have been demonstrated across various conditions;[29,47] however, no data were found in patients with hATTR.

Neurologic Impairment and Symptoms

Modified Neuropathy Impairment Score + 7 (Ionis Version)

The mNIS+7$_{Ionis}$ is a 346.3-point composite measure used to assess neurological impairment. It consists of clinical assessments (NIS component, maximum of 244 points) and neurophysiologic tests (modified +7 component, maximum of 102.32 points) (Table 30).[7]

The NIS components are:

- cranial and motor weakness components, which are based on physical examination of the lower limbs, upper limbs, and cranial nerves
- reflexes component, an assessment of a decrease in the muscle stretch reflex
- sensation component, an assessment of sensation loss in the fingers and toes.

The modified +7 components used in the NEURO-TTR study include electrophysiological measures of the function of small- and large-nerve fibres to determine the sum of five attributes of nerve conduction studies (∑5 NCS); QST of touch pressure and heat pain by body surface area; and change in heart rate with deep breathing to assess autonomic function.[44] A higher score on the mNIS+7$_{Ionis}$ indicates worse neurological function.

The modified Neuropathy Impairment Score + 7 (mNIS+7) was developed specifically for polyneuropathy in patients with hATTR, and different versions of the composite outcome measure have been used in hATTR clinical trials (Table 30). Suanprasert et al. conducted a retrospective review of 97 untreated patients with hATTR at the Mayo Clinic in Rochester, New York to determine the kind, severity, and distribution of polyneuropathy signs and nerve tests, the ability of the Neurologic Impairment Score (NIS+7) to represent these signs and tests, and the modifications needed to the NIS+7 to better measure polyneuropathy.[30] The NIS+7 differs from the mNIS+7$_{Ionis}$ in three ways:

- it does not include QST
- the ∑5 NCS consists of a different set of attributes (i.e., sural sensory nerve action potential [SNAP], tibial motor distal latency, peroneal compound muscle action potential [CMAP], peroneal motor nerve conduction velocity, and peroneal motor nerve distal latency)
- it includes a vibration-detection threshold to assess the function of large-nerve fibres.[44]

The study by Suanprasert et al.[30] found the NIS-sensation component did not adequately measure sensation loss, large-fibre sensory dysfunction was overemphasized compared with dysfunction of small sensory fibres, heart rate decrease with deep breathing did not adequately assess autonomic dysfunction, and the attributes of the ∑5 NCS could not all be evaluated in patients with hATTR.[30] The authors suggested that the evaluation of polyneuropathy in patients with hATTR could be improved by modifying the NIS+7 in the following aspects: replace vibration-detection threshold with QST, replace heart rate response to deep breathing with postural blood pressure or Q-Sweat, and replace the five nerve tests of ∑5 NCS with the modified set of five nerve tests described in Table 30.[30] To evaluate the mNIS+7 accurately and reliably, the authors recommended that assessments be conducted by specially trained experts.[30]

The clinometric performance of the mNIS+7$_{Ionis}$ was evaluated by Dyck et al.[31] Baseline assessments of neuropathy signs (NIS score) and the scores for the NIS+7, mNIS+7$_{Ionis}$,

PND, Norfolk QoL-DN, Dyck/Rankin, NSC, and the SF-36v2 were evaluated in the first 100 patients enrolled in the NEURO-TTR trial (inotersen versus placebo).

Validity: The mNIS+7$_{Ionis}$ was correlated strongly with the Norfolk QoL-DN score, PND stage, Dyck/Rankin score, and NSC score (Spearman rank correlation $r \geq 0.5$ or $r \leq -0.5$).[31,48] The mNIS+7$_{Ionis}$ was weakly to strongly correlated with the SF-36v2 ($r \geq 0.5$ or $r \leq -0.5$ or [$r \geq 0.25$ to $r < 0.5$ or $r \leq -0.25$ to $r > -0.5$]).[31]

Correlations for components of the mNIS+7$_{Ionis}$ were as follows:

- The NIS total score and the score for the NIS-weakness component were weakly to strongly correlated with the Norfolk QoL-DN and SF-36v2 ($r \geq 0.5$ or ≤ -0.5 or [$r \geq 0.25$ to $r < 0.5$ or $r \leq -0.25$ to $r > -0.5$]), and strongly correlated with PND stage, the Dyck/Rankin score, and the NSC score ($r \geq 0.5$ or $r \leq -0.5$).[31,48]
- The NIS-reflexes component was weakly correlated with the Norfolk QoL-DN, PND, Dyck/Rankin, and NSC ([$r \geq 0.25$ to $r < 0.5$ or $r \leq -0.25$ to $r > -0.5$] or $r > -0.25$ to $r < 0.25$).[31,48]
- The ∑5 NCS was not significantly correlated with the Norfolk QoL-DN, NSC, or SF-36v2, and was weakly to strongly correlated with PND stage and the Dyck/Rankin score ($r \geq 0.25$ to < 0.5 or $r \leq -0.25$ to $r > -0.5$).[31,48]
- QST touch pressure was strongly correlated with the Norfolk QoL-DN ($r \geq 0.5$ or $r \leq -0.5$), and weakly to strongly correlated with PND stage, the Dyck/Rankin score, and the SF-36v2 [($r \geq 0.5$ or $r \leq -0.5$) or ($r \geq 0.25$ to $r < 0.5$ or $r \leq -0.25$ to $r > -0.5$)].[31,48] The QST heat pain was not significantly correlated with any of the measures.[31]

Reliability: The test–retest reproducibility of the NIS total score, ∑5 NCS, and heart rate with deep breathing was high (Krippendorff $\alpha = 0.97$, $\alpha = 0.98$, and $\alpha = 0.93$, respectively).[31] Test–retest reproducibility for QST was lower (Krippendorff $\alpha = 0.57$; 0.44 for touch pressure and 0.65 for heat pain).[31] The repeat tests were conducted within a day or few days of the first test by the same examiners and, therefore, may have been influenced by recall. The authors noted that heart rate with deep breathing cannot be assessed in patients with a cardiac arrhythmia or electronic pacing.[30]

No studies were identified that estimated the MCID of the mNIS+7$_{Ionis}$. For the NIS in patients with diabetic polyneuropathy, the Peripheral Nerve Society has proposed that a mean difference between groups of two points is meaningful, as a change of two points represents a 50% change in sensation or muscle stretch reflexes and a 25% change in muscle strength.[8] However, this value is based on the smallest degree of change that a physician can detect rather than on any distribution or anchor-based statistical technique. Considering that the mNIS+7 score includes other components that are not part of the NIS, it is unclear if the two-point difference can be applied to the mNIS+7.

Table 30: Comparison of the Modified Neuropathy Impairment Score + 7, Modified Neuropathy Impairment Score (Ionis Version), and Neuropathy Impairment Score

Component	mNIS + 7[a] (Points)	mNIS + 7_{Ionis}[b] (Points)	NIS (Points)	Scoring Details
NIS-weakness[c]	192	192	192	Sum of five cranial nerve components and muscle weakness in 19 areas for left and right side of body; maximum score of 4 points for each item
NIS-sensation	NA	32	32	Sum of four sensory modalities assessed in the fingers and toes of left and right side of body; maximum score of 2 points for each item
NIS-reflexes	20	20	20	Sum of decrease in five reflexes for left and right side of the body; maximum score of 2 points for each item
Quantitative sensory testing	80	80	NA	Sum of sensory testing of touch pressure and heat pain by body surface area (up to 10 unilateral anatomical sites); maximum of 4 points per item
∑5 nerve conduction studies	10	18.6	NA	Sum of electrophysiological measure of small and large nerve–fibre function (ulnar CMAP, ulnar SNAP, sural SNAP, tibial CMAP, and peroneal CMAP); scored on one side of body with maximum of 3.72 points per item
Postural blood pressure	2	NA	NA	Change in blood pressure with standing; maximum of 2 points
Heart rate with deep breathing	NA	3.72	NA	Change in heart rate with deep breathing; maximum of 3.72 points
Total points[d]	304	346.3	244	

CMAP = compound muscle action potential; CSR = Clinical Study Report; mNIS+7 = modified Neuropathy Impairment Score + 7; mNIS+7_{Ionis} = modified Neuropathy Impairment Score (Ionis version); NA = not applicable; NIS = Neuropathy Impairment Score; SNAP = sensory nerve action potential.

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

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

[c] Includes the motor weakness and cranial components.

[d] Higher points indicate greater neurologic impairment.

Source: Adams et al., 2018;[24] Dyck et al., 2017;[31] CSR for NEURO-TTR study.[7]

Neuropathy Symptoms and Change

The NSC patient questionnaire consists of 38 questions concerning different neuropathy symptoms.[7] The NSC includes five domains: muscle weakness (19 questions); sensory – hypo/loss of sensation (three questions); sensory – paresthesia/hypersensation (seven questions); autonomic – gastrointestinal and urinary incontinence (four questions); and autonomic – non-gastrointestinal or urinary incontinence (five questions for men; three for women).[7] The muscle weakness domain is divided into four sub-domains: head and neck, chest, upper limbs, and lower limbs. The presence of symptoms is marked if, in the judgment of the examining neurologist, it occurred more frequently or more severely than in healthy individuals of the same age and sex and if the symptom was due to neuropathy. Symptom severity is graded as 1 (slight +), 2 (moderate ++) or 3 (severe +++).[7] If a symptom is not present, it is given a score of 0.[7] Each sub-domain and domain score is the total of all relevant questions. The total score is the sum of all domain scores and ranges from 0 to a maximum of 108 for women and 114 for men, with higher scores representing more severe disease.[7] Total domain scores are as follows: 57 points for muscle weakness; 9 points for sensory (hypo/loss of sensation); 21 points for sensory (paresthesia/ hypersensation); 12 for autonomic (gastrointestinal and urinary incontinence); and 9 points

for women and 15 points for men for autonomic (non-gastrointestinal or urinary incontinence).[7] The instrument also includes a change score, where the change in symptoms compared with the week before is rated on a seven-point scale from −3 (worse) to +3 (better).[7]

Validity: Baseline assessments of the NSC score, as well as neuropathy signs ([NIS], NIS+7, mNIS+7$_{Ionis}$, PND score, Norfolk QoL-DN, Dyck/Rankin score) and the SF-36v2 were evaluated in the first 100 patients enrolled in the NEURO-TTR trial (inotersen versus placebo) by Dyck et al.[31] The following correlations between the NSC score and other scales were found:

- The NSC weakness component was strongly correlated with the Norfolk QoL-DN, PND stage, Dyck/Rankin score, SF-36v2, and QST touch pressure (r ≥ 0.5 or ≤ −0.5); weakly to strongly correlated with mNIS+7$_{Ionis}$ (r ≥ 0.5 or ≤ −0.5 or [r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5]); and weakly to moderately correlated with ∑5 NCS (r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5).
- The NSC measure of sensation was strongly correlated with the Norfolk QoL-DN; weakly to strongly correlated with mNIS+7$_{Ionis}$, vibration-detection threshold, QST touch pressure, and SF-36v2 (r ≥ 0.5 or ≤ − 0.5 or [r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5]); and weakly to moderately correlated with ∑5 NCS, PND stage, and Dyck/Rankin score (r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5).
- The NSC measure of positive neuropathic sensory symptoms was strongly correlated with the Norfolk QoL-DN (r ≥ 0.5 or ≤ −0.5); weakly to strongly correlated with SF-36v2 (r ≥ 0.5 or ≤ -0.5 or [r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5]); weakly to moderately correlated with QST touch pressure (r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5); and weakly correlated with vibration-detection threshold and Dyck/Rankin score (r > −0.25 or r < 0.25).
- The NSC measure of pain was strongly correlated with the Norfolk QoL-DN (r ≥ 0.5 or ≤ −0.5) and weakly to moderately correlated with SF-36v2 (r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5).
- The NSC measure of autonomic severity was weakly to strongly correlated with mNIS+7$_{Ionis}$, ∑5 NCS, Dyck/Rankin score, and SF-36v2 (r ≥ 0.5 or ≤ −0.5 or [r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5]); weakly to moderately correlated with the Norfolk QoL-DN, QST touch pressure, and heart rate response to deep breathing (r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5); and weakly correlated with QST heat pain (r > −0.25 or r < 0.25).

No information was identified in the literature on the reliability, responsiveness, or the MCID of the NSC score in patients with hATTR or other neurological conditions.

Disease Staging Systems

A number of different classification systems have been used to score disease severity in patients with hATTR. The scoring system by Coutinho, the FAP stage, and the PND score are summarized in Table 31. These scoring systems are based largely on ambulation and do not consider autonomic dysfunction. The staging proposed by Coutinho was based on a review of 483 Portuguese patients with the V30M mutation who generally presented with early-onset polyneuropathy. Patients with other mutations or from other regions may show different clinical manifestations; thus, it is unclear if staging systems based on Coutinho adequately reflect the disease course for these patients.[25] Evidence of the validity and reliability of these staging systems was not found; however, in a retrospective natural history study of 283 patients with hATTR from France, Portugal, Italy, and the US, the FAP

and PND stage were positively associated with the NIS score, and the PND score was negatively associated with grip strength.[10]

Table 31: Comparison of Disease Staging Systems

Coutinho		FAP[a,b]		PND[a]	
		0	Asymptomatic	0	No symptoms
1	Does not require assistance with ambulation Disease is limited to lower limbs; slight weakness of the extensors of the big toes	I	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs	I	Sensory disturbances but preserved walking capability
				II	Impaired walking capacity but able to walk without a stick or crutches
2	Requires assistance with ambulation Motor signs progress in lower limbs with steppage and distal amyotrophies; the muscles of the hands begin to be wasted and weak	II	Assistance with ambulation required; mostly moderate impairment, progression to the lower limbs, upper limbs, and trunk	IIIa	Walking with the help of one stick or crutch
				IIIb	Walking with the help of two sticks or crutches
3	Confined to a wheelchair or bedridden Generalized weakness and areflexia	III	Bedridden or confined to a wheelchair; severe sensory, motor, and autonomic involvement of all limbs	IV	Confined to a wheelchair or bedridden

FAP = familial amyloidotic polyneuropathy; PND = polyneuropathy disability.

[a] Adams et al. (2015) classified patients with FAP stage II as PND stage IIIa or IIIb, and FAP stage III as PND stage IV.[10]

[b] Also based on the classification system described by Coutinho et al.[49]

Source: Ando et al.,[1] Adams et al.[32]

Nutritional Status

Modified Body Mass Index

Patients with hATTR are affected by wasting and, in these circumstances, body mass index (BMI) overestimates clinical status. A more accurate measure is the mBMI, which corrects for hypoalbuminemia and edema and is calculated by the product of BMI and serum albumin.[36] Among 27 patients with hATTR in Sweden, the mBMI was strongly correlated with number of years before death (r = 0.89) and with the duration of gastrointestinal symptoms (r = −0.66).[33] The mBMI was also correlated with PND score (P = 0.009).[33] Among 21 patients with hATTR who had a liver transplant, a preoperative mBMI < 700 kg g/L m^2 was associated with significantly lower overall survival compared with mBMI ≥ 700 kg g/L m^2 after transplant (median survival 5.2 months versus 78.8 months).[35] Another study compared the survival of patients with hATTR who received a liver transplant as part of an earlier series when severely malnourished patients were accepted (N = 34) with a later series of patients who were selected based on mBMI > 600 kg g/L m^2 (N = 27) in Sweden.[34] Survival was significantly prolonged in the later series of patients who had mBMI > 600 kg g/L m^2.[34]

Cardiovascular Biomarkers and Echocardiogram

Patients with hATTR polyneuropathy may also present with cardiomyopathy due to amyloid deposits in the heart. Cardiac manifestations of the disease include arrhythmias, heart failure, and sudden cardiac death. The degree to which polyneuropathy or cardiomyopathy is present depends on the genetic mutation (e.g., V30M mutation produces predominant

polyneuropathy whereas Val122Ile produces predominant cardiomyopathy), geographic location, and the individual.[1] Therefore, although inotersen is indicated specifically for hATTR polyneuropathy, the CADTH Common Drug Review has evaluated the evidence available for the following cardiac outcomes, which were exploratory in the NEURO-TTR study.

N-Terminal Prohormone of Brain Natriuretic Peptide

NT-proBNP is a cardiac biomarker that is released from the heart into the circulation in response to an increase in myocardial wall tension and stress and is associated with mortality in patients with hATTR.

In a large cohort study of 1,617 patients with transthyretin amyloidosis (1,452 with hereditary and 165 with wild type), factors associated with survival were examined.[40] During 1.2 years of follow-up, 115 patients died. Mortality rates increased with NT-proBNP quartile (Q1 = 1.7%, Q2 = 5.2%, Q3 = 21.7%, and Q4 = 71.3%). Patients with higher NT-proBNP quartile also presented with lower Karnofsky index, mBMI, and renal function. NT-proBNP was weakly correlated with mBMI (r = −0.236), moderately correlated with left atrial diameter (r = 0.337), and strongly correlated with septal thickness (r = 0.654) and LV posterior wall thickness (r = 0.649). In the Cox proportional hazards model, the predictors of survival in patients with hereditary hATTR were age, mBMI, mutation (V30M), brain natriuretic peptide, and NT-proBNP (Q1 to Q3 pooled versus Q4). In another study that included 60 patients with hATTR of the Thr60Ala mutation, NT-proBNP was significantly associated with survival in univariate (hazard ratio [HR] = 0.39; 95% CI, 0.16 to 0.96 for < 3,383 pg/mL versus ≥ 3,383 pg/mL) and multivariate (HR = 0.17; 95% CI, 0.03 to 0.92 for < 3,383 pg/mL versus ≥ 3,383 pg/mL) analyses.[37]

Damy et al. examined predictors of mortality in 198 patients with cardiac amyloidosis (118 with light-chain amyloidosis, 57 with hATTR, and 23 with wild-type transthyretin amyloidosis).[38] In a multivariate analysis among the subset of patients with transthyretin amyloidosis, NT-proBNP was a significant predictor of mortality.[38] In another study of 79 patients with cardiac amyloidosis (26 light-chain amyloidosis, 36 hATTR, and 17 wild-type transthyretin amyloidosis), NT-proBNP significantly increased the risk of major adverse cardiac events (MACE) (HR = 8.00; 95% CI, 2.67 to 23.93).[39] The optimal cut-off value for predicting MACE was an NT-proBNP value of 4,000 pg/mL.[39]

Echocardiogram: Left Ventricular Longitudinal Strain

LV longitudinal strain is a measure of impaired systolic function. Normal values are further from 0 (i.e., negative) and, as values approach 0, this indicates abnormality. Therefore, a negative change indicates improvement, whereas a positive change indicates worsening.

In one study, LV longitudinal strain was examined in 14 patients with hATTR with the V30M mutation (six with cardiac amyloidosis, four with extracardiac amyloidosis, and four without amyloidosis) and a control group of 14 healthy individuals without the mutation or cardiovascular disease.[50] The mean basal longitudinal strain, apical longitudinal strain (two, three, and four chambers), and mean longitudinal tension were all significantly higher (i.e., further from normal) compared with patients with extracardiac amyloidosis and, aside from three-chamber longitudinal strain, these measures were also higher compared with patients who had the V30M mutation but no disease.

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

strain was strongly correlated with LVEF (r = −0.55) and moderately correlated with LV wall thickness (r = 0.34).[42] In multivariable analysis, each incremental 1% increase in global LV longitudinal strain significantly increased risk of mortality from any cause (HR = 1.1; 95% CI, 1.01 to 1.19).[42] In another study of 79 patients with cardiac amyloidosis (26 light-chain amyloidosis, 36 hATTR, and 17 wild-type transthyretin amyloidosis), LV longitudinal strain correlated with cardiac amyloid burden, as assessed with late gadolinium enhancement on cardiac magnetic resonance (correlation not provided), and as assessed histologically in three hearts (r = 0.72).[39] Siepen et al. examined predictors of mortality in 191 patients with wild-type transthyretin amyloidosis and found that while global longitudinal strain was a significant predictor in univariate analysis, it lost significance in multivariate analysis.[45]

Global LV longitudinal systolic strain was assessed in 24 patients with light-chain amyloidosis.[43] Over a median follow-up of 487 days, 16 patients died and, in these patients, global longitudinal systolic strain decreased significantly from baseline (−10 ± 5% versus −12 ± 4%). Global longitudinal systolic strain was also strongly correlated with higher NT-proBNP at baseline (r = −0.677). In a univariate analysis, global longitudinal systolic strain was significantly associated with all-cause mortality (HR = 1.17; 95% CI, 1.02 to 1.35); however, statistical significance was lost in a multivariate model adjusted for age, gender, New York Heart Association class, and high-dose melphalan with autologous stem-cell transplantation (HR = 0.98; 95% CI, 0.67 to 1.45). In a larger study of 150 patients with light-chain amyloidosis (63 with cardiac amyloidosis and 87 without cardiac amyloidosis), global longitudinal strain was a significant predictor of survival in a multivariate Cox model (HR = 2.68; 95% CI, 1.07 to 7.13 for global longitudinal strain ≥ −14.81).[44]

The association between global longitudinal strain and mortality was examined in 546 patients undergoing echocardiography for known or suspected LV impairment.[41] Global longitudinal strain was calculated from three standard apical views using two-dimensional speckle tracking. Over a period of about five years, 91 patients died. Global longitudinal strain was significantly associated with mortality in nested Cox models (HR = 1.45; 95% CI, 1.19 to 1.77) and added to the predictive power of other clinical variables as measured by model χ^2. Intra-class correlation coefficients for inter-observer variability and intra-observer variability were 0.916 and 0.922, demonstrating good agreement.[41]

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

Echocardiogram: Left Ventricular Wall Thickness

LV wall thickness is assessed by echocardiogram to identify structural impairment due to remodelling from amyloid infiltrates. In 60 patients with hATTR of the Thr60Ala mutation, which causes cardiomyopathy as the predominant feature of hATTR,[1] LV posterior wall thickness was significantly associated with survival in univariate (HR = 0.42; 95% CI, 0.18 to 0.95 for < 17 mm versus ≥ 17 mm) and multivariate (HR = 0.17; 95% CI, 0.03 to 0.97 for < 17 mm versus ≥ 17 mm) analyses.[37] Among 39 patients with light-chain amyloidosis, LV wall thickness progression was higher in patients who died compared with survivors (2.02 ± 0.85 mm/month versus 0.19 ± 0.03 mm/month).[46] Progression of LV wall thickness was associated with survival in univariate and multivariate analyses.[46]

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

Echocardiogram: Left Ventricular Ejection Fraction

LVEF is assessed by echocardiogram to measure systolic dysfunction. Patients with wild-type (N = 18) and V122I mutant (N = 11) transthyretin amyloidosis, which is a mutation that causes cardiomyopathy as the predominant feature of hATTR,[1] were prospectively evaluated every six months for up to two years by Ruberg et al.[2] An LVEF < 50% was significantly associated with mortality in univariate analysis (HR = 4.12; 95% CI, 1.24 to 13.6).[2]

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

Appendix 6: Summary of the Extension Study

Aim

To summarize the findings of the open-label extension (Study CS3) of the NEURO-TTR trial and the six-month post-treatment evaluation period of NEURO-TTR.

Description

Study CS3 is an ongoing open-label extension study. Its primary objective is to evaluate the safety of inotersen in patients with hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy.[51] The information summarized in this appendix is based on a planned interim analysis that included data up to February 28, 2017.

Patients were eligible for enrolment in the extension study if they had completed the NEURO-TTR study (CS2), [redacted]

The planned duration of the study is five years (260 weeks). [redacted]

Efficacy outcomes reported included the modified Neuropathy Impairment Score + 7 (Ionis version) (mNIS+7$_{Ionis}$) and its individual components, the Norfolk Quality of Life-Diabetic Neuropathy questionnaire (Norfolk QoL-DN), the Short Form (36) Health Survey, version 2 (SF-36v2), [redacted]. Statistical testing was not conducted for the interim analysis, and efficacy data have been reported descriptively based on the available case data.

Safety assessments for the extension study period were based on [redacted]

[redacted]

Table 32: Details of the Extension Study

		CS3
Designs and Populations	**Study Design**	Open-label, single-arm study
	Locations	[redacted]
	Enrolled (N)	[redacted]
	Inclusion Criteria	Patients with hATTR with polyneuropathy who completed the NEURO-TTR RCT (Study CS2)
	Exclusion Criteria	[redacted]
Drugs	**Intervention**	[redacted][a]
	Comparator(s)	None
Duration	**Phase**	
	Screening	[redacted]
	Open-label	Up to 260 weeks (5 years)[a]
	Follow-up	[redacted]
Outcomes	**Primary End Point**	Safety
	Other End Points	Change from baseline in: • mNIS+7$_{Ionis}$ • Norfolk QoL-DN total score, symptom domain score, and physical functioning domain score [redacted] • NIS and components of the mNIS+7$_{Ionis}$ [redacted] • SF-36v2
Notes	**Publications**	None

[a] [redacted]

hATTR = hereditary transthyretin-mediated amyloidosis; mNIS+7$_{Ionis}$ = Modified Neuropathy Impairment Score + 7 (Ionis version); NIS = Neuropathy Impairment Score; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; RCT = randomized controlled trial; SC = subcutaneous; SF-36v2 = Short Form (36) Health Survey, version 2.

Source: Clinical Study Report for extension study CS3.[51]

Findings

As of the interim data cut-off (February 28, 2017), [redacted] patients were enrolled in the extension study, [redacted] of which had previously received placebo and [redacted] had received inotersen in the NEURO-TTR study. These patients represent [redacted] of patients who were originally randomized in the NEURO-TTR study and [redacted] of those who completed the study.

[redacted].

Of the [redacted] patients enrolled in the extension study, [redacted] discontinued inotersen (Table 33). This included [redacted] who had previously received placebo and [redacted] who had received inotersen in the NEURO-TTR study. The most common reasons for stopping therapy were [redacted].
The manufacturer stated that the most common reason for patients to be excluded from the FAS was that [redacted].

The longitudinal safety set included [redacted] patients who had received inotersen in the NEURO-TTR study and may or may not have continued to receive inotersen in the extension study.

Table 33: Disposition in Extension Study

	Placebo–Inotersen	Inotersen–Inotersen
Randomized and treated in NEURO-TTR, N	[redacted]	[redacted]
Completed NEURO-TTR, N	[redacted]	[redacted]
Enrolled in extension study, N	[redacted]	[redacted]
Discontinued, n (%)	[redacted]	[redacted]
Reason for Stopping Treatment, n (%)		
Adverse event	[redacted]	[redacted]
Investigator judgment	[redacted]	[redacted]
Voluntary withdrawal	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Other	[redacted]	[redacted]
FAS population, N (%)	[redacted]	[redacted]
Safety population, N (%)	[redacted]	[redacted]

FAS = full analysis set.

Source: Clinical Study Report for extension study CS3.[51]

At the start of the extension study, the demographics of the patients enrolled were [redacted]. Overall, the patients had a mean age of [redacted] were male and [redacted] were white (Table 34). The mean mNIS+7$_{Ionis}$ scores were [redacted] which suggests that those in the prior placebo group had more severe neuropathy at the start of the extension study.

Compared with the baseline characteristics of the NEURO-TTR study, the patients in the extension study were [redacted].

Table 34: Baseline Patient Characteristics in Extension Study

	Placebo–Inotersen N = 40	Inotersen–Inotersen N = 74	Total N = 114
Mean age (SD),[a] years	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Years since hATTR polyneuropathy diagnosis, mean (SD)	[redacted]	[redacted]	[redacted]
mNIS+7$_{Ionis}$,[a] mean (SD)	[redacted]	[redacted]	[redacted]
Norfolk QoL-DN, mean (SD)[a]	[redacted]	[redacted]	[redacted]
PND score,[a] n (%)			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
V	[redacted]	[redacted]	[redacted]
Genotype, n (%)			
V30M	[redacted]	[redacted]	[redacted]
Non-V30M	[redacted]	[redacted]	[redacted]
Diagnosed with cardiomyopathy, n (%)	[redacted]	[redacted]	[redacted]

hATTR = hereditary transthyretin-mediated amyloidosis; mNIS+7$_{Ionis}$ = modified Neuropathy Impairment Score +7 (Ionis version); Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PND = polyneuropathy disability; SD = standard deviation.

[a] At the start of extension study.

Source: Clinical Study Report for extension study CS3.[51]

The median duration of inotersen exposure during the extension study was [redacted] respectively (Table 35). [redacted]. The reason for treatment interruption was: [redacted].

In the longitudinal safety set (all patients who received inotersen in CS2 and may have continued in CS3), the median duration of inotersen exposure was [redacted] days.

Table 35: Exposure to Inotersen in Extension Study

	Extension Study		Longitudinal Safety Set
	Placebo–Inotersen N = 40	Inotersen–Inotersen N = 74	Inotersen N = 112
Duration of Inotersen Exposure (Days)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (P25, P75)	[redacted]	[redacted]	[redacted]

P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation.

Source: Clinical Study Report for extension study CS3.[51]

Descriptive data for the change from baseline in the mNIS+7$_{Ionis}$, Norfolk QoL-DN, and the SF-36v2 mental and physical component scores have been summarized in Table 35. Outcome data were reported for [redacted] of patients in the FAS at 26 and 52 weeks, respectively. [redacted]. The distribution of mNIS+7$_{Ionis}$ scores for extension study patients (during NEURO-TTR study CS2 and the extension study) are shown in Figure 5. There is [redacted]. There was no statistical testing conducted for the interim analysis; therefore, no conclusions can be made from these data.

Table 36: Summary of Efficacy Results in Extension Study

	Baseline		Change From Baseline to Week 26		Change From Baseline to Week 52	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
mNIS+7$_{Ionis}$ (FAS)						
Placebo–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Norfolk QoL-DN (FAS)						
Placebo–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36v2 MCS (FAS)						
Placebo–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36v2 PCS (FAS)						
Placebo–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FAS = full analysis set; MCS = mental component summary; mNIS+7$_{Ionis}$ = modified Neuropathy Impairment Score + 7 (Ionis version); Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PCS = physical component summary; SD = standard deviation; SF-36v2 = Short Form (36) Health Survey, version 2.

Source: Clinical Study Report for extension study CS3.[51]

Figure 5: Boxplot of Modified Neuropathy Impairment Score + 7 (Ionis Version) Absolute Values for Patients Enrolled in Extension Study CS3

Figure 5 contained confidential information and was redacted at the request of the manufacturer.

Source: Clinical Study Report for extension study CS3.[51]

At the start of the extension study, the [redacted] (Table 37). The median change in values over the first 39 weeks of the extension period were [redacted].

Table 37: Summary of Cardiac Outcomes in Extension Study

	Baseline		Change From Baseline to Week 13		Change From Baseline to Week 39	
	N	Median (P25, P75)	N	Median (P25, P75)	N	Median (P25, P75)
NT-proBNP, pmol/L (FAS)						
Placebo–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotersen–inotersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FAS = full analysis set; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; P25 = 25th percentile; P75 = 75th percentile.

Source: Clinical Study Report for extension study CS3.[51]

During the extension study, the percentage of patients whose polyneuropathy disability (PND) score had improved remained the same or worsened in the placebo–inotersen group [redacted] (Table 38). Whereas at 52 weeks, the percentage of patients who had worsened [redacted].

Table 38: Polyneuropathy Disability Score in Extension Study

	Placebo–Inotersen	Inotersen–Inotersen
PND Score		
Baseline, n (%)	[redacted]	[redacted]
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
V	[redacted]	[redacted]
Change from baseline to week 26, n (%)	[redacted]	[redacted]
Improved	[redacted]	[redacted]

	Placebo–Inotersen	Inotersen–Inotersen
Not changed	[redacted]	[redacted]
Worsened	[redacted]	[redacted]
Change from baseline to week 52, n (%)	[redacted]	[redacted]
Improved	[redacted]	[redacted]
Not changed	[redacted]	[redacted]
Worsened	[redacted]	[redacted]

PND = polyneuropathy disability.

Source: Clinical Study Report for extension study CS3.[51]

Overall, [redacted] of patients experienced an adverse event (AE), [redacted] experienced a serious adverse event (SAE) and [redacted] stopped treatment due to AEs during the extension study (Table 39). [redacted]

Table 39: Harms in Extension Study

	Extension Study[a]		Longitudinal Safety Set[b]
	Placebo–Inotersen N = 40	Inotersen–Inotersen N = 74	Inotersen N = 112
Patients with ≥ 1 adverse event, n (%)	[redacted]	[redacted]	[redacted]
Most common events[c]			
Fatigue	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Peripheral edema	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Injection-site erythema	[redacted]	[redacted]	[redacted]
Injection-site pain	[redacted]	[redacted]	[redacted]

	Extension Study[a]		Longitudinal Safety Set[b]
	Placebo–Inotersen N = 40	Inotersen–Inotersen N = 74	Inotersen N = 112
Injection-site rash	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Patients with adverse event leading to treatment discontinuation, n (%)	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 SAE, n (%)	[redacted]	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]	[redacted]

SAE = serious adverse event.

[a] The extension cohort includes all patients who were enrolled in the extension study CS3 and received at least one dose of the study drug.

[b] The longitudinal cohort included all patients who received at least one dose of inotersen in the NEURO-TTR study and who may or may not have continued to receive inotersen in the extension study.

[c] [redacted]

Source: Clinical Study Report for extension study CS3.[51]

The manufacturer specified [redacted]. A summary of these events for the extension study as well as the longitudinal safety set is provided in Table 39. For each adverse event type, [redacted].

During the extension study, [redacted] (Table 39). [redacted]

[redacted]

During the extension study, ocular events that were potentially related to vitamin A deficiency were reported by [redacted] (Table 40). Overall, [redacted] of patients experienced an injection-site AE, [redacted].

In total, [redacted] in CS2 and CS3 tested positive for inotersen anti-drug antibodies, of which [redacted] had persistently positive samples.

Table 40: Notable Harms in the Extension Study

Adverse Event, n (%)	Extension Study[a]		Longitudinal Safety Set[b]
	Placebo–Inotersen N = 40	Inotersen N = 74	Inotersen N = 112
Thrombocytopenia[c]	[redacted]	[redacted]	[redacted]
Renal impairment[d]	[redacted]	[redacted]	[redacted]
Ocular adverse events potentially related to vitamin A deficiency[e]	[redacted]	[redacted]	[redacted]
Adverse events at the injection site[f]	[redacted]	[redacted]	[redacted]

[a] The extension cohort includes all patients who were enrolled in the extension study CS3 and received at least one dose of study drug.

[b] The longitudinal cohort included all patients who received at least one dose of inotersen in the NEURO-TTR study and who may or may not have continued to receive inotersen in the extension study.

[c] [redacted]

[d] [redacted]

[e] [redacted]

[f] [redacted]

Source: Clinical Study Report for extension study CS3.[51]

Six-Month Post-Treatment Evaluation Period

If patients were not enrolled in the open-label extension, they entered a six-month post-treatment evaluation period during which time they received additional visits and a safety assessment. At the time of data cut-off, [redacted] patients completed the post-treatment evaluation period and an additional [redacted] patients were ongoing. The manufacturer provided data for the co-primary efficacy outcomes, Norfolk QoL-DN and mNIS+7$_{lonis}$, and key harms of thrombocytopenia and mortality for individual patients. CADTH reviewers compiled the individual-level patient data into aggregate means.

At 26 weeks in the post-treatment evaluation period, the Norfolk QoL-DN was available for [redacted] patients who received inotersen and [redacted] patients who received placebo. The mean Norfolk QoL-DN was [redacted] for inotersen and [redacted] for placebo. The overall Norfolk QoL-DN average for the [redacted] patients was [redacted]. The mNIS+7$_{lonis}$ was available for [redacted] patients who received inotersen and [redacted] patients who received placebo. The mean nNIS+7$_{lonis}$ was [redacted] for inotersen and [redacted] for placebo. The overall mNIS+7$_{lonis}$ average for the [redacted] patients was [redacted] in the inotersen group and [redacted] in the placebo group experienced thrombocytopenia (during the treatment period). [redacted] during the post-treatment evaluation period.

Critical Appraisal and Discussion

Study CS3 is an ongoing open-label extension study that enrolled patients with hATTR and polyneuropathy who had completed the NEURO-TTR study. [redacted] who had received inotersen 300 mg weekly by subcutaneous injection for a median of [redacted] days (placebo–inotersen group) or [redacted] days (inotersen–inotersen group).

[redacted].

Although efficacy data were reported, these data had a number of limitations. First, as this was an interim data analysis, the number of patients with data at various time points was limited. Specifically, mNIS+7$_{Ionis}$ results were reported for [redacted]. Moreover, it is unclear what proportion of the patients had missing data due to withdrawals or other reasons versus those who had not yet reached that follow-up time. In general, patients who withdraw from trials have worse clinical outcomes than those who continue. [redacted]. The results were reported descriptively, with no statistical analysis, and no imputation to explore the possible impact of missing data. There was no control group, and the reporting of harms and subjective outcomes may be biased due to the lack of blinding.

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