CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211172Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	October 5, 2018
From	Nick Kozauer, MD Billy Dunn, MD Robert Temple, MD
Subject	Summary Memorandum
NDA#	211172
Applicant	Ionis Pharmaceuticals, Inc.
Date of Submission	November 6, 2017
PDUFA Goal Date	October 6, 2018
Proprietary Name / Non-Proprietary Name	Tegsedi (inotersen)
Dosage form(s) / Strength(s)	Sterile, (b) (4) injection, 284 mg/1.5 mL (300 mg inotersen sodium/1.5 mL) in single use prefilled syringe.
Proposed Dose/Regimen	(b) (4) weekly SC doses of 300 mg.
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with hereditary TTR amyloidosis with polyneuropathy (hATTR-PN) (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is an autosomal dominant disorder caused by mutations in the transthyretin (TTR) gene, located on chromosome 18q. Wild-type TTR protein is primarily synthesized in the liver and exists in a tetrameric state transporting thyroxine (T_4) and vitamin A (retinol) in association with retinol binding protein (RBP). More than 120 different point mutations in the TTR gene have been identified that lead to hATTR amyloidosis. A replacement of valine by methionine at position 30 (V30M) is the most common mutation causing hATTR amyloidosis. These mutations result in protein misfolding, aggregation, and deposition in the peripheral and central nervous system, heart, kidneys, eyes, bone, and gastrointestinal tract. Symptom onset typically occurs between 20 and 70 years of age, with death occurring within 5 to 12 years of onset, most commonly from cardiac dysfunction, infection, or cachexia. Many patients experience a prominent neuropathy defined by the presence of peripheral neuropathy and autonomic dysfunction [referred to as hATTR-polyneuropathy (hATTR-PN)]. The global prevalence of hATTR-PN is estimated to be between 5,000 and 10,000 persons, with the highest rates occurring in certain endemic countries such as Portugal and Sweden.

Onpattro (patisiran), a small interfering ribonucleic acid (siRNA), was approved for the treatment of the polyneuropathy of hATTR amyloidosis in adults in August 2018 (it was the first approval for this indication).

Inotersen is a 2'-O-(2-methoxyethyl) [2' MOE] phosphorothioate antisense oligonucleotide (ASO) that selectively binds to TTR messenger ribonucleic acid (mRNA) causing degeneration of both wild-type and mutant TTR mRNA. The dose of inotersen that is proposed for marketing has been demonstrated to reduce serum TTR protein levels by an average of 70%.

The applicant has provided data from Study ISIS-410915-CS2 (CS2, in this memorandum); a 66-week, randomized, double-blind, placebo-controlled trial in adult patients with hATTR-PN. This trial evaluated a 300 mg dose of inotersen administered subcutaneously (SC) every 3 weeks (following 3 loading doses in Week 1) compared to placebo. The trial evaluated outcomes on the modified Neuropathy Impairment Scale+7 (mNIS+7); an objective evaluation of polyneuropathy with a maximum score of 346.2 points (where higher scores indicate greater severity of disease) consisting of a clinical neurological examination and tests of nerve conduction, sensation, and postural blood pressure. Placebo-treated patients declined (i.e., had higher scores) at the expected rate in the absence of treatment of 26 points during the 66 weeks of the trial, whereas the average scores in inotersen-treated patients declined only 6 points. The clinical meaningfulness of these results was confirmed by the results of the Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN) scale; a patient-reported subjective assessment of the clinical impact of polyneuropathy with a maximum score of 140 points (where higher scores indicate greater severity of disease). Inotersen-treated patients essentially remained stable during the 66 weeks of the trial, worsening by only 1 point, whereas placebo-treated patients worsened by 13 points. This pattern of limited worsening and even stability in the signs and symptoms of patients' polyneuropathy is unexpected in the natural history of the disease. The longer-term benefits of treatment are unknown, and the trial was not designed to, and did not, demonstrate an effect of treatment on survival. The efficacy results from Study CS2 establish the effectiveness of inotersen for the treatment of the polyneuropathy of hATTR amyloidosis in adults.

Inotersen, however, causes serious and potentially fatal adverse reactions, including thrombocytopenia, glomerulonephritis, inflammatory and immune effects (e.g., serious neurologic adverse reactions), hepatic toxicity, and hypersensivity reactions.

In Study CS2, 25% of inotersen-treated patients had platelet counts below 100 x 10^9/L, compared to 2% of placebo-treated patients; 14% of inotersen-treated patients had platelet counts below 75 x 10^9/L (the level below which primary hemostasis is generally impaired), compared to 0% of placebo-treated patients. Three inotersen-treated patients (3%) had sudden and severe platelet reductions below 25 x 10^9/L; a level associated with the potential for fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. One of these cases resulted in a fatal intracranial hemorrhage. Both gradual and precipitous decreases in platelet counts were observed. Frequent clinical and laboratory monitoring can mitigate the risk of severe thrombocytopenia, but may not prevent all cases. Additionally, there is a risk that some platelet counts may be uninterpretable because of a reaction between a component of the collection tube [ethylenediaminetetra-acetic acid (EDTA)] and antiplatelet antibodies (in these cases repeat testing with a different anticoagulant can be conducted).

In Study CS2, 3 inotersen-treated patients (3%) developed glomerulonephritis, compared to no placebo-treated patients. Cessation of inotersen treatment alone was not sufficient to resolve the glomerulonephritis in these cases, and immunosuppressive therapy was required. One of the 3 patients did not receive immunosuppressive therapy and remained dialysis-dependent. Frequent clinical and laboratory monitoring can mitigate the risk of renal toxicity, but may not prevent all cases.

ASO drugs are known to cause inflammatory and immune changes. A case of stroke and carotid artery dissection occurred 2 days after the first dose of inotersen and was associated with what appeared to be a cytokine release syndrome. There were also individual cases in inotersen-treated patients of anti-neutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis and autoimmune hepatitis with primary biliary cirrhosis. In addition, serious neurological adverse reactions were observed (in addition to stroke and artery dissection) that appeared to be consistent with inflammatory and immune effects, including individual cases of suspected encephalitis and myelitis. Further, the observed thrombocytopenia and glomerulonephritis were also likely to have been immune-mediated. Frequent clinical and laboratory monitoring can lead to the early detection of some adverse inflammatory and immune reactions; however, events such as stroke and artery dissection cannot be detected until after their occurrence.

ASO drugs are known to accumulate in the liver. In the inotersen development program, 8% of inotersen-treated patients had alanine aminotransferase (ALT) levels at least 3 times the upper limit of normal (ULN), compared to 3% of placebo-treated patients; 3% of inotersen-treated patients had ALT levels at least 8 times the ULN, compared to 0% of placebo-treated patients. No Hy's Law cases were identified. Laboratory monitoring can help mitigate the risk of hepatotoxicity.

Hypersensitivity reactions associated with antibodies to inotersen led to treatment discontinuation in 7 inotersen-treated patients. There is no known way to mitigate this risk.

Wild-type TTR reduction leads to reduction in vitamin A levels. Patients in the inotersen development program were instructed to take the recommended daily allowance of vitamin A, and no vitamin A-related ocular toxicities were observed. Vitamin A supplementation will be recommended in labeling.

In the setting of the clearly established effectiveness of inotersen for the treatment of a serious disease with only one FDA-approved therapy, the safety profile of inotersen does not preclude approval. However, a risk evaluation and mitigation strategy (REMS) with elements to ensure safe use (ETASU) is

required to educate patients and providers about the risks of thrombocytopenia and glomerulonephritis and to ensure that appropriate clinical monitoring occurs. These risks will also be described in a boxed warning in the label. In addition, the WARNINGS AND PRECAUTIONS section of the label will provide detailed descriptions and monitoring recommendations related to thrombocytopenia, glomerulonephritis and renal toxicity, stroke and artery dissection, inflammatory and immune effects, hepatoxicity, hypersensitivity, the potential for an antiplatelet antibody/EDTA interaction, and (b) (4). Further, a REMS registry must be established to further characterize the risks of thrombocytopenia, glomerulonephritis, and neurologic toxicity (e.g., stroke, artery dissection, and vasculitis). Suspected cases of cytokine release syndrome in the post-approval setting will also need to be characterized. Finally, expedited post-approval safety reporting will be necessary for the safety concerns described in the WARNINGS AND PRECAUTIONS section of the label.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is an autosomal dominant disorder caused by mutations in the transthyretin (TTR) gene. Wild-type TTR protein is primarily synthesized in the liver and exists in a tetrameric state transporting thyroxine (T_4) and vitamin A (retinol) in association with retinol binding protein (RBP). More than 120 different point mutations in the TTR gene have been identified that lead to hATTR amyloidosis. A replacement of valine by methionine at position 30 (V30M) is the most common mutation causing hATTR amyloidosis. These mutations result in protein misfolding, aggregation, and deposition in the peripheral and central nervous system, heart, kidneys, eyes, bone, and gastrointestinal tract. Symptom onset typically occurs between 20 and 70 years of age, with death occurring within 5 to 12 years of onset, most commonly because of cardiac dysfunction, infection, or cachexia. Many patients experience a prominent neuropathy defined by the presence of peripheral neuropathy and autonomic dysfunction [referred to as hATTR-polyneuropathy (hATTR-PN)]. • The global prevalence of hATTR-PN is estimated to be between 5,000 and 10,000 persons, with the highest rates occurring in certain endemic countries such as Portugal and Sweden.	HATTR amyloidosis is a serious disease, leading to significant disability and death.
Current Treatment Options	• Onpattro (patisiran), a small interfering ribonucleic acid (siRNA), was approved for the treatment of the polyneuropathy of hATTR amyloidosis in adults in August 2018. • Published literature suggests that orthotopic liver transplantation may be effective at stabilizing disease progression in some patients (e.g., patients with V30M mutations).	There is only one FDA-approved treatment for the polyneuropathy of hATTR amyloidosis in adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The applicant has provided data from Study CS2; a 66-week, randomized, double-blind, placebo-controlled trial in adult patients with hATTR-PN. This trial evaluated a 300 mg dose of inotersen administered as a weekly subcutaneous (SC) injection compared to placebo. • The trial's primary efficacy analysis demonstrated a highly statistically significant treatment effect on the modified Neuropathy Impairment Scale +7 (mNIS+7); an objective evaluation of the signs and symptoms of polyneuropathy. Mean mNIS+7 scores in inotersen-treated patients demonstrated significantly less worsening (increase in scores) during the trial compared to placebo-treated patients. • A similar pattern of treatment effects was observed on the Norfolk Quality of Life Diabetic Neuropathy (Norfolk QoL-DN) scale, which supports the clinical meaningfulness of the objective mNIS+7 scores.	This application has established that inotersen is effective for the treatment of the polyneuropathy of hATTR amyloidosis in adults. Inotersen-treated patients in Study CS2 demonstrated significantly less worsening compared to placebo-treated patients on both objective and subjective evaluations of polyneuropathy. The longer-term benefits of inotersen treatment are unknown. Study CS2 was not designed to, and did not, demonstrate a benefit on survival.
Risk and Risk Management	• In Study CS2, 25% of inotersen-treated patients had platelet counts below 100 x 10^9/L, compared to 2% of placebo-treated patients; 14% of inotersen-treated patients had platelet counts below 75 x 10^9/L (the level below which primary hemostasis is generally impaired), compared to 0% of placebo-treated patients. Three inotersen-treated patients (3%) had sudden and severe platelet reductions below 25 x 10^9/L; a level associated with the potential for fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. One of these resulted in a fatal intracranial hemorrhage. Additionally, there is a risk that some platelet counts may be uninterpretable because of a reaction between a component of the collection tube [ethylenediaminetetra-acetic acid (EDTA)] and antiplatelet antibodies (in these cases repeat testing with a different anticoagulant can be conducted). • In Study CS2, 3 inotersen-treated patients (3%) developed glomerulonephritis, compared to no placebo-treated patients (0%). Cessation of inotersen treatment alone was not sufficient to resolve the glomerulonephritis in these cases, and immunosuppressive therapy was required. One of the 3 patients did not receive immunosuppressive therapy and remained dialysis-dependent. • ASO drugs are known to cause inflammatory and immune changes. A case of stroke and carotid artery dissection occurred 2 days after the first dose of inotersen and was associated with what appeared to be a cytokine	In the setting of the clearly established effectiveness of inotersen for the treatment of a serious disease with only one FDA-approved therapy, the safety profile of inotersen does not preclude approval. A risk evaluation and mitigation strategy (REMS) with elements to ensure safe use (ETASU) is necessary to address the risks of thrombocytopenia and glomerulonephritis. These risks will also be described in a boxed warning in the label. The WARNINGS AND PRECAUTIONS section of the label will need to provide detailed descriptions and monitoring recommendations related to thrombocytopenia, glomerulonephritis and renal toxicity, stroke and artery dissection, inflammatory and immune effects, hepatoxicity, hypersensitivity, the potential for an antiplatelet antibody/EDTA interaction, and (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	release syndrome. There were also individual cases in inotersen-treated patients of anti-neutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis and autoimmune hepatitis with primary biliary cirrhosis. In addition, serious neurological adverse reactions were observed (in addition to stroke and artery dissection) that appeared to be consistent with inflammatory and immune effects, including individual cases of suspected encephalitis and myelitis. Further, the cases of thrombocytopenia and glomerulonephritis were also likely to be immune-mediated. • ASO drugs are known to accumulate in the liver. In the inotersen development program, 8% of inotersen-treated patients has alanine aminotransferase (ALT) levels at least 3 times the upper limit of normal (ULN), compared to 3% of placebo-treated patients; 3% of inotersen-treated patients had ALT levels at least 8 times the ULN, compared to 0% of placebo-treated patients. No Hy's Law cases were identified. • Hypersensitivity reactions associated with antibodies to inotersen led to treatment discontinuation in 7 inotersen-treated patients. • Wild-type TTR reduction leads to reductions in vitamin A levels. Patients in the inotersen development program were instructed to supplement with the recommended daily allowance of vitamin A, and no vitamin A-related ocular toxicities were observed. Vitamin A supplementation will also be recommended in labeling.	A REMS registry must be established to further characterize the risks of thrombocytopenia, glomerulonephritis, and neurologic toxicity (e.g., stroke, artery dissection, and vasculitis). Suspected cases of cytokine release syndrome in the post-approval setting will also need to be characterized. Expedited post-approval safety reporting is necessary for the safety concerns described in the WARNINGS AND PRECAUTIONS section of the label.

2. Background

This application contains data in support of the safety and effectiveness of inotersen, an antisense oligonucleotide (ASO), administered as a weekly subcutaneous (SC) injection, for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). Inotersen is a new molecular entity (NME) that has not been approved for any indication and has not previously been the subject of any marketing application.

Onpattro (patisiran), a small interfering ribonucleic acid (siRNA), was approved for the treatment of the polyneuropathy of hATTR amyloidosis in adults in August 2018.

HATTR amyloidosis is a life-threatening autosomal dominant disorder, caused by more than 120 identified mutations in the transthyretin (TTR) gene, located on chromosome 18q. Wild-type TTR protein (also referred to as prealbumin) is primarily synthesized in the liver (and to a lesser extent the choroid plexus and retinal pigment epithelium) and exists in a tetrameric state, transporting thyroxine (T4) and vitamin A (retinol) in association with retinol-binding protein (RBP). The various hATTR amyloidosis mutations lead to misfolding of the TTR protein, which results in protein aggregation and amyloid deposition in the peripheral and central nervous system, heart, kidneys, eyes, bone, and gastrointestinal tract. A replacement of valine by methionine at position 30 (V30M) is the most common TTR protein abnormality causing hATTR amyloidosis. Symptom onset typically occurs between 20 and 70 years of age. Death generally occurs within 5 to 12 years after onset, most often because of cardiac dysfunction, infection, or cachexia.

Three forms of the disease are often described, although patients will often experience more than one form clinically. The neuropathic form [hereditary transthyretin-mediated amyloidosis polyneuropathy (hATTR-PN), historically referred to as transthyretin familial amyloid polyneuropathy (TTR-FAP)], is defined by the presence of peripheral neuropathy and autonomic dysfunction. The leptomeningeal form is defined by the presence of stroke, intracranial hemorrhage, hydrocephalus, ataxia, spastic paralysis, seizures, dementia, psychosis, and vision impairment. The cardiac form [hereditary transthyretin-mediated amyloidosis cardiomyopathy (hATTR-CM)] is defined by the presence of arrhythmia, cardiomegaly, heart failure, and death.

The global prevalence of hATTR-PN is estimated to be between 5,000 and 10,000 individuals, with the highest rates occurring in certain endemic countries such as Portugal and Sweden.

Inotersen is a 2'-O-(2-methoxyethyl) [2' MOE] phosphorothioate ASO that selectively binds to complementary strands of TTR messenger ribonucleic acid (mRNA). This binding results in the enzymatic degeneration of both wild-type and mutant TTR mRNA by RNAase.

The applicant has provided data from a single adequate and well-controlled clinical trial as the primary basis of support of the effectiveness of inotersen for the treatment of the polyneuropathy of hATTR amyloidosis in adults.

The regulatory history of the inotersen development program is detailed in Dr. Christopher Breder's clinical review.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson-Lee (Dr. Wilson-Lee's review lists the entire OPQ team involved with the review of this application). OPQ recommends approval of this application.

The OPQ review notes that inotersen is formulated as a sterile solution for once-weekly SC injection provided in a pre-filled syringe (and thus considered a drug-device combination product). The device constituent parts of the combination product were found to be adequate by the Center for Devices and Radiologic Health (CDRH) reviewer.

The OPQ review concludes that a (b) (4) month retest date should be granted for the drug substance when stored at (b) (4) C when stored protected from light. Based on the real-time stability data on three batches, an expiration dating period of 18 months is assigned when the drug product packages are stored refrigerated at 2-8°C and protected from light. In addition, following distribution to patients, the in-use shelf-life of 6 weeks is acceptable when the drug product is stored at up to 30°C (86°F) and protected from light. All manufacturing facilities were found to be acceptable.

Dr. Haoheng Yan from OPQ conducted a review of the immunogenicity assay used in the inotersen development program. Dr. Yan concludes that the anti-drug antibody (ADA) assay is appropriately validated and suitable for detecting anti-inotersen antibodies in plasma samples (see also the additional discussion in the Clinical Pharmacology section of this memorandum).

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. David Hawver, with Dr. Lois Freed performing a secondary review. Dr. Hawver concludes that the application is approvable from a pharmacology/toxicology standpoint. The following are among the principal conclusions from Dr. Hawver's review:

- In the chronic toxicity studies in mouse, rat, and monkey, accumulation of basophilic granules (consistent with drug-related material) was observed in multiple organs (e.g., liver, kidney, lymph nodes) along with associated inflammatory responses known to be associated with ASOs.

- Renal toxicity was observed in the two highest dose groups in the 26-week rat study (increases in urine protein/creatinine and albumin/creatinine ratios, glomerular cellularity, and glomerular matrix), as well as the 13-week monkey study (degeneration/regeneration of renal proximal tubular epithelial cells).

- Severe thrombocytopenia was observed in the 39-week monkey study and was associated with petechiae, bruising, and internal hemorrhages. These findings necessitated euthanasia in 2 animals. Thrombocytopenia is a known adverse effect of ASOs.

- Safety margins for the proposed to-be-marketed dose based on the area under the curve (AUC) at the no observed adverse effect levels (NOAELs) for severe thrombocytopenia in monkeys and renal toxicity in rates were approximately 2-fold.

- Key findings from a standard battery of reproductive and developmental toxicity study in mouse and rabbit include premature delivery and reductions in maternal and fetal body weights in the high-dose group in the rabbit embryofetal developmental study.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Drs. Mariam Ahmed (the primary reviewer), Venkatesh Atul Bhattaram, Theingi Thway, Hobart Rogers, Christian Grimstein, Kevin Krudys, and Sreedharan Sabarinath (the clinical pharmacology team lead). The final signatory for the OCP review was Dr. Mehul Mehta. OCP recommends the approval of this application.

Table 1 summarizes the conclusions of the OCP review with respect to the pharmacologic and clinical pharmacokinetic properties of inotersen:

Table 1: Summary of OCP Review Findings

Mechanism of action	Inotersen is a 2'-O-(2-methoxyethyl) [2' MOE] phosphorothioate ASO inhibitor of both mutant and wild type human TTR production. Inotersen selectively binds to TTR mRNA causing degeneration of both mutant and wild type TTR mRNA.
Pharmacokinetics	Following SC administration, median time to maximum plasma concentration ($_{Tmax}$) was 1.5 to 4 hours.
Variability	Inter-individual variability in plasma $AUC_{0\text{-last}}$ (%CV) for inotersen ranged from 28% to 44%. Inter-individual variability in plasma C_{trough} (%CV) levels for inotersen ranged from 17% to 66%.
Immunogenicity	No immunogenicity assessment was performed in a Phase 1 study (Study CS1) with healthy subjects. Antibodies to inotersen were formed in about 30% of patients treated with inotersen in the 66-week controlled efficacy trial included in the application [Study ISIS 420915-CS2 (Study CS2)] and 40% in the open-label extension [Study ISIS 420915-CS3 (Study CS3)]. Overall, 40% (45/114) of treated patients were positive for treatment-emergent ADA. However, the immunogenicity assay is only capable of detecting IgG isotypes, so the overall incidence of ADAs may be greater than reported. There was no apparent effect of ADAs on efficacy or platelet counts; with the caveat that the contribution of non-IgG ADA isotypes is unknown. Hypersensitivity reactions associated with anti-inotersen ADAs are discussed in the clinical safety section of this memorandum.
Distribution	Inotersen distributes rapidly to the liver and kidney. Inotersen is more than 94% bound to human plasma proteins.
Metabolism	Inotersen is metabolized by endonucleases to form shorter, inactive oligonucleotides that are further metabolized by exonucleases.
Excretion	The mean terminal elimination half-life in plasma ranges between 2 to 4 weeks. Inotersen is mainly excreted in the urine as chain-shortened nucleotides that are not considered active. Urinary recovery of unchanged inotersen is limited to less than 0.05% after a single dose administration within the first 24 hours; less than 1.1% was excreted in urine after the 6th dose.
QT prolongation	A QT-Interdisciplinary Review Team (QT-IRT) review was conducted by Drs. Lars Johannesen and Christine Garnett. The QT-IRT review notes that a requirement for a Thorough QT (TQT) study was waived because of the low likelihood of direct ion channel interactions. The review also concludes that the nonclinical data suggest a low potential for inotersen to directly inhibit the hERG potassium channel. Further, no large changes in the mean QTc interval (>20ms) were evident in a randomized, placebo-controlled trial in healthy volunteer subjects.

The following applicant figure, copied from the OCP review, demonstrates that patients receiving inotersen in Study CS2 achieved an average 70% reduction in serum TTR protein levels, compared to an 8% reduction in patients receiving placebo (assessments were obtained prior to dosing at the

respective study visits). Maximum reductions in serum TTR protein levels were observed by Week 13, with a consistent effect through Week 65 (the last visit at which they were assessed).

Figure 1: Mean (95% confidence intervals) Percent TTR reduction from Baseline over Time in Study CS2

The OCP review raises the possibility that the use of a lower dose of inotersen than was evaluated in Study CS2 could result in an improved safety profile while maintaining similar clinical efficacy. Modeling suggests that the expected reductions in serum TTR levels (b) (4)

The OCP review finds that intrinsic factors, including age, race, gender, and renal or hepatic impairment, do not impact the systemic exposures of inotersen, noting that such effects would not be anticipated, as inotersen is primarily metabolized by nucleases.

The OCP review notes that because inotersen is administered intravenously, a food-drug interaction is not expected. Additionally, *in vitro* drug interaction studies suggest that inotersen is not a substrate of or inhibitor for any major cytochrome (CYP) enzymes and transporters; therefore, the drug-drug interaction liability of inotersen is minimal.

Based on the preceding conclusions, the OCP review finds the applicant's proposed dosing regimen acceptable.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Dr. Christopher Breder was the clinical reviewer for this application. Dr. Tristan Massie was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead.

Study ISIS-420915-CS2 (CS2)

A single clinical trial, Study CS2, was intended to provide substantial evidence of the effectiveness of inotersen for the treatment of the polyneuropathy associated with hATTR in adults.

Study CS2 was a 66-week, randomized, double-blind, placebo-controlled trial in adult patients with polyneuropathy caused by hATTR. The trial was conducted at 24 investigational sites located in 10 countries. A total of 172 patients were randomized in a 2:1 ratio to receive 300 mg doses of inotersen administered subcutaneously every week (following 3 loading doses in Week 1) (n=113) or placebo (n=60). Randomization was stratified 1) by the previous use of agents intended to stabilize TTR-protein tetramers (tafamidis or diflunisal) versus absence of such previous use (neither drug is FDA-approved for the treatment of hATTR amyloidosis; tafamidis is approved in Europe and diflunisal is used off-label in many countries), 2) by disease stage (Stage 1 [does not require assistance with ambulation while Stage 2 disease does require assistance with ambulation)], and 3) by the presence of a V30M TTR mutation versus non-V30M mutations.

Patients were required to be between 18 to 82 years of age, have a diagnosis of hATTR amyloidosis with a documented mutation in the TTR gene, and have documented amyloid deposition assessed by biopsy. Patients were also required to have Stage 1 or Stage 2 polyneuropathy and have a baseline Neuropathy Impairment Score (NIS) score of 10 to 130 (higher scores indicate more severe polyneuropathy). Patients with current use of purported tetramer stabilizers were excluded.

The co-primary efficacy endpoints were the change from baseline to Week 66 in modified NIS+7 (mNIS+7) and the Norfolk-Quality of Life-Diabetic Neuropathy Scale (Norfolk-QoL-DN) scores.

As Dr. Breder details in his review, the mNIS+7 comprises the NIS and the +7. The NIS is a clinical exam-based neuropathy evaluation assessing both weakness (NIS-W) and reflexes (NIS-R)]; the +7 is an objective evaluation of small and large nerve fiber function, including NCS and quantitative sensory testing (QST), as well as measurements of autonomic function [heart rate deep breathing (HRDB)]. Scores range from 0 to 346.32, with higher scores indicating more severe neuropathy. The correlation between mNIS+7 scores and clinical function is variable; however, the majority of patients with scores of 100 or greater will be reliant on the use of assist devices for ambulation.

The mNIS+7 appears capable of detecting small changes in its components that are not obviously clinically meaningful. For that reason, it is important that the results of the analysis of the mNIS+7 be considered together with the results of the Norfolk-QoL-DN. The Norfolk-QoL-DN is 35-item patient-reported measure that evaluates patients' perception of impairment with respect to physical functioning/large fiber neuropathy, activities of daily living, neuropathy symptoms, small fiber

neuropathy, and autonomic dysfunction. The version of the Norfolk QoL-DN that was used in the trial had a maximum possible score of 136, with higher scores indicating greater impairment.

The primary analysis of the co-primary efficacy endpoints was performed using a mixed-effects model repeated measures (MMRM) approach. Dr. Massie notes that the analyses were conducted in a stepwise approach; i.e., if the null hypothesis for the mNIS+7 was rejected, then the null hypothesis for the Norfolk QoL-DN questionnaire total score was tested. However, if the null hypothesis for the mNIS+7 was not rejected, testing for the Norfolk QoL-DN questionnaire total score would be considered exploratory. No adjustment was needed for multiple testing (both endpoints were tested at a 2-sided alpha of 0.05) as both had to be successful.

Study CS2 enrolled 173 patients. The mean age was 59 years (range: 27 to 81 years). Sixty-nine percent of patients were male, 92% were White/Caucasian, 2% were Black, and 2% were Asian. Patients were from North America (48%), Europe (35%), and South America/Australia (17%). The mean disease duration since diagnosis was 64 months. The mean baseline NIS was 45 points. Overall, 50% of patients had V30M mutations, and 55% of patients had previously used either tafamidis and/or diflunisal. Drs. Breder and Massie conclude that the baseline demographics and disease-specific characteristics were generally similar between the treatment arms.

Overall, 34 patients (20%) discontinued study treatment early (23% versus 13% in the inotersen- and placebo-treated groups, respectively). The most common reasons for patient discontinuation were adverse events (AEs), consent withdrawal, and disease progression.

The results of the primary efficacy analyses were highly statistically significant in favor of inotersen. At Week 66, mNIS+7 scores worsened (increased) from baseline by least squares (LS) mean of 5.8 points in the inotersen group, whereas the LS mean score increased by a mean of 25.5 points in the placebo group [LS mean difference: -19.73 points (p<0.001)]. Results are shown in Table 2.

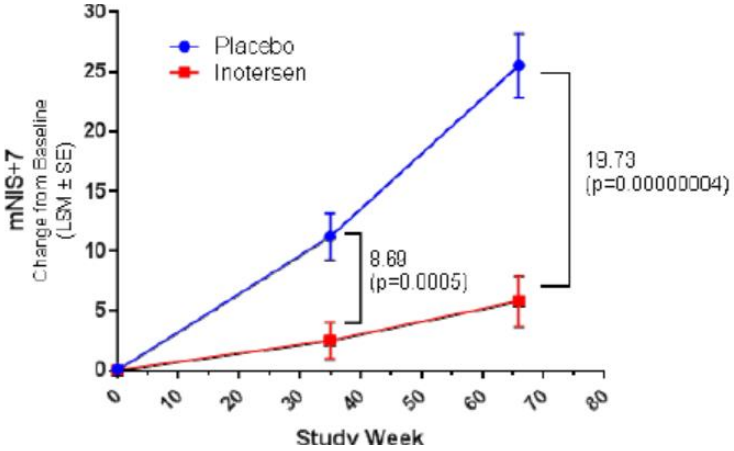
Table 2: Clinical Efficacy Results from Study CS2

Endpoint	Baseline		Change from Baseline to Week 35 (LS Mean)		Inotersen-Placebo Treatment Difference at Week 35 – LS Mean (95% CI)	p-value (nominal)	Change from Baseline to Week 66 (LS Mean)		Inotersen-Placebo Treatment Difference at Week 66 – LS Mean (95% CI)	p-value
	Inotersen	Placebo	Inotersen	Placebo			Inotersen	Placebo		
mNIS+7[b, c]	80.2	75.3	2.5	11.2	-8.7 [-13.5,-3.9]	0.0005	5.8	25.5	-19.7 [-26.4,-13.0]	<0.001
Norfolk QoL-DN[b, d]	48.7	48.7	0.8	7.0	-6.1 [-11.8,-0.5]	0.0325	1.0	12.7	-11.7 [-18.3, -5.1]	<0.001

CI, confidence interval; LS, least squares; mNIS, modified Neuropathy Impairment Score; QoL-DN, Quality of Life – Diabetic Neuropathy;
[a] All endpoints analyzed using the mixed-effect model repeated measures (MMRM) method.
[b] A lower value indicates less impairment/fewer symptoms.
[c] The analysis population for the mNIS+7 analysis included N=95 TEGSEDI patients and N=56 placebo patients
[d] The analysis population for the Norfolk QOL-DN analysis included N=94 TEGSEDI patients and N=57 placebo patients

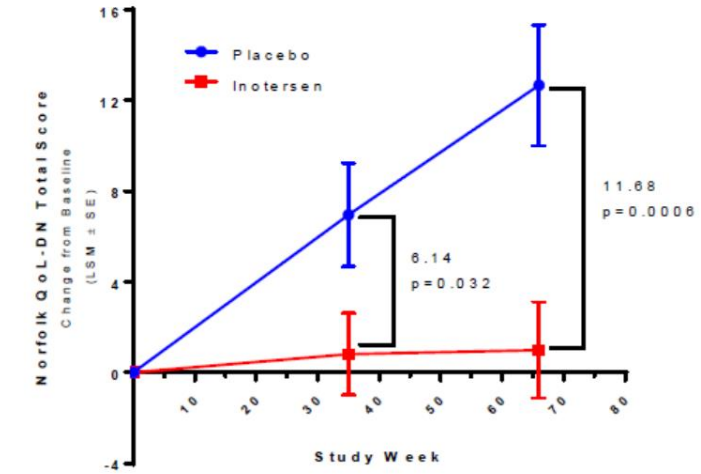
The following figure, reproduced from the application, presents the results of the analysis of the mNIS+7.

Figure 2: Study CS2 – mNIS+7 Change from Baseline (FAS Population)



The results of the analysis of the Norfolk-QoL-DN were also highly statistically significant in favor of inotersen. At Week 66, Norfolk-QoL-DN scores worsened (increased from baseline) by least squares (LS) mean of 1.0 points in the inotersen group, whereas the LS mean score increased by a mean of 12.7 points in the placebo group [LS mean difference: -11.7 points ($p<0.001$)]. The following figure, reproduced from the application, presents the results of the analysis of the Norfolk QoL-DN.

Figure 3: Study CS2 – Norfolk QoL-DN Change from Baseline at Week 66 (FAS Population)



Source: Module 5.3.5.1, CS2 CSR, Table 2.02
Abbreviations: SE=standard error

Dr. Massie's review comments on a number of sensitivity analyses that are all consistent with the results of the prespecified co-primary endpoint analyses.

The trial also evaluated 5 polyneuropathy-focused secondary endpoints, including the Norfolk QoL-DN Symptoms Domain Score Stage 1, the Norfolk QoL-DN Physical Functioning/Large Fiber Domain Score Stage 2, body mass index (BMI), the NIS Composite Score, and the Modified +7 Composite Score. With the exception of BMI which can be considered a measure of nutritional status in hATTR, the additional measures are subcomponents of the co-primary endpoints described previously. The following table, modified from Dr. Massie's review, presents the results of these secondary endpoint analyses. Note again that increased scores constitute disease worsening.

Table 3: Study CS2 – Results of Additional Secondary Efficacy Endpoint Analyses

Endpoint	Change from Baseline at Month 18 LS Mean (SEM)		Inotersen - Placebo Treatment Difference LS Mean (95% CI)	*p*-value
	Inotersen	Placebo		
Norfolk QoL-DN Symptoms Domain Score Stage 1	-1.4 (0.6)	1.1 (0.8)	-2.5 (-4.5, -0.6)	0.012
Norfolk QoL-DN Physical Functioning/Large Fiber Domain Score Stage 2	0.8 (2.0)	9 (2.5)	-8.3 (-14.7, -1.8)	0.013
BMI	-0.3 (0. 2)	-0.8 (0.2)	0.5 (0.0, 1.0)	0.051
NIS Composite Score	5.4 (1.4)	18.7 (1.8)	-13.3 (-17.7, -8.9)	<0.001
Modified +7 Composite Score	0.5 (1.2)	7.0 (1.5)	-6.5 (-10.3, -2.7)	<0.001

The statistical analysis plan (SAP) did not contain a prespecified plan to control for Type I error in the analysis of these secondary endpoints, so the results displayed in Table 2 are descriptive only. However, all of these endpoints were highly nominally positive with the exception of BMI (nominal p-value of 0.051). Taken together, these results further support the effectiveness of inotersen.

Dr. Massie also concludes that the efficacy of inotersen was consistent across subgroups defined by age, gender, race, and region.

Open-Label Extension Data

Drs. Breder and Massie discus the findings from Study CS3; an uncontrolled open-label trial that enrolled patients who had completed Study CS2 (N=114 at the February 28, 2017, interim analysis; ongoing). The results of the analyses of the various efficacy endpoints from Study CS3 are presented in their review. These data are challenging to interpret because of the lack of a concurrent control group and the potential for observer-bias in some of the outcome measures. However, the stability of the various clinical efficacy measures over the course of this trial is consistent with the clinical benefit observed in Study CS2.

Exploratory Cardiac Endpoint Analyses

(b) (4)

Dr. Preston Dunnmon from the Division of Cardiovascular and Renal Products (DCRP) conducted a consultative review for this application.

All patients who were enrolled in Study CS2 underwent transthoracic echocardiography at baseline and at Week 65 (or early withdrawal). Patients could consent to participate in a substudy (the ECHO substudy) where an additional echocardiogram would be obtained at Week 41 or 47 if they had a left ventricular (LV) wall thickness of 13 mm or greater at Baseline. The protocol further defined a cardiomyopathy (CM)-ECHO subgroup that included all of the patients in the ECHO subgroup, as well as any patient who had a diagnosis of TTR-cardiomyopathy at baseline (by history only) but was not in the ECHO subgroup. The following table, based on the data in Dr. Dunnmon's consultation, indicates the enrollment in the ECHO and CM-ECHO subgroups.

Table 4: Cardiac Analysis Populations (Randomized Patients)

	Placebo (N=60) N (%)	Inotersen 300 mg (N=113) N (%)	Total (N=173) N (%)
ECHO Subgroup	22 (36.7)	44 (38.9)	66 (38.2)
CM-ECHO Subgroup	33 (55.0)	75 (66.4)	108 (62.4)

Dr. Dunnmon notes that patients in the inotersen CM-ECHO subgroup had a longer time since onset of cardiomyopathy symptoms (45 versus 34 months) and somewhat higher (worse) baseline N-terminal pro b-type natriuretic peptide (NT-proBNP) levels.

The application presents the results of the analyses of Global Longitudinal Strain (GLS); a sensitive echocardiographic assessment of systolic function. Results of the exploratory analyses of additional echocardiographic parameters and NT-proBNP levels are also provided in the application. None of the analyses of the cardiac endpoints in Study CS2 were controlled for Type I error.

Dr. Dunnmon reports the applicant's conclusions that there were no nominally significant differences between treatment arms in the change from baseline to Week 65 in GLS in either the ECHO (p=0.3) or CM-ECHO subgroups (p=0.8). Both groups had minimal GLS worsening from baseline. Nominally significant differences in the change from baseline in interventricular septum thickness, posterior wall thickness, and LV mass favoring inotersen in the ECHO subgroup are described by the applicant as shown in the following table.

Table 5: Exploratory Analyses of Cardiac Wall Thickness (Study CS2; ECHO subgroup)

Exploratory endpoint	Placebo	Inotersen	Difference in LSM (Inotersen – Placebo) Nominal p-value
	Change from Baseline to Week 65 N LSM (SE)	Change from Baseline to Week 65 N LSM (SE)	
Interventricular septum thickness (cm)	16 0.09 (0.07)	35 -0.10 (0.05)	-0.19 0.02
Posterior wall thickness (cm)	16 0.06 (0.07)	35 -0.10 (0.05)	-0.16 0.04
LV Mass (g)	16 11.72 (12.65)	35 -18.64 (8.77)	-30.36 0.03

The applicant also reports nominally significant differences in the change from Baseline in NT-proBNP levels between treatment arms favoring inotersen at Weeks 13 and 35, but not 65, in the overall trial population. Differences in the change from baseline in NT-proBNP levels between treatment arms of

a similar magnitude were also observed in the CM-ECHO group, although these results failed to reach nominal significance.

Dr. Dunnmon concludes that Study CS2 is unable to establish the effectiveness of inotersen for the cardiac manifestations of TTR amyloidosis. He comments that the imaging and serum biomarkers that were evaluated do not directly assess a clinically meaningful benefit to patients and are not established to predict any such benefit (b) (4) .

Efficacy Conclusions

The persuasiveness of the efficacy results from Study CS2 supports the approval of inotersen for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. The study results have a number of characteristics, cited by FDA's 1998 Guidance "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*," that can provide evidence of effectiveness from a single study. Inotersen's treatment effect was highly statistically significant on the study's primary neuropathy efficacy endpoint (mNIS+7) and on an endpoint the evaluated the clinical impact of neuropathy (Norfolk QoL-DN). The results were robust to any reasonable sensitivity analysis. The study was large (given the size of the patient population) and multicenter; no single study site provided an unusually large fraction of the patients, and no single investigative site was disproportionately responsible for the observed treatment effect. The primary finding was supported by multiple polyneuropathy-focused secondary endpoints. Although the analyses of these secondary endpoints were not controlled for Type I error, the consistency of the findings is highly supportive of the results of the primary efficacy analysis. Results were generalizable across important subsets based on demographic and baseline disease characteristics. Finally, and importantly, the pharmacodynamic data, demonstrating a remarkable reduction in serum TTR, are consistent with the clinical efficacy data.

(b) (4) . PK/PD modeling along with an analysis of the CS3 data where loading doses were not used for patients initially treated with placebo in Study CS2 suggest that the absence of these doses would have a minimal impact on effectiveness. Additionally, there is some indication that the incidence of hypotension during the first week of treatment may be reduced in the absence of loading doses.

The open-label extension data from Study CS3 are consistent with the efficacy results of Study CS2 and provide some additional support of effectiveness.

Inotersen will be indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

8. Safety

Dr. Evelyn Mentari conducted the safety review of this application. Dr. Sally Jo Yasuda, the safety team lead, has also written a comprehensive supervisory review. Dr. Wiley Chambers from the Office

of New Drugs (OND) conducted a consultative safety review. Dr. Breder, the clinical efficacy reviewer, reviewed the electrocardiographic (ECG) findings from Study CS2.

The following table, copied from Dr. Mentari's review, summarizes the extent of exposure to inotersen in the applicant's development program.

Table 6: Inotersen Safety Population: Duration of Exposure

Dosage	Number of patients exposed to the study drug				
	≥ 1 dose	≥ 6 months	≥ 12 months	≥ 24 months	≥ 36 months
Any dose	N= 203	N= 125	N= 109	N= 58	N= 18
Inotersen 300 mg weekly	N= 160	N= 125	N= 109	N= 58	N= 18

Approximately 52% of inotersen-treated patients experienced dosing interruptions, compared to 38% of placebo-treated patients. Most cases of dosing interruption were related to platelet-related concerns (e.g., low platelet counts or missing platelet counts). I agree with Drs. Mentari and Yasuda that the current safety database is adequate in the context of a rare disease such as hATTR amyloidosis.

Dr. Mentari comments that the applicant's original submission excluded certain laboratory values that were categorized as "unconfirmed" in its analyses of nadir platelet counts, renal parameter abnormalities, and hepatobiliary abnormalities. However, Dr. Mentari concluded that most of the excluded laboratory measurements were not consistent with laboratory errors and should not be excluded. In response to an Agency request, revised tables and analyses were provided that included all measured laboratory values.

Dr. Mentari finds that the applicant's process for coding adverse event (AE) terms was generally appropriate. However, Dr. Mentari notes that verbatim terms were frequently coded to multiple different equivalent preferred terms (PTs), which resulted in the splitting of AEs across several PT categories [e.g., platelet-related AEs (including PTs of thrombocytopenia and platelet count decreased) occurred in 24% of patients, compared to the applicant's table listing of 13%, which included only the PT of thrombocytopenia].

The following are important safety findings that were identified by Drs. Mentari and Yasuda.

Deaths

In Study CS2, 5/112 (4.4%) of inotersen-treated patients died, compared to 0/60 (0%) of placebo-treated patients. Dr. Mentari notes that one death, caused by severe thrombocytopenia and intracranial hemorrhage, appeared to be related to inotersen. Dr. Mentari concludes that the other 4 deaths in Study CS2 were related to disease progression. 11/161 (6.8%) of inotersen-treated patients died in Study CS2 and CS3, combined (i.e., 6 additional deaths in Study CS3). Dr. Mentari considers one death in Study CS3, caused by autoimmune hepatitis and primary biliary sclerosis, was possibly related to inotersen (discussed under a separate subheading below). The other 5 deaths in Study CS3 were related to disease progression.

Discontinuations

16/112 (14.3%) of inotersen-treated patients had at least one AE that led to permanent treatment discontinuation during Study CS2, compared to 2/60 (3.3%) of placebo-treated patients. The most common reasons for permanent discontinuation of inotersen included thrombocytopenia, glomerulonephritis, and injection site reactions.

Treatment-Emergent Adverse Events

Table 6, reproduced from Dr. Mentari's review, summarizes the most common treatment-emergent adverse events (TEAEs) that occurred in Study CS2.

Table 7: Adverse Reactions Reported in At Least 5% of Inotersen-Treated Patients and that Occurred At Least 5% More Frequently or At Least Two Times More Frequently than Placebo-Treated Patients (Study CS2)

	Inotersen (N=112) %	Placebo (N=60) %
Injection site reactions[a]	49	10
Nausea	31	12
Headache	26	12
Fatigue	25	20
Thrombocytopenia	24	2
Fever	20	8
Peripheral edema	19	10
Chills	18	3
Anemia	17	3
Vomiting	15	5
Myalgia	15	10
Decreased renal function	14	5
Arrhythmia[b]	13	5
Arthralgia	13	8
Pre-syncope or syncope	13	5
Decreased appetite	10	0
Paresthesia	10	3
Dyspnea	9	3
Elevated liver function test	9	3
Orthostasis	8	2
Influenza like illness	8	3
Contusion	7	2
Bacterial infection[c]	7	3
Eosinophilia	5	0
Dry mouth	5	2

[a] Includes bruising, erythema, hematoma, hemorrhage, induration, inflammation, mass, edema, pain, pruritus, rash, reaction, swelling, and urticaria.

[b] Includes arrhythmia, atrial fibrillation, atrial flutter, bradyarrhythmia, bradycardia, extrasystoles, sinus arrhythmia, sinus bradycardia, supraventricular extrasystoles, tachycardia, and ventricular extrasystoles.

[c] Includes bacteremia, cellulitis staphylococcal, clostridium difficile infection, conjunctivitis bacterial, cystitis Escherichia, *Helicobacter* gastritis, *Helciobacter* infection, Staphylococcal infection.

ECG Findings

Dr. Breder conducted a review of the ECG results from Study CS2. Dr. Breder concludes that inotersen may cause a prolongation of the QRS complex. Six of 112 (5.4%) inotersen-treated patients had a maximum QRS complex greater than 160 msec that represented a greater than 25% increase from baseline, compared to 1/60 (1.7%) of placebo-treated patients. When patients with baseline QRS

complexes greater than 160 msec at baseline were excluded from the analysis population, 5/100 (5%) of the inotersen-treated patients had a maximum QRS complex greater than 160 msec that represented a 50% increase from baseline, compared to no placebo-treated patients.

The mechanism for this finding is uncertain; however, there is a theoretical possibility that the removal of amyloid from the myocardium has the potential to induce conduction abnormalities. This finding should be described in the prescribing information (PI).

Adverse Events of Special Interest

The following AEs of special interest will be discussed below:

- Thrombocytopenia
- Glomerulonephritis and Renal Toxicity
- Inflammatory and Immune Effects
- Hepatic toxicity
- Ocular Toxicity
- Hypersensitivity

Thrombocytopenia

The following table, copied from Dr. Mentari's review, summarizes the frequency of platelet count reductions in Studies CS2 and CS3.

Table 8. Patients with Decreased Platelet Measurements (Central and Local Laboratory Values). Studies CS2 and CS3.

	CS2 (On-Study) (CS2 Safety Set)		CS3 (On-Study) (CS3 Safety Set)		All Inotersen-Treated (CS2 and CS3)
	Placebo (N=60)	Inotersen 300 mg (N=112)	Placebo-Inotersen (N=49)	Inotersen-Inotersen (N=85)	Inotersen 300 mg (N=161)
Value, n (%)					
≥30% decrease from Baseline	3 (5.0)	84 (75.0)	41 (83.7)	72 (84.7)	134 (83.2)
≥50% decrease from Baseline	1 (1.7)	22 (19.6)	21 (42.9)	39 (45.9)	68 (42.2)
<140 x 10^9/L	12 (20.0)	62 (55.4)	36 (73.5)	60 (70.6)	111 (68.9)
<100 x 10^9/L	1 (1.7)	28 (25.0)	20 (40.8)	28 (32.9)	58 (36.0)
<75 x 10^9/L	0	16 (14.3)	9 (18.4)	12 (14.1)	31 (19.2)
<50 x 10^9/L	0	3 (2.7)	1 (2.0)	4 (4.7)	8 (5.0)
<25 x 10^9/L	0	3 (2.7)	0	0	3 (1.9)

Platelet measurement normal range: 140 – 400 x 10^9/L

As the table indicates, inotersen treatment resulted in significant decreases in platelet counts in a substantial fraction of patients. Dr. Mentari emphasizes that platelet counts less than 75 x 10^9/L (the level below which primary hemostasis is generally considered to be impaired) occurred in 16/112 (14.3%) of inotersen-treated patients compared to 0/60 (0%) of placebo-treated patients. Of concern, 3 inotersen-treated patients (2.7%) had severe thrombocytopenia (less than 25 x 10^9/L), which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. Dr. Mentari's review provides a detailed discussion of these cases, one of which resulted in a fatal intracranial hemorrhage associated with a platelet count of less than 10 x 10^9/L. Prior to this

death, platelet counts were obtained every 2-6 weeks in Study CS2. Subsequently, the protocol was amended to obtain weekly platelet counts.

Drs. Mentari and Yasuda note that the thrombocytopenia caused by inotersen treatment can occur gradually or precipitously. All 3 cases of severe thrombocytopenia in Study CS2 involved rapid and unpredictable declines in platelet counts (i.e., normal platelet counts were reported prior to the nadir values). All 3 cases occurred within 3 months of treatment initiation and were found to have antiplatelet IgG antibodies. Two of the cases had uninterpretable platelet measurements at some point caused by platelet clumping, a phenomenon that Dr. Mentari notes may be the result of an interaction between the antiplatelet antibodies and the ethylenediaminetetra-acetic acid (EDTA) present in the blood collection tube. In Studies CS2 and CS3, platelet counts in 11 patients declined from at least 100 x 10^9/L to less than 75 X 10^9/L within 2 weeks (including a patient who had a reduction from 100 x 10^9/L to 40 x 10^9/L in 1 week).

In Studies CS2 and CS3, 27 patients had their dosing paused for platelet counts less than 75 x 10^9/L until their platelet counts recovered to at least 100 X 10^9/L. After the first dosing pause, 18 patients resumed full dosing, but 6 of those patients were not able to maintain full dosing (receiving fewer than 10 full doses) and 12 patients resumed dosing at varying reduced dosing regimens (usually 150-160 mg/week). (b) (4)

Dr. Mentari concludes that the etiology of the inotersen-induced thrombocytopenia is not well established and suggests that it may be multifactorial with an immune-mediated component. Dr. Mentari notes than in CS2, all 9 inotersen-treated patients who developed treatment-emergent positive antiplatelet antibodies developed treatment-emergent thrombocytopenia. Inotersen-treated patients without positive antiplatelet antibody tests or with baseline positive antiplatelet antibody tests had nadir platelet counts ranging from moderate to normal levels.

Dr. Mentari finds that patients with baseline platelet counts of less than 200 x 10^9/L had lower nadir platelet counts compared to patients with baseline platelet counts of at least 200 x 10^9/L; these patients were also 6-7 times more likely to have nadir platelet counts less than 75 x 10^9/L. Dr. Mentari did not find any relationship between age, sex, or race and the magnitude of platelet count reductions.

Dr. Mentari recommends the following guidelines for platelet monitoring and related dosing adjustments in response to altered platelet counts for the inotersen PI.

Table 9: Agency-Recommended Thrombocytopenia Monitoring Guidelines for Inotersen

Platelet count ($x10^9$/L)	Monitoring Frequency	Dosing
At least 100	Weekly	Continue to dose weekly.
At least 75 to less than 100	Weekly	Discontinue treatment. Do not restart unless platelet value is greater than 100.
At least 50 to less than 75	Twice weekly until 3 successive values above 75 then weekly monitoring.	Discontinue treatment. Do not restart inotersen in patients with thrombocytopenia, unless there have been 3 successive values above 100 and the benefit of TEGSEDI outweighs the risk of thrombocytopenia and potential bleeding.
At least 25 to less than 50	Twice weekly until 3 successive values above 75 then weekly monitoring. Consider more frequent monitoring if additional risk factors for bleeding are present.[#]	Discontinue treatment. Do not restart inostersen in patients with thrombocytopenia, unless there have been 3 successive values above 100 and the benefit of inotersen outweighs the risk of thrombocytopenia and potential bleeding. Corticosteroids recommended. Consider discontinuation of any antiplatelet angents or anticoagulants.
Less than 25[*†]	Daily until 2 successive values above 25. Then monitor twice weekly until 3 successive values above 75. Then weekly monitoring until stable.	Stop inotersen. Corticosteroids recommended. Consider discontinuation of any antiplatelet angents or anticoagulants.

*It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline *[see Warnings and Precautions (5.1)]*.

[#] Additional risk factors for bleeding include age >60 years, receiving anticoagulant or antiplatelet medicinal products, or prior history of major bleeding events.

[†] Patients who discontinue therapy with TEGSEDI due to platelet counts below 25 $x10^9$/L should not reinitiate therapy.

These recommendations are necessary for the safe use of inotersen. The recommendation for a minimum frequency of weekly monitoring of platelet counts is supported by the available data. Rapid decreases in platelet counts were observed in the development program (e.g., one patient that had a reduction from 100 x 10^9/L to 40 x 10^9/L in 1 week). The fact that serious platelet-related adverse reactions were not observed in Study CS2 after weekly platelet monitoring was instituted is not reassuring as the trial was fully enrolled and patients were beyond the period of greatest risk of precipitous platelet declines in the first few months of treatment. Additionally, there are likely to be at least some unforeseen laboratory delays and imperfect patient adherence to the prescribed monitoring in clinical practice that further support the need for rigorous monitoring.

The risk of thrombocytopenia and the associated clinical complications will be addressed in the Risk Evaluation and Mitigation Strategy (REMS) as well as a boxed warning and in the WARNINGS AND PRECAUTIONS sections of the PI.

Glomerulonephritis and Renal Toxicity

Dr. Mentari notes that ASOs have been shown to accumulate in renal proximal tubule cells in nonclinical studies. Glomerulonephritis, a pro-inflammatory condition, has been observed in clinical and nonclinical studies with ASOs.

In Study CS2, 23/112 (20.5%) of inotersen-treated patients experienced a TEAE related to renal toxicity compared to 6/60 (10%) of placebo-treated patients. These events included decreases in glomerular filtration rate (GFR), glomerulonephritis, proteinuria, and renal failure, and were considered serious in 7/112 (6.2%) of inotersen-treated patients compared to 1/60 (1.7%) of placebo-treated patients.

Three of the 122 (6.2%) inotersen-treated patients had biopsy-confirmed glomerulonephritis, compared to 0/60 (0%) of placebo-treated patients. In all 3 cases the glomerulonephritis was accompanied by nephrotic syndrome with proteinuria greater than 3.5g/24h that continued to worsen after the cessation of inotersen treatment. Two of the 3 cases improved after treatment with prednisolone/cyclophosphamide or corticosteroids, respectively. The other case did not receive immunosuppressive therapy and remained dialysis-dependent.

Dr. Mentari also describes a case of immune-mediated renal toxicity in an inotersen-treated patient in Study CS2 with systemic anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis and renal involvement (discussed under the Inflammatory and Immune Effects heading below).

Drs. Mentari and Yasuda recommend that the PI for inotersen require that a urinalysis, quantitative urine protein, and serum creatine are obtained before the initiation of treatment and then every 2 weeks thereafter. This frequency of monitoring is necessary given the importance of early intervention in suspected cases of glomerulonephritis. Drs. Mentari and Yasuda also recommend that treatment with inotersen is permanently discontinued if the urine protein to creatinine ratio (UPCR) is greater than 1000 mg/g.

The risk of glomerulonephritis will be addressed in the REMS as well as a boxed warning and in the WARNINGS AND PRECAUTIONS sections of the PI, the latter of which will also include a broader discussion of renal toxicity.

Inflammatory and Immune Effects

Dr. Mentari notes that inflammatory and immune changes are known effects of ASOs. Thrombocytopenia, glomerulonephritis, and autoimmune hepatitis/primary biliary cirrhosis represent AEs that are consistent with an inflammatory or immune-mediated etiology and are discussed in the relevant subheadings of this memo. Cases of neurologic toxicity and vasculitis that appear to be inflammatory or immune-mediated in nature are discussed below.

Carotid Dissection and Stroke

Dr. Mentari discusses a case of a 53-year old male patient in Study CS2 who experienced symptoms that appeared to be consistent with a cytokine release syndrome following the first dose of inotersen (e.g., nausea, vomiting, muscle weakness, muscle spasms, and fecal incontinence). These symptoms persisted to the following day where the patient also had difficulty eating, a headache, and was "screaming gibberish." His condition deteriorated and on Day 10 a computed tomography (CT) scan and CT angiogram suggested an embolic stroke and carotid artery dissection that were estimated to have occurred shortly after the inotersen dose was administered. There was no evidence of atrial

fibrillation and the patient had no history of atrial fibrillation at baseline. The patient also had an elevated C-reactive protein on Day 3 that remained elevated on Day 13; cytokine levels were not assessed.

Drs. Mentari and Yasuda provide a detailed discussion of this case in their reviews and conclude that the patient's presentation was likely caused by inotersen-induced cytokine release syndrome. They stress the unpredictability of this risk and the importance of patient awareness and early intervention.

Myelopathy

Dr. Mentari discusses the case of a 52-year old inotersen-treated female patient who experienced gait disturbance on Day 75 with walking difficulty and myelopathy on Day 226. Treatment was continued at that point and she experienced paraparesis with subsequent worsening approximately 1 month later. She was hospitalized on Day 270 for worsening ataxia and pyramidal signs with a left vestibular neuritis. Examination of the patient's cerebrospinal fluid (CSF) and magnetic resonance imagining (MRI) during that hospitalization did not reveal any clear etiology for her presentation. Inotersen was held between Weeks 40-42. Importantly, the patient's paraparesis worsened after re-challenge with inotersen at Week 43.

Drs. Mentari and Yasuda conclude that this case was likely related to inotersen and was potentially consistent with vasculitis; a known class effect of ASOs.

Encephalitis

Dr. Mentari discusses a case of a 46-year old male inotersen-treated patient in Study CS2. This patient was dosed sporadically during the first 5 months of treatment because of the presence of proteinuria. Approximately 1 month after restarting treatment the patient developed intermittent right-sided lumbar pain that increased over several days and was associated with a 9 kg weight loss and asthenia. Dosing was held beginning on Day 234 because of severe vomiting and encephalitis. On Day 266 the patient continued to experience lumbar pain, headache, and the sudden onset of impaired speech (word-finding difficulty). CT imaging was normal. CSF analyses revealed elevated protein levels and a lymphocyte-predominant pleocytosis. The encephalitis resolved on Day 284 following treatment with antibiotics and intravenous dexamethasone. Inotersen treatment was restarted on Day 333 without a recurrence.

Drs. Mentari and Yasuda conclude that this case is consistent with CNS inflammation that is possibly related to inotersen given its known pro-inflammatory effects.

ANCA-Positive Vasculitis

Dr. Mentari discusses a case of a 58-year old male patient who received inotersen in both Studies CS2 and CS3. He began dosing in Study CS3 approximately 3 years after his last dose in Study CS2. After his first dose in Study CS3, he went on a 2-week vacation to Cuba. He reported "arthritic" symptoms in his hands, feet, knees, and shoulders during his trip, followed by erythematous cutaneous lesions in his lower limbs. The patient was subsequently diagnosed with PR3-ANCA vasculitis and was treated with prednisolone, cyclophosphamide, and azathioprine.

Drs. Mentari and Yasuda conclude that in the absence of other systemic disease or exposures associated with ANCA-positive vasculitis, that this case is likely related to inotersen given its known pro-inflammatory effects.

Hepatic Toxicity

Dr. Mentari notes that the liver is a known site of ASO accumulation and therefore inotersen has the potential to be hepatotoxic.

In Study CS2, 14/112 (12.5%) of inotersen-treated patients reported TEAEs related to abnormal liver function, compared to 4/60 (7%) of placebo-treated patients. As Dr. Yasuda notes, these events were primarily elevated liver enzyme values [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase AP)] but also included events of ascites, hypoalbuminemia, increased international normalized ratio (INR), and prolonged prothrombin time.

The following applicant table, copied from Dr. Mentari's review, summarizes the hepatobiliary laboratory abnormalities that were observed in Studies CS2 and CS3.

Table 10. Patients with Hepatobiliary Laboratory Abnormalities: Studies CS2 and CS3

	CS2 On-Study (CS2 Safety Set)		CS3 On-Study (CS3 Safety Set)		Longitudinal (Longitudinal Safety Set)	Inotersen Integrated Set
Category, n (%)	Placebo (N=60)	Inotersen 300 mg (N=112)	Placebo-Inotersen (N=49)	Inotersen-Inotersen (N=85)	Inotersen 300 mg (N=112)	Inotersen 300 mg (N=161)
ALT and/or AST at least 3x ULN and Total Bilirubin at least 2x ULN	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.6%)
ALT at least 3x ULN	2 (3.3%)	9 (8.0%)	1 (2.0%)	2 (2.4%)	11 (9.8%)	12 (7.5%)
ALT at least 5x ULN	1 (1.7%)	4 (3.6%)	1 (2.0%)	1 (1.2%)	5 (4.5%)	6 (3.7%)
ALT at least 8x ULN	0 (0.0%)	3 (2.7%)	1 (2.0%)	0 (0.0%)	3 (2.7%)	4 (2.5%)
ALT at least 10x ULN	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.6%)
ALT at least 20x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AST at least 3x ULN	1 (1.7%)	5 (4.5%)	1 (2.0%)	2 (2.4%)	6 (5.4%)	7 (4.3%)
AST at least 5x ULN	1 (1.7%)	2 (1.8%)	0 (0.0%)	1 (1.2%)	3 (2.7%)	3 (1.9%)
AST at least 8x ULN	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.2%)
AST at least 10x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AST at least 20x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Bilirubin at least 1.5x ULN	2 (3.3%)	7 (6.3%)	4 (8.2%)	5 (5.9%)	9 (8.0%)	13 (8.1%)
Total Bilirubin at least 2x ULN	1 (1.7%)	3 (2.7%)	2 (4.1%)	0 (0.0%)	3 (2.7%)	5 (3.1%)

As the table indicates, 9/112 (8.0%) of inotersen-treated patients in Study CS2 had ALT levels at 3 times the upper limit of normal (ULN), compared to 2/60 (3.3%) of placebo-treated patients; 3/112 (2.7%) of inotersen-treated patients had ALT levels at least 8 times the ULN, compared to 0/60 (0%) of placebo-treated patients. No Hy's Law cases (elevated transaminases greater than 3 times the ULN, with bilirubin greater than 2 times ULN) were identified.

Dr. Mentari also discusses a case of a 65-year old male inotersen-treated patient who died of autoimmune hepatitis and primary biliary cirrhosis (PBC). The patient's symptoms (vomiting and ascites) began approximately 2.5 years after initiating inotersen treatment, with his death occurring approximately 3 months after the onset of symptoms. Dr. Mentari comments that PBC is generally the result of a genetic susceptibility impacted by a triggering event that initiates an autoimmune attack on the bile duct cells. Dr. Mentari reiterates that inflammatory and immune changes are a known class effect of ASOs and concludes that this case is possible related to inotersen treatment. Dr. Mentari additionally discusses a case of a 64-year old male patient who received placebo in Study CS2

and inotersen in Study CS3. This patient had normal liver function tests prior to Study CS3 and was subsequently hospitalized with cholestatic jaundice on Study Day 464. This case had no clear etiology, although Dr. Mentari notes that the patient had hilar stricture which can be caused by an autoimmune process.

I agree with Drs. Mentari and Yasuda that the hepatobiliary effects of inotersen over a longer duration of therapy in more patients are unknown and need to be assessed. I also agree that these risks should be described in the WARNINGS AND PRECAUCTIONS section of the PI and that AST, ALT, and total bilirubin levels should be obtained at baseline and monitored every 4 months during inotersen treatment.

Ocular Toxicity

Wild-type TTR transports vitamin A in association with RBP. Because inotersen reduces both wild-type and mutant TTR, patients in the clinical development program were instructed to take the recommended daily allowance of vitamin A. The applicant also evaluated the ocular safety of inotersen in the development program. Dr. Wiley Chambers, the ophthalmology consultant, conducted a review of the ocular safety data. Dr. Chambers found no evidence of ocular vitamin A deficiency with inotersen and agreed that the applicant's suggestion to supplement patients with vitamin A in clinical practice is appropriate. The product label will recommend that patients be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

Hypersensitivity

Dr. Mentari notes that in Studies CS2 and CS3, 7/161 (4%) of inotersen-treated patients stopped treatment because of a hypersensitivity reaction. These reactions were associated with antibodies to inotersen and generally occurred within 2 hours of dosing. Four additional patients with antibodies to inotersen received reduced doses because of hypersensivity-related AEs.

I agree with the recommendation from Drs. Mentari and Yasuda to include a history of hypersensivity to inotersen as a contraindication to treatment and to describe the cases of hypersensitivity with anti-inotersen antibody formation in the WARNINGS AND PRECAUTIONS section of the PI.

Safety Conclusions

Inotersen causes serious and potentially fatal adverse reactions. However, in the setting of the clearly established effectiveness of inotersen for the treatment of hATTR-PN, a rare and serious disease with only one FDA-approved therapy, the safety profile of inotersen does not preclude approval. It is critical, though, that every effort be made to ensure that patients and prescribers are well informed about the risks of treatment, that appropriate clinical and laboratory monitoring is reliably performed, and that additional information regarding the known serious risks of treatment is accrued in the postmarketing setting, considering the small size of this rare disease development program.

A REMS with elements to ensure safe use (ETASU) is required to educate patients and providers about the risks of thrombocytopenia and glomerulonephritis and to ensure that appropriate clinical monitoring is occurring. Additionally, the WARNINGS AND PRECAUTIONS section of the PI will need to provide detailed descriptions and monitoring recommendations related to thrombocytopenia, glomerulonephritis and renal toxicity, stroke and artery dissection, inflammatory and immune effects, hepatoxicity, hypersensitivity, the potential for an antiplatelet antibody/EDTA interaction, and (b) (4) Further, a REMS registry must be established to further characterize the risks of

thrombocytopenia, glomerulonephritis, and neurologic toxicity (e.g., stroke, artery dissection, and vasculitis). Finally, expedited post-approval safety reporting will be necessary for the safety concerns described in the WARNINGS AND PRECAUTIONS section of the PI.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the clinical trial design is acceptable, and the efficacy findings were clear, and the safety profile, despite the considerable serious toxicity, was acceptable for the lethal disease being treated. Labeling will make prescribers fully aware of the risks, allowing them to inform patients and decide whether to use the drug.

10. Pediatrics

Pediatric Research Equity Act (PREA) requirements were not triggered for this orphan indication.

11. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP) issues were identified in Dr. Breder's review.

Dr. Breder concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

The Office of Scientific Investigations (OSI) reviewer for this application was Dr. Roy Blay. Three clinical sites were inspected during the review of this application (Drs. Coelho [Portugal], Cruz [Brazil], and Gertz [Rochester, MN]). Dr. Blay concludes that the data generated by these sites appear acceptable. The final classification of the inspections of Drs. Coelho and Cruz was No Action Indicated (NAI). The final classification of the inspection of Dr. Gertz was Voluntary Action Indicated (VAI).

Dr. Blay also notes that there were concerns raised (b) (4) Therefore, certified copies of the test booklets from all study sites (other than those inspected) were requested. Dr. Blay calculated NIS scores from randomly selected booklets and compared with the applicant's listings. Based on that exercise, Dr. Blay concluded that the NIS scores at baseline and at Week 66 of his sample were consistent with the data listings for the 12 patients that were evaluated across 8 sites (1/3 of all sites).

The Controlled Substance Staff (CSS) reviewer for this application was Dr. Joshua Hunt. Dr. Hunt concluded that based on the pharmacology of this drug product and the lack of clinical abuse-related adverse events that there is no abuse potential with inotersen.

12. Labeling

See the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

13. Postmarketing Commitments/Requirements

The Division of Risk Management (DRISK) reviewer for the application was Dr. Robert Pratt. A REMS with ETASU to address the risks of thrombocytopenia and glomerulonephritis is required for the safe use of inotersen. The goals of the REMS will be:

- Ensuring that prescribers are educated on the risk of serious bleeding due to severe thrombocytopenia and the risk of glomerulonephritis associated with inotersen.

- Ensuring that prescribers counsel patients on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis, enroll patients in the inotersen REMS Program, and adhere to the related monitoring and treatment recommendations in the PI.

- Ensuring that patients are educated to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis and understand the need to have platelet counts and renal function monitored.

Patients will be issued a Patient Guide and a Wallet Card that describe how to recognize and respond to the signs and symptoms of serious bleeding and glomerulonephritis and detail the required laboratory monitoring. Prescribers will complete a Patient Enrollment Form that documents patient's platelet levels and renal function (eGFR, urinalysis, and UPCR) prior to the first dose of inotersen. During treatment, prescribers will submit a Patient Status Form every 90 days that documents adherence to the required platelet and renal monitoring. The REMS also requires that patient's renal and platelet function are assessed for 8 weeks following the discontinuation of treatment.

The following will be <u>postmarketing requirements</u>:

- A prospective observational study in adult patients with polyneuropathy of hereditary transthyretin-mediated amyloidosis recruited from the REMS registry. The primary objectives are to characterize the risks of serious thrombocytopenia, glomerulonephritis, stroke and cervicocephalic arterial dissection, and CNS vasculitis with respect to time course of onset, preventative laboratory monitoring, and identification of risk factors. An adequate number of patients should be enrolled and followed throughout their participation in the REMS registry to allow for the characterization of serious thrombocytopenia, glomerulonephritis, stroke and cervicocephalic arterial dissection, and CNS vasculitis. The protocol should specify an appropriate comparator population(s) to which observed incidence rates will be compared.

Draft Protocol Submission:	03/2019
Final Protocol Submission:	12/2019
Study Completion:	12/2024
Final Report Submission:	05/2025

- A clinical study to characterize adverse events occurring within one day of inotersen administration to adult patients with polyneuropathy of hereditary transthyretin-mediated amyloidosis. Characterize the events in individual patients and overall with respect to time course of adverse event onset, vital sign changes, preventive measures, treatment required, risk factors, and subsequent adverse outcomes. An adequate number of patients should be enrolled and followed throughout their treatment with inotersen to allow for the characterization of adverse

events occurring within one day of inotersen administration (e.g., hypersensitivity, cytokine release syndrome).

Draft Protocol Submission:	03/2019
Final Protocol Submission:	12/2019
Study Completion:	12/2024
Final Report Submission:	05/2025

- Establish a worldwide Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Tegsedi (inotersen) during pregnancy. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.

Draft Protocol Submission:	12/2018
Final Protocol Submission:	10/2019
Study/Trial Completion:	11/2030
Final Report Submission:	11/2031

- A two-year carcinogenicity study of inotersen in rat.

Final Report Submission:	10/2018 (The study is complete and the report is available.)

14. Recommended Comments to the Applicant

The approval letter will instruct the applicant to conduct enhanced pharmacovigilance for the safety concerns described in the WARNINGS AND PRECAUTIONS section of the PI, including expedited reporting of these events and the provision of specified summary information in periodic reports.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER
10/05/2018

WILLIAM H Dunn
10/05/2018

ROBERT TEMPLE
10/05/2018