CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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<u>OTHER REVIEW(S)</u>

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Memo: Tegsedi (inotersen)
Version: 2018-01-24

Date:	October 4, 2018
Reviewer:	Michelle Iannacone, PhD, MPH Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Division Deputy Director:	Sukhminder Sandhu, PhD, MPH Division of Epidemiology I
Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Tegsedi (inotersen)
Application Type/Number:	NDA 211172 (IND 113968)
Applicant/sponsor:	Ionis Pharmaceuticals, Inc.
OSE RCM #:	2018-638

Reference ID: 4330475

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Tegsedi's (inotersen) proposed indication is for treatment of hereditary transthyretin-mediated (TTR) amyloidosis (hATTR) polyneuropathy in adults. Tegsedi (also known as ISIS 420915) is a 2′-O (2-methoxyethyl) - modified phosphorothioate antisense oligonucleotide (ASO) which targets messenger RNA of human TTR by binding in a complementary sequence specific manner, thereby inhibiting the production of both mutant and wild-type TTR protein.[a] The strategy of treating patients with hATTR with Tegsedi is to reduce the levels of mutated and wild-type TTR protein secreted by the liver, the primary source of TTR production and a primary organ for ASO distribution after systemic delivery. By decreasing the amount of liver-derived TTR protein circulating in the plasma, Tegsedi treatment likely results in a decrease in the formation of TTR amyloid fibril deposits and thus slowing or halting disease progression.

Tegsedi is administered as a subcutaneous injection by the patient, caregiver, or healthcare worker, as a single-dose, prefilled syringe (including a safety syringe device).[b] The recommended dosage is 284 milligrams. [redacted] (b) (4) doses should be administered once every week [redacted] (b) (4)

1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. There were no exposed pregnancies in the clinical trials and the animal studies showed there were no effect on organogenesis and no detectable Tegsedi in fetal tissue.
The following describes the proposed language in the Tegsedi Product Label.[b]

Pregnancy Risk

<u>Risk Summary</u>

[redacted] (b) (4) Tegsedi treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking Tegsedi. Vitamin A is essential for normal embryofetal development; however, excessive levels of Vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by Tegsedi and of vitamin A supplementation are unknown.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of

[a] New Drug Application (NDA) Clinical Safety Review. NDA 211172 Tegsedi (inotersen). Accessed September 7, 2018. DARRTS Reference ID: Pending.
[b] Tegsedi Product label. DARRTS Reference ID: Pending.

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major birth defects and miscarriage for the indicated population is unknown.

Animal Data

(b) (4)

[redacted]

Postmarket Requirement

The information discussed above in Section 1.2 is included in the Tegsedi product label. However, the data are limited and insufficient to determine a drug-associated risk of pregnancy, birth, and infant outcomes. Further evaluation in the post-marketing setting is necessary for appropriate education of patients and prescribers when considering the use of Tegsedi during pregnancy. Further, the product label includes the following language: "Instruct patients that if they are pregnant or plan to become pregnant while taking Tegsedi they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus."

A PMR will be necessary to evaluate the effects of Tegsedi during pregnancy. A worldwide Pregnancy Surveillance Program has been proposed to further evaluate safety risks associated with Tegsedi treatment in pregnant women with hATTR and their offspring.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

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☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☒ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☐ Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes and Covariates: ARIA is not sufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked to Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: Current ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Other parameters were not formally discussed given that the mother-infant linkage is not currently available in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

As of September 24, 2018, the proposed PMR language is:

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

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complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.

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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/

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10/04/2018

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Department of Health and Human Services
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Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	October 4, 2018
Reviewer:	Michelle R. Iannacone, PhD Division of Epidemiology I
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Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo
Drug Name:	Tegsedi (inotersen)
Application Type/Number:	NDA 211172 (IND 113968)
Applicant/sponsor:	Ionis Pharmaceuticals, Inc.
OSE RCM #:	2018-1903

Reference ID: 4332400

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type					
-Initial					
-Interim					
-Final	X	X	X	X	X
Source of safety concern					
-Peri-approval	X	X	X	X	X
-Post-approval					
Is ARIA sufficient to help characterize the safety concern?					
Safety Outcome:	Thrombo-Cytopenia	Glomerulo-nephritis	Stroke	Cervico-cephalic Arterial Dissection	CNS Vasculitis
-Yes					
-No	X	X	X	X	X
If "No", please identify the area(s) of concern.					
-Surveillance or Study Population	X	X	X	X	X
-Exposure					
-Outcome(s) of Interest	X	X		X	X
-Covariate(s) of Interest	X	X			
-Surveillance Design/Analytic Tools					

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A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Tegsedi's (inotersen) proposed indication is for treatment of hereditary transthyretin-mediated (TTR) amyloidosis (hATTR) polyneuropathy in adults.[a,b] Tegsedi (also known as ISIS 420915) is a 2′-O (2-methoxyethyl) (2′-MOE)-modified phosphorothioate antisense oligonucleotide (ASO) which targets messenger RNA (mRNA) of human TTR by binding in a complementary sequence specific manner, thereby inhibiting the production of both mutant and wild-type TTR protein.[b] The strategy of treating patients with hATTR with Tegsedi is to reduce the levels of mutated and wild-type TTR protein secreted by the liver, the primary source of TTR production and a primary organ for ASO distribution after systemic delivery. By decreasing the amount of liver-derived TTR protein circulating in the plasma, Tegsedi treatment likely results in a decrease in the formation of TTR amyloid fibril deposits and thus slowing or halting disease progression. This strategy is similar to orthotopic liver transplantation (OLT), with the exception that inotersen also reduces wild-type TTR in addition to mutated TTR.[b] Given that wild-type TTR can continue to deposit as amyloid following liver transplantation and contribute to disease progression, this distinction may represent a therapeutic advantage for inotersen treatment over OLT.

Hereditary ATTR is a rare and fatal disease caused by mutations in the gene that codes for TTR, a carrier protein for thyroxine and vitamin A. Single-point gene mutations destabilize the normal tetrameric structure of the TTR protein, causing its dissociation into free monomers. These monomers misfold and subsequently aggregate into insoluble, extracellular fibril deposits, causing cell degeneration and death. Accumulation of amyloid deposits in multiple organ systems, particularly the nervous system, gastrointestinal tract, kidney, and heart, causing a range of disease manifestations including progressive polyneuropathy, which includes sensorimotor neuropathy and autonomic neuropathy.

Tegsedi is administered as a subcutaneous injection by the patient, caregiver, or healthcare worker, as a single-dose, prefilled syringe (including a safety syringe device).[a] The recommended dosage is 284 milligrams. (b) (4) t doses should be administered once every week (b) (4)

Inflammatory and immune effects are characteristic of the class of antisense oligonucleotide drugs. In clinical studies of Tegsedi patients, serious inflammatory- and immune-related adverse reactions were observed, the most serious of which included immune thrombocytopenia and immune glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis.[b] Platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine

[a] Tegsedi Product Label. DARRTS Reference ID: 4328677.
[b] New Drug Application (NDA) Clinical Safety Review. NDA 211172 Tegsedi (inotersen). Accessed September 7, 2018. DARRTS Reference ID: Pending.

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ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin must be measured prior to treatment and continue to be monitored after treatment initiation, as directed.

Tegsedi will be available only through a restricted program under a mandatory Risk Evaluation and Mitigation Strategy (REMS), which includes a registry, due to safety concerns of thrombocytopenia and glomerulonephritis (see Section 1.2 below).

1.2. Describe the Safety Concern

The safety of Tegsedi was studied in a placebo-controlled trial (CS2) of adults, aged 27 to 78 years (mean age was 59 years), with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR).[b] There were 112 patients in the Tegsedi-treated group and 60 patients in the placebo-controlled group. Among the 112 patients treated with Tegsedi, 68.8% were male and 93.8% were Caucasian. Baseline disease characteristics were similar between both groups. The primary known safety issues identified with Tegsedi include thrombocytopenia, glomerulonephritis, and neurotoxicity (including stroke, cervicocephalic arterial dissection, and central nervous system (CNS) vasculitis).

1.2.1 Thrombocytopenia

A normal platelet count ranges from 140 to 400 x 10^9 /L. Thrombocytopenia is defined by platelet counts less than 140 x 10^9 /L. Tegsedi causes reductions in platelet counts that may result in sudden and unpredictable thrombocytopenia that can be serious or life-threatening. In study CS2, platelet counts less than 100 x 10^9/L occurred in 28 (25%) of Tegsedi patients compared to 1 (2%) of placebo patients. Platelet counts less than 75 x 10^9/L occurred in 16 (14%) of Tegsedi patients, compared to 0 placebo patients. Further, 3 (3%) Tegsedi patients had sudden, severe thrombocytopenia (less than 25 x 10^9/L), which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage; one patient experienced a fatal intracranial hemorrhage.

The Tegsedi product label will include a boxed warning for thrombocytopenia as follows:

- Tegsedi causes reductions in platelet count that may result in thrombocytopenia that can be serious or life-threatening. (5.1)
- Testing prior to and monitoring during treatment is required. (2.4, 5.2)

1.2.2 Glomerulonephritis

Glomerulonephritis, considered a result of the drug's proinflammatory effect, is known to occur with antisense oligonucleotide drugs. Tegsedi can cause glomerulonephritis that may result in dialysis-dependent renal failure. In study CS2, glomerulonephritis occurred in three patients (3%) treated with Tegsedi and no patients treated with placebo.[b]

Accumulation of antisense oligonucleotides in proximal tubule cells of the kidney, sometimes leading to increased tubular proteinuria, has been described in preclinical studies.[a],[b] Urine protein to creatinine ratio (UPCR) greater than five times the upper limit of normal occurred in 15% of Tegsedi patients, compared to 8% in placebo patients. Increases in serum creatinine greater than 0.5 mg/dL from baseline occurred in 11% of Tegsedi patients, compared to 2% in placebo patients.[a]

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The Tegsedi product label will include a boxed warning for glomerulonephritis as follows:

- Tegsedi can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. (Section 5.2)
- Testing prior to and monitoring during treatment is required. (Sections 2.4, 5.2)

Risk Management Strategies for thrombocytopenia and glomerulonephritis:

On account of the risks of serious bleeding due to severe thrombocytopenia and glomerulonephritis (see *Warnings and Precautions* (Sections 5.1, 5.2), Tegsedi will be available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Tegsedi REMS Program.

1.2.3 Neurotoxicity Outcomes

Tegsedi may cause stroke, cervicocephalic arterial dissection, and CNS vasculitis; though the mechanism of action is unknown. In study CS2, 1 of 161 (0.6%) Tegsedi patients experienced carotid arterial dissection and stroke. This event occurred within 2 days of the first Tegsedi dose, a time when the patient also had symptoms of cytokine release (e.g., nausea, vomiting, muscular pain and weakness) and a high sensitivity C-reactive protein level greater than 100 mg/L. There is no known way to prevent or reduce the risk of cervicocephalic arterial dissection or stroke after use of Tegsedi.

In addition to stroke and carotid arterial dissection, there was a single case of antineutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis.

The Tegsedi label will include the following text in the *Warnings and Precautions*:

- Stroke and Cervicocephalic Arterial Dissection: Educate patient on symptoms of stroke and central nervous system arterial dissection (b) (4) instruct them to seek help as soon as possible if symptoms (b) (4) occur (Section (b) (4))

1.2.4 Existing Treatments

The standard of care for this disease was orthotopic liver transplant, which does not cure the disease because the wild-type TTR can continue to accumulate at the site of prior lesions post-transplant. Onpattro (patisiran) was recently approved in August 2018 and is currently the only FDA approved treatment for polyneuropathy related to hereditary transthyretin-mediated amyloidosis in adults. Onpattro is a lipid complex injection, for intravenous use only. Onpattro was approved with no boxed warning, REMS, or postmarketing requirement for observational safety concerns, other than a pregnancy study.

Additional FDA approved antisense oligonucleotide drugs include fomivirsen, mipomersen, etenlirsen, and nusinersen. These products were approved without boxed warnings and only mipomersen was issued an observational PMR study to investigate hepatotoxicity, malignancy, and new diagnoses of autoimmune disorders.

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1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

The FDAAA purpose of the postmarket requirement is to assess the known serious risks of thrombocytopenia, glomerulonephritis, and neurotoxicity outcomes.

1.4. Statement of Purpose

The Division of Neurological Products (DNP), with concurrence from OSE, requires a postmarket observational study to assess the known serious risk for thrombocytopenia, glomerulonephritis, and neurotoxicity outcomes from Tegsedi. DNP requires detailed, prospective, descriptive narrative information from postmarketing settings (including laboratory data) to inform appropriate clinical strategies for evaluating the risk of thrombocytopenia, glomerulonephritis from Tegsedi to supplement existing labeling efforts (e.g., boxed warning).

The drug will be approved with a REMS registry that will obtain information about the long-term safety of Tegsedi, and to determine if the risk mitigation efforts are adequate. The registry will give access to all patients receiving the drug who may voluntarily participate in a post marketing study that evaluates the incidence of severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis. The purpose of this memo is to evaluate and weigh the capabilities of ARIA against the alternative observational PMR study comprised of the cohort of patients in the REMS registry for safety surveillance.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Hereditary transthyretin amyloidosis polyneuropathy affects an estimated 10,000 people worldwide. The size of the patient population in the United States is estimated to not exceed 6,400 patients.[c] Tegsedi is only available through the Tegsedi REMS program and will include a mandatory registry that will serve as the source population for the postmarket requirement.

ARIA is under consideration for the above mentioned, known serious outcomes with the goal to obtain more descriptive information to mitigate risk. The study design is not hypothesis driven, and therefore, there are no *a priori* levels of risk to consider. The Agency expects that the Sponsor will make efforts within reasonable means to maximize the inclusion of the patients on the REMS Registry in the PMR.

[c] Coelho T, Ericzon B, Falk R, et al. A Physician's Guide to Transthyretin Amyloidosis. Amyloidosis Foundation. 2008; 1-16.

Reference ID: 4332400

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Tegsedi (inotersen) is an antisense oligonucleotide inhibitor of human transthyretin (TTR) protein synthesis indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. The patient population will include adult patients from the indicated population.

2.2 Is ARIA sufficient to assess the intended population?

Hereditary transthyretin amyloidosis polyneuropathy is a rare disorder making it difficult to capture a sufficient sample of Tegsedi users in Sentinel. There may also be issues with sufficient market uptake given the boxed warning and ETASU REMS to address thrombocytopenia and glomerulonephritis. The recent approval of Onpattro may also affect the market uptake of Tegsedi.

As mentioned previously in Section 1.1, Tegsedi will be approved with a mandatory REMS Registry for the U.S. population. The Registry will assist in maximizing the number of patients available for information in the postmarket observational study. For this reason, the study population will be better captured in postmarket study nested in the REMS registry cohort, then in the ARIA system.

3 EXPOSURES

3.1 Treatment Exposure

The exposure of interest is incident use of Tegsedi.

The recommended dose of Tegsedi is 284 mg injected subcutaneously once weekly by the patient, caregiver, or healthcare workers, as a single-dose, prefilled syringe. (b) (4) doses should be administered once every week.

3.2 Comparator Exposure

The study population is Tegsedi exposed patients. The postmarketing requirements requests an appropriate comparator, to compare the rate of these adverse events in Tegsedi patients to an appropriate background rate. In addition to this comparison, the purpose of the PMR is to also obtain additional qualitative, descriptive data to obtain more detailed information on the safety risk to add to the product labeling to further mitigate the risk.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to capture patients with pharmacy benefits who receive at least one dispensing of Tegsedi, and potentially other drug exposures in a comparator population.

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4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest include thrombocytopenia, glomerulonephritis, and neurotoxicity outcomes (including stroke, cervicocephalic arterial dissection, and CNS vasculitis).

A literature review of algorithms or codes to identify thrombocytopenia resulted in studies that included populations that would not be generalizable to the Mini-Sentinel distributed database (MSDD).[d] Studies that have successfully identified thrombocytopenia, such as those conducted in the Vaccine Safety Datalink, have relied on medical record review and laboratory results.

APPENDIX 2 Positive Predictive Value of *International Classification of Diseases, Ninth Revision* (ICD-9) Diagnosis Codes and Platelets Counts in Predicting a Confirmed Cases of Immune Thrombocytopenic Purpura upon Chart Review

Platelet Counts	Diagnosis Code Group	ITP Case		PPV, %
		Yes	No	
Years 2000–2004[a]				
1 count <50K and	287.31 ITP	0	0	—
1 count <50K and	Other TP code[b]	50	70	41.7
2 counts <50K and	No code	2	15	11.8
Total		52	85	38.0
Years 2005–2008				
1 count <50K and	287.31 ITP	90	24	78.9
1 count <50K and	Other TP code[b]	63	113	35.8
2 counts <50K and	No code	1	20	4.8
Total		154	157	49.5

PPV, positive predictive value; TP, thrombocytopenic purpura; ITP, immune thrombocytopenic purpura.
[a] Immune thrombocytopenic purpura (287.31) was not routinely used until 2005.
[b] 287, 287.0, 287.1, 287.2, 287.3 287.30, 287.39, 287.4, 287.5, 287.8, 287.9.

Source: The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents, www.pediatrics.org/cgi/doi/10.1542/peds.2011-1111

In contrast, studies identifying stroke in health care claims data from ICD-9 diagnostic codes 434.x, 432.x or 434.x demonstrated PPVs greater than 80%.

Stroke outcomes identified with ICD-10 codes have not yet been evaluated as part of Sentinel's Healthy Outcome of Interest Validations and Literature Reviews. However, we expect that PPV will be similar to the ICD-9 codes.

The validity of glomerulonephritis, cervicocephalic arterial dissection, and CNS vasculitis outcomes has not been assessed in the Sentinel Health Outcome of Interest Validations and Literature Reviews. A search of the published literature revealed no validation studies.

[d] https://www.sentinelinitiative.org/sentinel/surveillance-tools/validations-lit-review

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4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA could identify stroke adequately. However, given that hATTR polyneuropathy is a rare disorder, the uptake of Tegsedi will be too low to evaluate. Therefore, it may be difficult to estimate accurately in Sentinel the incidence of stroke among Tegsedi users. ARIA is currently unable to reliably identify the additional outcomes discussed in Section 4.1.

5 COVARIATES

Covariates of Interest

Case narratives and laboratory-based information for patients that experience thrombocytopenia, glomerulonephritis, and neurologic toxicity are important for informing the safety profile of patients treated with Tegsedi. Several covariates, including history of kidney disease and laboratory abnormalities were deemed highly desirable by DNP to help clarify clinical factors and develop mitigation strategies. Prior to initiating Tegsedi, several biological tests are required, including: platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. After initiating Tegsedi, the following biological measures are required to monitor safety: platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. These measures should be obtained during treatment with Tegsedi and for 8 weeks following discontinuation of treatment. Collection of these data on factors that may help reduce the incidence of adverse events and increase safe use of Tegsedi could possibly be used to inform the product label.

5.1 Is ARIA sufficient to assess the covariates of interest?

No. Answers to the safety concerns requires laboratory results conducted on blood and urine samples. ARIA would only capture the occurrence of the laboratory and not the results, which are necessary to assess both baseline and post-exposure clinical status. In contrast, the REMS registry would have access to the medical records and laboratory results to assess any possible deterioration in baseline end organ function.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The study design would be a longitudinal, prospective study and patients will be followed throughout their participation in the REMS registry. The study will obtain descriptive data to better describe the safety issues.

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6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA is sufficient with respect to design / analytic tools available to assess the question of interest.

7 NEXT STEPS

In summary, although FDA has previously deemed ARIA sufficient to study stroke outcomes, this product's restricted distribution, boxed warnings, availability of alternative therapies with better safety profiles, and the mandatory REMS registry enrollment, render the REMS registry a far better setting in which to conduct safety surveillance. Furthermore, the remaining outcomes of interest (thrombocytopenia, glomerulonephritis, and neurotoxicity) require access to laboratory results or chart review to validate the diagnostic codes.

As a result of the Signal Assessment Meeting deliberations and documented in this ARIA memo, ARIA was deemed insufficient to study thrombocytopenia, glomerulonephritis, and neurotoxicity outcomes and the related epidemiological and clinical data among hATTR-PN patients using Tegsedi treatment. The next step is for OND to communicate to the Sponsor the expectations for the PMR. The proposed PMR language is as follows:

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.

Reference ID: 4330400

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/s/

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10/04/2018

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10/04/2018

Safety Team Leader Review

Date	October 4, 2018
From	Sally Usdin Yasuda
Subject	Safety Team Leader Review
NDA/BLA # **Supplement#**	NDA 211172
Applicant	Ionis Pharmaceuticals
Date of Submission	November 6, 2017
PDUFA Goal Date	July 6, 2018
Proprietary Name / Non-Proprietary Name	Tegsedi/Inotersen
Dosage form(s) / Strength(s)	Solution for subcutaneous injection, 284 mg inotersen (300 mg inotersen sodium salt)/1.5 ml
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with hereditary transthyretin amyloidosis (hATTR) (b) (4)
Recommendation on Regulatory Action	If efficacy is demonstrated and a risk mitigation evaluation strategy and labeling could reasonably address the risks such that the benefits of inotersen outweigh the risks, then I recommend approval.
Recommended Indication(s)/Population(s) (if applicable)	

1. Benefit-Risk Assessment

Reference ID: 4330680

Risk Summary and Assessment

Inotersen is proposed to be used for treatment of hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN). This review evaluates the safety of inotersen. If efficacy is demonstrated and the benefits of inotersen outweigh the risks in migraine, then I recommend that approval be accompanied a Risk Evaluation and Mitigation Strategies (REMS) program, medication guide, and labeling language that includes a boxed warning to mitigate the risks.

This document reviews the risk profile of inotersen. I summarize the findings of Dr. Evelyn Mentari and I agree with her recommendations regarding risk and strategies to reduce the risk. Please refer to Dr. Chris Breder's review for discussion of Analysis of Condition and Current Treatment Options and Benefit.

Risk:

Inotersen is associated with severe, potentially fatal adverse effects. Inotersen causes thrombocytopenia, glomerulonephritis, inflammatory and immune effects including serious neurologic adverse reaction effects on the liver, and hypersensitivity reactions. Based on the mechanism of action, it is expected to lead to a decrease in serum vitamin A levels.

- Platelet counts less than 100X 10^9/L occurred in 25% of inotersen patients, compared with 2% of placebo patients. Platelet counts less than 75 x 10^9/L (the level below which primary hemostasis is generally considered to be impaired) occurred in 14% of inotersen patients compared to 0 placebo patients. Three inotersen patients (3%) had sudden, severe thrombocytopenia (less than 25 X 109/L) which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. One patient experienced a fatal intracranial hemorrhage. Platelet monitoring, patient education regarding signs and symptoms of thrombocytopenia, and prompt medical assessment and treatment can mitigate this risk. However, the decrease in platelets can occur precipitously and unpredictably, and the risk remains even with intensive monitoring. Consider the risk of bleeding with concomitant use of antiplatelet, thrombolytic, or anticoagulant drugs.
- Inotersen can cause glomerulonephritis and renal toxicity that may result in dialysis-dependent renal failure. Glomerulonephritis occurred in 3 patients (3%) treated with inotersen and no patients treated with placebo. IN these glomerulonephritis cases, stopping inotersen alone was not sufficient to resolve manifestations of glomerulonephritis and immunosuppressive medication was required for clinical improvement. One patient did not receive immunosuppressive treatment and remained dialysis-dependent. Renal laboratory monitoring and cessation of inotersen according to recommended laboratory criteria can mitigate this risk but will not eliminate the risk of severe renal toxicity.
- Carotid arterial dissection occurred within 2 days of the first inotersen dose in 1 patient who had symptoms of cytokine release (e.g. nausea, vomiting, muscular pain, and weakness) and a high sensitivity C-reactive protein level greater than 100 mg/L at that time. There

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is no known way to prevent or reduce the risk of cervicocephalic arterial dissection or stroke after use of inotersen.

- Inflammatory and immune changes are an effect of antisense oligonucleotide drugs. In clinical studies, serious inflammatory and immune adverse reactions occurred in inotersen patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of anti-neutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis and a single case of autoimmune hepatitis with primary biliary cirrhosis in a patient with a family history of primary biliary cirrhosis. Neurologic serious adverse reactions consistent with inflammatory and immune effects occurred in inotersen patients, in addition to stroke and carotid arterial dissection. One patient developed paraparesis in the absence of radiologic evidence of spinal cord compression. Another patient developed progressive lumbar pain, weight loss, headache, vomiting, and impaired speech with no confirmed infection.
- The liver is a site of accumulation of antisense oligonucleotides. In clinical studies, 8 % of inotersen subjects had an increased alanine aminotransferase (ALT) at least 3 X the upper limit of normal ((ULN) compared to 3% of placebo subjects; 3% of inotersen subjects had an ALT at least 8X ULN compared to no placebo subjects. Periodic measurement of liver tests may mitigate risks to the liver with inotersen.
- Severn inotersen subjects stopped treatment because of hypersensitivity reactions associated with antibodies to inotersen. There is no known way to prevent or mitigate this risk.
- Based on the mechanism of action of inotersen, it is expected that inotersen treatment will lead to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A may mitigate this risk in patients taking inotersen.

Paragraph #5: Analysis and Recommendation with Respect to Safety:

If inotersen is approved, I recommend a boxed warning with recommendations for monitoring and administration to mitigate the risks of thrombocytopenia and glomerulonephritis. The Warnings and Precautions section of the label should have additional description of thrombocytopenia, glomerulonephritis and renal toxicity, stroke and cervicocephalic arterial dissection, inflammatory and immune effects, liver effects, hypersensitivity, uninterpretable platelet counts because of a reaction between antiplatelet antibodies and ethelenediaminetetra-acetic acid (EDTA), and [redacted] (b) (4). I recommend using the REMS patient registry as a basis for a post-marketing requirement to characterize further the risks of thrombocytopenia, glomerulonephritis, and neurologic toxicity (e.g. CNS arterial dissection, stroke, CNS vasculitis) in the post-marketing setting. I recommend postmarketing evaluation of hypersensitivity and cytokine release syndrome within 1 day of administration of inotersen. I also recommend postmarketing evaluation of outcomes of pregnancy in women exposed to inotersen. I recommend enhanced pharmacovigilance (i.e., expedited reporting, provision of specified summary information in periodic reports) for the safety issues described in the Warnings and Precautions section of the inotersen label. I recommend a medication guide to educate patients about these risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. Breder's review of clinical efficacy.	
Current Treatment Options	• Please refer to Dr. Breder's review of clinical efficacy.	
Benefit	• Please refer to Dr. Breder's review of clinical efficacy.	
Risk	• The safety database for inotersen includes all patients from the Phase 3 placebo-controlled study and the open-label extension study in patients with hATTR-PN. Drug exposure is adequate, but longer durations of exposure may occur in the postmarketing setting. The safety database did not include patients with Stage 3 (wheelchair bound) hATTR-PN. • The most common adverse reactions in the Phase 3 placebo-controlled study were: injection site reactions (40%); nausea (31%), headache (26%), fatigue (25%),; thrombocytopenia (24%), and fever (20%). • Platelet counts less than 100 X 10^9/L occurred in 25% of inotersen patients compared with 2% of placebo patients. Platelet counts less than 75 X 109/L occurred in 14% of TEGSEDI patients, compared to 0 placebo patients. Three TEGSEDI patients (3%) had sudden, severe thrombocytopenia (less than 25 x 109/L), which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. One patient experienced a fatal intracranial hemorrhage. Platelet monitoring, patient education regarding the signs and symptoms of thrombocytopenia, and facilitating prompt medical assessment and treatment can mitigate this risk. However, the decrease in platelets can occur precipitously and unpredictably. Even with intensive monitoring, the risk remains. Consider the potential risk of bleeding from thrombocytopenia when considering concomitant use of antiplatelet, thrombolytic, or anticoagulant drugs.	Major safety issues of thrombocytopenia and glomerulonephritis occur at the proposed dose of inotersen. Inflammatory and immune effects are characteristic of the drug class, including serious adverse events of neurotoxicity (e.g., stroke, myelopathy). Hepatic accumulation is a class effect, and inotersen patients had increases in liver laboratory tests. Seven inotersen patients stopped treatment because of hypersensitivity reactions associated with antibodies to inotersen. Based on the mechanism of action, inotersen is expected to decrease vitamin A levels. The safety issues can have life-threatening outcomes. The magnitude for serious harm after approval is unknown. Adherence to monitoring of platelets and renal laboratory parameters is necessary, and failure to adequately monitor, recognize signs and symptoms, and provide prompt medical treatment in the postmarketing setting would increase the risk of adverse and potentially life-threatening outcomes.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Inotersen can cause glomerulonephritis and renal toxicity that may result in dialysis-dependent renal failure. Glomerulonephritis occurred in three patients (3%) treated with inotersen and no patients treated with placebo. In these glomerulonephritis cases, immunosuppressive medication was required for clinical improvement, and stopping inotersen alone was not sufficient to resolve manifestations of glomerulonephritis. One patient did not receive immunosuppressive treatment and remained dialysis-dependent. Renal laboratory monitoring and cessation of inotersen according to recommended laboratory criteria can mitigate this risk but will not eliminate the risk of severe renal toxicity. • One clinical study patient experienced carotid arterial dissection within 2 days of the first inotersen dose, a time the patient also had symptoms of cytokine release (e.g., nausea, vomiting, muscular pain and weakness) and a high sensitivity C-reactive protein level greater than 100 mg/L. There is no known way to prevent or reduce the risk of cervicocephalic arterial dissection or stroke after use of inotersen. • Inflammatory and immune changes are an effect of antisense oligonucleotide drugs. In clinical studies, serious inflammatory and immune adverse reactions occurred in inotersen patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)-positive systemic vasculitis and a single case of autoimmune hepatitis with primary biliary cirrhosis in a patient with a family history of primary biliary cirrhosis. Neurologic serious adverse reactions consistent with inflammatory and immune effects occurred in inotersen patients, in addition to stroke and carotid arterial dissection. One patient developed myelopathy and paraparesis in the absence of radiologic evidence of spinal cord compression. Another patient developed progressive lumbar pain, weight loss, headache, vomiting, and impaired speech with no confirmed infection. • The liver is a site of accumulation of antisense oligonucleotides. In	

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	clinical studies, 8% of inotersen patients had an increased ALT at least 3 X ULN, compared to 3% of placebo patients; 3% of inotersen patients had an ALT at least 8 X ULN, compared to no placebo patients. Periodic measurement of liver tests may mitigate risks to the liver with inotersen. • Seven inotersen patients stopped treatment because of hypersensitivity reactions associated with antibodies to inotersen. There is no known way to prevent or mitigate this risk. • Based on the mechanism of action of inotersen it is expected that inotersen treatment will lead to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A may mitigate this risk in patients taking inotersen. • Safety in the postmarketing setting: Laboratory values as markers of thrombocytopenia, renal, and liver adverse events were closely monitored in clinical studies, and close monitoring will be necessary in the postmarketing setting. • Other uncertainties: Optimal treatment for glomerulonephritis after inotersen use is not known; Risk of adverse outcomes in pregnancy has not been characterized.	
Risk Management	• A patient registry as a postmarketing requirement will help to evaluate the main safety risks of inotersen in the postmarketing setting. • Strong product labeling including a boxed warning and a Medication guide with recommendations for monitoring of laboratory parameters to mitigate risks, including thrombocytopenia and glomerulonephritis. However, even with adequate monitoring, some patients will likely experience serious adverse events.	A patient registry as a post-marketing requirement will help to evaluate the main safety risks in the post-marketing setting. Postmarketing evaluation will help characterize the risk of hypersensitivity and cytokine release syndrome occurring within 1 day of inotersen administration. Postmarketing evaluation of outcomes of pregnancy in women taking inotersen will help characterize risks of inotersen use during pregnancy.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		A boxed warning should be included in the label to describe the risks of thrombocytopenia and glomerulonephritis and to provide recommendations for monitoring. A medication guide should be required to describe these risks and symptoms of concern, and to highlight the need for prompt medical attention.

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2. Background

This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Evelyn Mentari, of the inotersen NDA 211172 and provides my conclusions and recommendations regarding the safety findings and management of the risks. I also note the reviews from Dr. Wiley Chambers (ophthalmology consult), Dr. Laurel Menapace (Division of Hematology Products), and Dr. Lars Johannesen and Christine Garnett (QT-IRT). Dr. Haoheng Yan reviewed the suitability of the anti-drug antibody assay and Dr. Chris Breder reviewed the immunogenicity data and the ECG data other than QT data.

- *The product information and the applicant's proposals*

Inotersen is a 2'-*O*-(2-methoxyethyl)[2'-MOE] antisense oligonucleotide that, according to the sponsor, binds to transthyretin (TTR) mRNA, resulting in RNase H1-mediated degradation of the TTR mRNA, preventing production of the TTR protein. According to the applicant, this results in decreased levels of mutated and wild-type TTR protein secreted by the liver, likely resulting in a decrease in the formation of TTR amyloid fibril deposits, and slowing or halting disease progression. The proposed indication is treatment of patients with hereditary transthyretin amyloidosis (hATTR) [redacted] (b) (4) is not approved for any other indication in the United States or anywhere in the world.

The proposed doses (to be given subcutaneously) are:

- [redacted] (b) (4)
- [redacted] (b) (4) doses of 284 mg administered once every week. [redacted] (b) (4)

The Sponsor included as events of special interest ocular adverse events potentially related to vitamin A deficiency, thrombocytopenia, and renal impairment.

- *Therapeutic context*

Hereditary ATTR is a rare, progressive, irreversible, and fatal disease, according to the sponsor. The applicant states that average life expectancy is 3 to 15 years after diagnosis. The applicant states that significant cardiomyopathy is associated with poorer prognosis and that patients typically die due to malnutrition and cachexia, renal failure, and cardiac disease. Life-threatening autonomic dysfunction develops in many patients, affecting the cardio-circulatory, gastrointestinal, and genitourinary systems, with symptoms including orthostatic hypotension (leading to dizziness and falls), gastrointestinal symptoms of diarrhea, constipation, vomiting, and gastroparesis, urinary symptoms, fecal incontinence, and erectile dysfunction. Amyloid deposits in kidney are common and can result in renal failure. Cardiac involvement occurs in 80% of ATTR, according to the sponsor, with conduction abnormalities and arrhythmias, cardiomyopathy, and heart failure. According to the applicant, the worldwide prevalence of hATTR with polyneuropathy (predominant involvement of peripheral nerves and gastrointestinal tract), is approximately 10,000 patients.

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Current treatment for hATTR includes orthotopic liver transplantation. Tafamidis is approved in Europe, Japan, and other countries for treatment of ATTR in adults with Stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment, and in some countries in patients with more advanced states. Diflunisol, an NSAID, has been used off label. There are no approved treatments in the United States.

- *Regulatory background and marketing history*

Please refer to reviews by Dr. Chris Breder and Dr. Evelyn Mentari.

3. Product Quality

Please refer to the CMC review.

4. Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical reviews.

5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review. The following information regarding pharmacokinetics and pharmacodynamics is from Clinical Overview provided by the applicant and reflects the findings most relevant to safety.

- Peak plasma concentrations occur within 1.5 to 4 hours following subcutaneous injection.
- Mean plasma concentrations decreased more than 90% from Cmax by 24 hours after injection. However, elimination half-life is approximately 1 month.
- Inotersen is highly protein bound (>94%). In nonclinical studies, liver and kidney contain the highest tissue concentrations.
- Elimination is primarily through metabolism via nucleases.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Please refer to Dr. Chris Breder's review of efficacy.

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8. Safety

8.1 Safety Review Approach

Dr. Mentari analyzed the following 3 main subject pools in the analyses of inotersen clinical safety:

- Placebo-controlled subjects (Study CS2)
- Integrated Set: All subjects with familial amyloid polyneuropathy treated with inotersen (Studies CS2 and CS3)
- Longitudinal Safety Set: Subjects who received inotersen in Study CS2 and continued receive inotersen in Study CS3

The studies making up the pools are shown in the table below, adapted from Dr. Mentari's review.

Study	Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen	Number of Subjects	Duration of Treatment / Study Status Report Type
CS1	Safety, tolerability, PK In healthy volunteers	Phase 1, DB, PC, Dose-Escalation Study	Inotersen single doses: 50 -400mg; Multiple doses: 50-400 mg; 3 times in Week 1 followed by once-weekly Weeks 2-4	Total 65, Single-dose: 12 on inotersen and 4 on placebo, Multiple- dose: 39 on inotersen and 10 on placebo	1 day for Single-dose cohorts; 21 days for multiple-dose cohorts Complete
CS2	Efficacy, safety in patients with hATTR-PN	A Phase 2/3 Randomized, DB, PC	Inotersen 300 mg or placebo; 3 times in Week 1 followed by once weekly Weeks 2–65	172 (112 on inotersen; 60 on placebo)	15 months Complete to 6-month post- treatment follow-up visit
CS3	Safety, efficacy in patients with hATTR-PN	An Open-Label Extension Study	Inotersen 300mg weekly; SC	114 total 40 treated with placebo in CS2; 74 treated with inotersen in CS2.	Up to 3 years On-going; interim CSR

DB = Double blind; PC=Placebo-controlled; Doses given subcutaneously (SC)

8.2 Review of the Safety Database

<u>Adequacy of the drug exposure experience (i.e., the safety database)</u>

I agree with Dr. Mentari that because hATTR-PN is a rare disease, the overall subject exposure in the inotersen clinical development program is adequate. I also agree that duration of treatment and patient demographics are acceptable with respect to safety evaluation.

Dr. Mentari shows that 203 subjects (including healthy volunteers) were exposed to at least 1 dose of inotersen, and 160 were exposed to 300 mg weekly. She shows that 125 were exposed at the proposed dose for at least 6 months and 109 for at least 1 year. There is little exposure beyond 12

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months (58 treated for at least 24 months and 18 treated for at least 36 months). Dr. Mentari notes that although the exposure does not meet ICH guidelines of 1500 total and 500 for 6 months, because hATTR is a rare disease, there is no specific minimum number of patients that should be studied to establish clinical safety , and she shows that exposure does meet ICH guidelines for treatment of 1 year.

Dr. Mentari shows that approximately 52% of patients who received inotersen in CS2 or CS3 had their dosing paused (compared to approximately 38% of placebo patients), in most cases because of low platelet counts, missing platelet counts, or another reason related to platelets.

Approximately 70% of patients were male. Approximately 94% of patients were white, and approximately 92% not Hispanic or Latino. The age range was approximately 27 – 82 years of age, and approximately 50% of patients were at least 65 years old. Demographics were similar between drug and placebo and across studies.

Subjects were included if they had Stage 1 (does not require assistance with ambulation) or Stage 2 (requires assistance with ambulation) hATTR-PN. Dr. Mentari notes a slightly higher percentage of placebo subjects with Stage 1 hATTR-PN (70.0%), compared to inotersen subjects (66.1%). She notes that 40.2% of inotersen subjects were diagnosed with hATTR-CM at CS2 study entry, compared to 36.7% of placebo subjects.

8.3 Adequacy of Applicant's Clinical Safety Assessments

Dr. Mentari notes that in the original submission, the Sponsor excluded some laboratory values that were categorized with the sponsor as "unconfirmed". On FDA request, revised tables with all measured laboratory values were provided and those data were evaluated by Dr. Mentari. Dr. Mentari notes that the Sponsor's process for recording adverse events was appropriate. Dr. Mentari has provided an analysis that combines similar adverse event terms that were originally split in some cases.

8.4 Safety Results

Dr. Mentari has identified a number of important safety concerns that occurred in the clinical trials to a greater extent in subjects receiving inotersen than placebo in Study CS2. These include serious events of thrombocytopenia and glomerulonephritis as well as other inflammatory and immune-mediated events including hypersensitivity reactions, and effects on liver enzymes.

In this section I first discuss the deaths in the database. Then I provide a general overview of the safety results regarding SAEs, discontinuations, significant adverse events, and TEAEs, followed by labs, vital signs, and electrocardiograms, and immunogenicity. Next I discuss Submission Specific Safety Issues. I finish Section 8.4 with a summary of the additional safety explorations discussed in Dr. Mentari's review).

<u>Deaths</u>

Five deaths (5/112; 4.4%) occurred in inotersen-treated patients in the placebo-controlled trial (CS2) compared to 0 of 60 placebo-treated patients. Eleven deaths occurred in CS2 and CS3

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combined (11 of 161 inotersen subjects, 6.8%). One death in CS2 was due to intracranial hemorrhage following severe thrombocytopenia that appears to be associated with the use of inotersen. One death in CS3 was due to autoimmune hepatitis and primary biliary cirrhosis and may be related to the use of inotersen. Four of the deaths in CS2 and 5 of the 6 deaths in CS3 appear related to disease progression.

I agree with Dr. Mentari that 4 deaths in controlled study CS2 appear to be related to disease progression (*cachexia* in subjects (b) (6) and (b) (6); *congestive cardiac failure and cachexia* in subject (b) (6); and *intestinal perforation* in subject (b) (6) that I agree is consistent with a complication of hATTR).

Subject (b) (6) a 35 y.o. male in Study CS2, had an *intracranial hemorrhage* subsequent to severe thrombocytopenia. The subject had normal platelet counts at baseline and on Days 5, 15, 30, and 52. Three months after the first inotersen dose (Day 87) he developed treatment-emergent IgG antiplatelet antibodies, and the platelet count was not interpretable because of clumping. There were no reported symptoms of thrombocytopenia until Study Day 121, when the subject suddenly lost consciousness and began bleeding from the mouth. Upon hospitalization, his platelet count was $<10 \times 10^9$/L, and he was diagnosed with intracranial hemorrhage. His neurological function rapidly deteriorated, and he died on Study Day 122 after receiving a total of 19 doses of inotersen. (Last inotersen dose was administered on Study Day 115.) Please refer to discussion of inotersen-associated thrombocytopenia for detailed consideration of this issue. *I agree with Dr. Mentari that this event was related to inotersen*.

I agree with Dr. Mentari that 5 of the 6 additional deaths in Study CS3 are unlikely related to inotersen, and likely related to disease progression (or complication of procedure in the case of liver transplant). These occurred in subjects (b) (6) (*congestive cardiac failure*), (b) (6) (*cardiac rupture after liver transplant*), (b) (6) (*acute cardiac failure, septic shock and bacteremia* in the setting of advanced hATTR with 20 lb weight loss in 2 months prior to death), (b) (6) (*peripheral neuropathy*), and (b) (6) (*endocarditis* with history of cardiac arrhythmia with pacemaker).

Subject (b) (6), a 65 y.o. male, died of *autoimmune hepatitis and primary biliary cirrhosis (PBC)* after approximately 3 years of exposure to inotersen (142 doses). The patient had no known history of liver disease or PBC, although there was a family history of PBC in a first degree relative. Dr. Mentari notes that first degree relatives of patients with PBC have a 1-6% prevalence of development of PBC, and that in addition to genetic susceptibility a triggering event that initiates the autoimmune attack on bile duct cells is a requirement. Dr. Mentari notes that inflammatory and immune changes are recognized as a class effect of antisense oligonucleotides, and a range of immune events have been seen with inotersen. Please refer to discussion of liver events and of immune events in Dr. Mentari's review and in my memo. *I agree with Dr. Mentari that this death may be related to inotersen.*

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[1] This subject also developed decreased renal function proteinuria, and edema and I agree this possibly could have been related to inotersen and may have contributed to death.

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SAEs and Discontinuations and TEAEs overall

Overall, the frequency of SAEs for inotersen in the controlled trial CS2 was approximately 1.5 times that of placebo, driven by differences in Cardiac Disorders, Gastrointestinal Disorders, Nervous System Disorders, Metabolism and Nutrition disorders, and Renal and Urinary Disorders that occurred 2 to 5 times more frequently for inotersen than for placebo. The frequency of discontinuations due to adverse events for inotersen in the controlled trial was approximately 4 times that of placebo overall with the largest difference due to Nervous System Disorders. The rates of SAEs, discontinuations due to adverse events, and TEAEs in CS2 and CS3 combined were similar to those in inotersen treated subjects in CS2 alone.

Patients with SAEs, Discontinuations Due to Adverse Events, or TEAEs in hATTR trials

	Study CS2		All (CS2 and CS3)
	Inotersen (N=112) n (%)	Placebo (N=60) n (%)	Inotersen (N=161) n (%)
All SAEs	36 (32.1)	13 (21.7)	60 (37.3)
Discontinuations	16 (14.3)	2 (3.3)	27 (16.8)
TEAEs	111 (99)	60 (100)	145 (95)

Serious adverse events (SAEs)

As Dr. Mentari shows, SAEs occurred in approximately 32% of inotersen treated subjects in CS2 compared to approximately 22% of placebo-treated subjects. The most frequent were infections (approximately 10% in inotersen and 8% in placebo), cardiac disorders (approximately 8% for inotersen vs 3% for placebo), gastrointestinal disorders (approximately 6% for inotersen vs 2% for placebo), nervous system disorders (approximately 5% for inotersen vs 2% for placebo), and metabolism and nutrition disorders and renal and urinary disorders (both approximately 5% for inotersen and none for placebo). In CS2 and CS3 combined, the risk of SAEs for inotersen was slightly greater than inotersen in CS2 alone, with SAEs generally primarily in the same system organ classes as in CS2 alone.

Cardiac SAEs

Dr. Mentari shows that approximately 8% (n=9) of inotersen treated subjects and 3% (n=2) of placebo treated subjects had cardiac disorders SAEs in CS2 (and 9.3% of inotersen subjects in CS2 and CS3 combined). These SAEs included primarily congestive cardiac failure that occurred more frequently in inotersen (n=7) than placebo with additional events in CS3, as well as 2 events of sinus arrest in CS2 (none on placebo), 2 events of atrioventricular block (Subject [redacted] (b) (6) who was a 73 y.o. male with hATTR-cardiomyopathy and symptomatic congestive heart failure at baseline, with *first degree AV block* in CS2, 5 months after starting inotersen and who died 1 year later from complications of heart failure; Subject [redacted] (b) (6) who was a 73 y.o. male with hATTR-cardiomyopathy at baseline who had *complete AV block* in CS3, 5 months after starting inotersen that resolved with a pacemaker) and 2 patients with SAEs of *bradyarrhythmias*: bradycardia/bradyarrhythmia (subject [redacted] (b) (6)) and sinus bradycardia/sinus arrest/cardiac failure (subject [redacted] (b) (6) who had a history of congestive heart failure, right bundle branch

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block, and inferior infarct on multiple medications including metoprolol and diuretics). The sponsor states on p.59 of the summary of clinical safety that all of the patients with cardiac SAEs had underlying cardiomyopathy. Dr. Mentari notes that the percentage of subjects diagnosed with hATTR-CM at CS2 entry was greater in inotersen subjects compared to placebo subjects and *I agree that this baseline imbalance may have contributed to the increased frequency of cardiac disorders SAES in inotersen compared to placebo. Given the expected findings of dysrhythmias and heart block in this population, it is difficult to attribute the 2 events of atrioventricular block to inotersen (with 1 vs 0 for placebo in CS2, and 1 case in the open label study).*

Gastrointestinal SAEs

SAEs of gastrointestinal disorders occurred in 6.3% of inotersen subjects vs 1.7% of placebo subjects (n=1; vomiting) in Study CS2 and in 7.5% of inotersen subjects overall. These were individual events in CS2 Dr. Mentari notes the SAE of intestinal perforation/mesenteric arterial occlusion in subject [redacted] (b) (6) discussed under deaths, the SAE of pancreatitis in subject [redacted] (b) (6) in CS3 (and she notes that pancreatitis can be a manifestation of amyloidosis), and an SAE of vomiting as a result of an SAE of encephalitis in CS2 inotersen-treated subject [redacted] (b) (6). There was 1 SAE of gastrointestinal hemorrhage in CS2 (subject [redacted] (b) (6)) that was thought due to hemorrhoids and no action was taken with study drug. *The gastrointestinal SAEs do not appear drug related.*

Nervous System Disorders SAEs

SAEs of nervous system disorders occurred in 5.4 % of inotersen subjects vs 1.7% of placebo subjects (n=1; neuralgia) in Study CS2 and in 8.1% of inotersen subjects overall. In CS2 the SAEs were single events. They included *dementia and myoclonus* (14 months after starting inotersen in subject [redacted] (b) (6) with cognitive deterioration starting 2 years prior to the and with "evidence of slight Parkinson's disease") that I agree with Dr. Mentari is unlikely related to inotersen. Dr. Mentari also identified single SAEs of *encephalopathy and memory impairment* in subject [redacted] (b) (6) that I agree are unlikely related to inotersen in the setting of acute illness of sepsis, pneumonia, and hyponatremia, and an SAE of *peripheral neuropathy* in subject [redacted] (b) (6) that was a progression of hATTR-PN disease.

SAEs of *embolic stroke* ([redacted] (b) (6)), *myelopathy and neuritis* ([redacted] (b) (6) who subsequently had SAEs of deep venous thrombosis and pulmonary embolism possibly due to immobility), and *seizure* [redacted] (b) (6) in CS2 are discussed in section XXXX discussing nervous system AEs, as are *dizziness* that occurred in CS3 (n=1) and *syncope* (1 event in CS2 and 4 in CS3). An SAE of *intracranial hemorrhage* (subject [redacted] (b) (6)) was discussed under deaths; an additional SAE of *intracranial hemorrhage* (subject [redacted] (b) (6)) occurred in CS3 in the setting of syncope and a fall in a patient anticoagulated with dabigatran.

Metabolism and Nutrition Disorders SAEs

SAEs related to metabolism and nutrition disorders occurred in 6 patients on inotersen (5.4%) and none on placebo in CS2 and in 10 patients (6.2%) in CS2 and CS3 combined. These SAEs included *dehydration, cachexia, hyponatremia, malnutrition, and fluid retention*, and are *most likely caused by amyloidosis or concurrent disease or occurred due to gastrointestinal adverse events observed with inotersen.* Dr. Mentari notes that manifestations of amyloidosis can contribute to conditions such as these. She also notes, as discussed above, that more inotersen subjects had gastrointestinal adverse events such as nausea and vomiting and constitutional

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symptoms that could also contribute to dehydration, cachexia, and malnutrition. Finally, she notes that 1 SAE of dehydration occurred in the setting of diuretic medication adjustment, and 1 SAE of hyponatremia/fluid retention occurred in the setting of congestive heart failure.

Infection SAEs occurred slightly more frequently for inotersen than for placebo, but there did not seem to be a cluster of any specific type of infection.

Renal and Urinary Disorders SAEs are included in the discussion of Glomerulonephritis and Renal Toxicity, beginning on page 20 of this memo.

Hepatobiliary disorders SAEs are included in the discussion of Hepatic Toxicity beginning on page 24 of this memo.

Discontinuations

In CS2, 16 patients on inotersen (14.3%) and 2 on placebo (3.3) discontinued due to at least 1 treatment emergent adverse event (TEAE), and 16.8 of inotersen treated subjects overall discontinued due to an adverse event. As Dr. Mentari shows, reasons for permanent discontinue of inotersen included thrombocytopenia, glomerulonephritis, hypersensitivity reactions (generally occurring within 2 hours of administration), constitutional symptoms (such as fever, chills, pain, myalgia), and an injection site reaction of pruritus. These events have been discussed under SAEs or elsewhere in Dr. Mentari's review and my memo.

Significant Adverse Events

In CS2, approximately 22% of adverse events for placebo and approximately 28% of adverse events for inotersen were categorized as severe[2]. Most adverse events categorized as severe are discussed elsewhere in Dr. Mentari's review and in my memo. Most were single events. As Dr. Mentari notes, severe adverse events not discussed elsewhere are generally consistent with manifestation of amyloidosis (e.g., cachexia, skin ulcer, peripheral ischemia, gastrointestinal symptoms such vomiting and constipation).

Treatment Emergent Adverse Events and Adverse Reactions

Dr. Mentari shows adverse events from CS2 that occurred in at least 5% of inotersen subjects and at least 5% more frequently than or at least twice as frequently as in placebo subjects. Her presentation is based on the preferred terms as provided by the sponsor as well as her combination of similar terms. I agree with her presentation and I provide that below:

	Inotersen (N=112) %	Placebo (N=60) %
Injection site reactions[a]	49	10
Nausea	31	12
Headache (headache and migraine)	26	12
Fatigue	25	20

[2] Summary of Clinical Safety, p. 86.

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Thrombocytopenia (and platelet count decreased)	24	2
Fever (pyrexia)	20	8
Peripheral edema	19	10
Chills	18	3
Anemia[b]	17	3
Vomiting	15	5
Myalgia	15	10
Decreased renal function[c]	14	5
Arrhythmia[d]	13	5
Arthralgia (arthralgia, arthritis, spinal osteoarthritis)	13	8
Pre-syncope or syncope	13	5
Decreased appetite	10	0
Paresthesia	10	3
Dyspnea	9	3
Elevated liver function test (hepatic enzyme increased, ALT or AST increased, LFT abnormal, and transaminases increased)	9	3
Orthostasis (postural dizziness, orthostatic hypotension, orthostatic intolerance)	8	2
Influenza like illness	8	3
Contusion	7	2
Bacterial infection [e]	7	3
Eosinophilia (eosinophilia and eosinophil count increased)	5	0
Dry mouth	5	2

[a] bruising, erythema, haematoma, haemorrhage, induration, inflammation, mass, oedema, pain, pruritus, rash, reaction, swelling, urticaria
[b] Anaemia, Anaemia macrocytic, Haematocrit decreased, Haemoglobin decreased, Iron deficiency anaemia, Red blood cell count decreased
[c] Acute kidney injury, Blood creatinine increased, Blood urea increased, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal failure, Renal impairment, and Urine output decreased
[d] Arrhythmia, Atrial fibrillation, Atrial flutter, Bradyarrhythmia, Bradycardia, Extrasystoles, Sinus arrhythmia, Sinus bradycardia, Supraventricular extrasystoles, Tachycardia, and Ventricular extrasystoles.
[e] Bacteraemia, Cellulitis staphylococcal, Clostridium difficile infection, Conjunctivitis bacterial, Cystitis Escherichia, Helicobacter gastritis, Helicobacter infection, and Staphlococcal infection

Dr. Mentari notes that constitutional symptoms AEs of nausea, chills, fatigue, diarrhea, headache, and myalgia occurred within 1 day of inotersen administration. She notes that whether premedication may reduce the frequency of these post-administration reactions has not been evaluated.

Dr. Mentari also notes that there may be multiple mechanisms for these events, but they can be related to the ability of antisense oligonucleotides to stimulate the innate immune system, including release of inflammatory cytokines. She notes that in 7/161 (4%) of CS2 and CS3 subjects, hypersensitivity AEs occurring within 1 day of inotersen administration were associated with antibodies to inotersen, and caused discontinuation of treatment. Dr. Mentari

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also observed that in CS2, injection site reactions occurred in 49% of inotersen subjects vs 10% of placebo subjects and that these reactions were more common in subjects with a positive anti-inotersen antibody test.

Laboratory Findings

Other than laboratory chemistry values associated with renal or liver disease, Dr. Mentari finds that changes serum chemistry (calcium, glucose, potassium, magnesium) were similar in inotersen and placebo groups. She found an increased frequency of Grade 3-4 hyponatremia in 6.3% of inotersen subjects vs 0 placebo subjects, but notes that those cases were associated with renal disease or cardiac disease. She notes that grade 2-3 hypophosphatemia occurred in 7.2% of inotersen subjects vs 0 placebo subjects, but that this generally occurred in patients with renal disease.

Regarding hematology changes, changes in platelet count are discussed under the section of my memo regarding thrombocytopenia. Grade 2-3 anemia with hemoglobin levels of 7.3 to < 10g/dL occurred in 12.6% of inotersen subjects vs 1.7% of placebo subjects. Dr. Mentari notes that etiologies include thrombocytopenia, and increased frequency of AEs related to hemorrhages, renal disease, and the acute phase response in the setting of increased inflammation. Dr. Mentari notes an increase in B lymphocyte levels in CS2 with increased IgG and IgM concentrations in inotersen vs placebo.

Vital Signs

Please refer to Dr. Mentari's review for details regarding vital signs findings. She finds a larger percentage of inotersen subjects with systolic blood pressure < 90 mm Hg or diastolic < 50 mm Hg in inotersen treated subjects vs placebo and notes that syncope and presyncope adverse events were also more frequent in inotersen subjects than in placebo subjects.

Electrocardiograms (ECGs)

Dr. Breder reviewed ECG interval changes in CS2. Please refer to his findings, included in Dr. Mentari's review, for details. He notes an imbalance in QRS prolongation for inotersen vs placebo. Six of 112 (5.4%) inotersen-treated patients had QRS intervals greater than 160 msec and more than 25% greater than baseline vs 1/60 (1.7%) of placebo-treated patients. Excluding patients with baseline greater than 160 msec, 5/100 (5%) of inotersen patients vs no placebo-treated patients had QRS greater than 160 msec, representing a 50% increase from baseline. As Dr. Breder notes, the background cardiac disease in hATTR amyloidosis patients complicates the interpretation of these findings. There is a theoretical possibility that removal of amyloid from the myocardium could result in conduction abnormalities. I agree with Dr. Breder's recommendation to include a description of this finding in the prescribing information.

QT

A thorough QT study was waived. As discussed above, at QT-IRT consult evaluated QT data from study420915-CS1 and determined that the data collected in that study supports concluding an absence of large mean increases (>20 ms) in the QTc interval.

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Immunogenicity

The immunogenicity assay validation was reviewed by Dr. Haoheng Yan who recommended that the anti-drug antibody (ADA) assay is appropriately validated and suitable for detecting anti-inotersen antibodies in patient plasma samples from the clinical studies in this NDA submission. Dr. Mentari has found that 7 of 161 (4%) of inotersen subjects (subjects (b) (6) stopped treatment because of a hypersensitivity reaction associated with antibodies to TEGSEDI.

Dr. Chris Breder reviewed safety related to immunogenicity overall. He notes that ADA were formed in approximately 30% of inotersen-treated patients in CS2. In the CS2 inotersen-treated patients who were ADA negative at baseline Dr. Breder notes several adverse events with an incidence of at least 10% greater in ADA-positive patients than in ADA-negative patients. As Dr. Breder shows, the numbers of patients with these events in some cases were very small. The relationship between ADA and adverse reactions from inotersen is not clear. However, I agree with Dr. Breder's recommendation to note this observation in the prescribing information.

Submission Specific Safety Issues

Dr. Mentari considers the following in her discussion of submission specific safety issues:

- Thrombocytopenia
- Glomerulonephritis and Renal Toxicity
- Inflammatory and Immune Effects
- Hepatic Toxicity
- Ocular Toxicity
- Hemorrhages

Thrombocytopenia

Inotersen causes thrombocytopenia. Platelet counts less than 75 x 10^9/L occurred in 11% of inotersen subjects vs 0 placebo subjects. Three inotersen subjects (3%) had severe thrombocytopenia (less than 25 X 109/L), one of whom had a fatal intracranial hemorrhage. The onset of thrombocytopenia can be precipitous and in some patients platelet counts fell from at least 100 x 10^9/L to less than 75 X 10^9/L within 2 weeks.

In CS2, platelet counts less than 100 x 10^9/L occurred in 23% of inotersen subjects vs 3% of placebo subjects. Platelet counts less than 75 x 10^9/L (the level below which primary hemostasis is generally considered to be impaired) occurred in 11% of inotersen subjects vs 0 placebo subjects. Dr. Mentari notes that 3 (3%) inotersen subjects had severe thrombocytopenia (less than 25 X 10^9/L) which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. As previously discussed, Subject (b) (6) had a fatal intracranial hemorrhage with a platelet count of less than 10 X 10^9/L.

The onset of thrombocytopenia can be gradual or precipitous. Dr. Mentari shows examples of patients with fluctuating platelet counts and nadir counts occurring after more than 2 years of

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dosing. Dr. Mentari also shows the time course of events for the 3 subjects (Subjects (b) (6) with severe thrombocytopenia; in all 3 cases the onset was precipitous and unpredictable, with normal platelet counts immediately prior to the nadir counts. All three were noted to have IgG antiplatelet antibodies at the time of the nadir count. Two of those subjects had an uninterpretable platelet measurement at one point due to platelet clumping. In all three patients the events occurred within approximately 3 months. Subject (b) (6) reportedly did not have symptoms of thrombocytopenia until the day of the event. The other two subjects continued treatment despite symptoms of thrombocytopenia; their platelet counts improved after inotersen discontinuation and glucocorticoid treatment. *Of note, prior to the fatal event, platelet measurements were generally scheduled 2-6 weeks apart (including in these 3 subjects). After the fatal event, protocols were amended to include weekly platelet measurements.* Dr. Mentari notes that in studies CS2 and CS3, 11 subjects had a fall in platelet count from at least 100 x 10^9/L to a count of less than 75 X 10^9/L within 2 weeks and identifies subject (b) (6) that had a reduction from 100 x 10^9/L to 40 x 10^9/L in 1 week. She notes that (b) (4) *For confirmed platelet counts of less than 100 x 10^9/L, I agree with her recommendation for weekly monitoring for the duration of exposure and monitoring (and more frequently for platelet counts of less than 75 X 10^9/L).* Dr. Mentari notes that in clinical studies, 32% of subjects had at least 1 platelet count of less than 100 X 10^9/L, and in the postmarketing setting it is likely that a similar proportion of patients will need to follow a similar dosing regimen. Dr. Mentari recognizes that platelet results may not be available at the recommended frequency and notes that in CS3, 24% of subjects had at least 1 dose held because no platelet value was available in the last 14 days (including because of missed lab assessments or uninterpretable sample).

Dr. Mentari notes a temporary decrease in platelet count with administration of 3 loading doses in the first week. She notes that the reduction, that was not clinically significant, was a short-term effect and is correlated with plasma inotersen levels.

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

The etiology of inotersen-induced thrombocytopenia is not known. It may be an immune-mediated mechanism in some cases but could be multifactorial. Dr. Mentari notes that in clinical studies, the sponsor tested for antiplatelet antibodies to evaluate an immune mechanism for platelet declines. Antiplatelet antibody testing was performed in selected patients (n=37 for inotersen and n=18 for placebo in CS2) including most subjects with platelet declines to less than 100 x 10^9/L. Dr. Mentari notes than in CS2, all 9 inotersen

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subjects who developed treatment-emergent positive antiplatelet antibodies developed treatment emergent thrombocytopenia. Inotersen patients with results of no positive antiplatelet antibody test or with baseline positive antiplatelet antibody test had nadir platelet counts ranging from moderate thrombocytopenia to normal platelet levels. Thirteen of 23 (56.5%) of inotersen subjects with a nadir platelet count of < 75 x 10^9/L in CS3 had a treatment emergent positive antiplatelet antibody test shortly before or at the time of platelet decline. I agree with Dr. Mentari that antiplatelet antibody testing may be useful in the evaluation of individual inotersen patients with thrombocytopenia, but that this testing would not be a screening tool for thrombocytopenia with the use of inotersen, in part because baseline antiplatelet antibodies that are not clinically relevant may complicate the interpretation of testing.

Regarding risk factors for thrombocytopenia, Dr. Mentari shows that patients with baseline platelets less than 200 x 10^9/L have lower nadir platelet values than patients with baseline platelets of at least 200 X 10^9/L and had a 6-7 X increase risk of having a nadir platelet count less than 75 X 10^9/L. Dr. Mentari notes that age, sex, or race did not affect the magnitude of platelet count reduction.

Dr. Mentari notes that in study CS2, 26 of 112 (23%) inotersen subjects had at least 1 clumped platelet sample. In 2 cases of severe thrombocytopenia less than 25 X 10^9/L, one of which resulted in death, clumped platelet samples caused a delay in diagnosis and treatment. She notes that in both cases the subjects tested positive for treatment-emergent anti-platelet antibodies detected shortly before or at the time of the severe reduction in platelet count. She notes that platelet clumping can be caused by a reaction between antiplatelet antibodies and ethylenediaminetetra-acetic acid (EDTA) in the blood collection tube. *I agree with Dr. Mentari's recommendation that if platelet count is uninterpretable, patients and prescribers should obtain a repeat measurement as soon as possible, and that a different anticoagulant such as citrate or heparin should be used with repeat testing.*

Glomerulonephritis and Renal Toxicity

Dr. Mentari notes that nonclinical studies have found accumulation of antisense oligonucleotides in proximal tubule cells of the kidney. Glomerulonephritis, considered a pro-inflammatory effect, has also been described in nonclinical and clinical studies of antisense oligonucleotides. Inotersen can cause glomerulonephritis and renal toxicity that may result in dialysis-dependent renal failure. Diagnosis may be complicated by ATTR-related kidney disease that includes chronic renal failure and proteinuria. Renal monitoring will be required to mitigate the risks of inotersen associated renal toxicity.

In CS2, 223 of 112 (20.5%) of inotersen subjects had a treatment-emergent renal impairment adverse event, compared to 6 of 60 (10%) placebo subjects. In CS3, 9 of 114 (7.9%) subjects had a treatment-emergent renal impairment adverse event. These events (adverse event preferred terms) included glomerular filtration rate decreased, glomerulonephritis, proteinuria, and renal failure.

Dr. Mentari finds that 3 of 112 (3%) inotersen subjects (subjects [redacted] (b) (6) vs 0 placebo subsects had *biopsy-confirmed glomerulonephritis* that began

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approximately 3 to 13 months after starting inotersen. All 3 subjects had normal estimated glomerular filtration rate (eGFR) at baseline. In all 3 cases, glomerulonephritis was accompanied by *nephrotic syndrome* with proteinuria greater than 3.5 g/24 hours. Proteinuria continued to worsen after cessation of inotersen. Subjects [redacted] (b) (6) improved after treatment with prednisolone/cyclophosphamide and corticosteroids alone, respectively. Subject [redacted] (b) (6) did not receive immunosuppressive therapy and remained dialysis-dependent. Dr. Mentari notes that the subject had bacteremia which may have contributed to the decision to avoid immunosuppression and notes that patients with active infection requiring systemic antiviral or antimicrobial therapy were excluded from the clinical studies.

Dr. Mentari notes that renal impairment adverse events categorized as serious or severe occur in 7 of 112 (6.2%) inotersen subjects vs 1 of 60 (1.7%) placebo subjects, including the 3 cases of biopsy confirmed glomerulonephritis, 2 cases with baseline elevated urine protein that she considers unlikely related to inotersen, and 2 cases possibly related to inotersen. She also notes a case of immune-mediated renal toxicity in Subjects [redacted] (b) (6). with systemic anti-neutrophil cytoplasmic autoantibody (ANCA)-positive vasculitis with renal involvement, discussed under Immune Effects, below. Dr. Mentari notes that it is difficult to assess whether increased protein is related to inotersen because proteinuria can be a clinical feature of hATTR-related kidney disease. She does show that inotersen subjects had more frequent decreases in eGFR and more frequent increases in urine protein and in serum creatinine than placebo subjects.

I agree with Dr. Mentari's recommendation, based on the potential for rapid onset and progression of glomerulonephritis, that urinalysis, quantitative urine protein, and serum creatinine be monitored every 2 weeks. I agree with her recommendation to stop inotersen if urine protein to creatinine ratio (UPCR) is greater than 1000 mg/g which she notes was generally done in the clinical studies. Dr. Mentari notes that in addition to monitoring and treatment to preserve renal glomerular function, inotersen patients with glomerulonephritis will require monitoring and treatment for nephrotic syndrome and its manifestations that may include edema, hypercoagulability with venous or arterial thrombosis, increases susceptibility infection, protein malnutrition, hypovolemia, urinary loss of hormones, and hyperlipidemia.

Inflammatory and Immune Effects of Inotersen

As Dr. Mentari notes, inflammatory and immune changes are recognized as a class effect of antisense oligonucleotides. She notes findings of vasculitis in multiple organs in nonclinical studies. She notes that adverse reactions consistent with an inflammatory or immune etiology in the inotersen clinical studies include immune thrombocytopenia, glomerulonephritis, neurologic toxicity (carotid dissection and stroke, myelopathy, and encephalitis), vasculitis, and autoimmune hepatitis/Primary biliary cirrhosis. Neurologic toxicity and vasculitis will be addressed in this section.

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- Carotid Dissection and Stroke

Subject (b) (6) was a 53 y.o. subject with Stage 2 hATTR-PN and cardiomyopathy with NYHA class II heart failure[3], and a history of hypertension and evidence of myocardial infarction on baseline ECG, and no history of atrial fibrillation. Pre-treatment vital signs included blood pressure of 110/63 and heart rate 68 bpm. On Study Day 1 after receiving the first dose, the subject had symptoms that Dr. Mentari believes are consistent with cytokine release syndrome that included nausea, vomiting, muscular/leg weakness, muscle spasms, and anal incontinence. These symptoms continued on Day 2 as well as inability to move her eyes, an episode of screaming gibberish, a diffuse headache, and difficulty eating, along with a temperature of 100.4 ° F on Day 3. Her conditioned worsened and a computed tomography (CT) scan of the head on Day 10 and CT angiogram of head and neck suggested an embolic stroke and arterial dissection that had occurred shortly after a single dose of inotersen, with no evidence of atrial fibrillation. The patient had elevated C-reactive protein on study day 3 that remained elevated on study day 13. Cytokines were not measured in study CS2. Please refer to Dr. Mentari's review for details.

Dr. Mentari states that the carotid dissection and embolic stroke occurred after symptoms consistent with cytokine release syndrome and increased inflammation. Lee et al have reviewed diagnosis and management of cytokine release syndrome (CRS) that results from immune activation and can have life-threatening toxicity[4]. CRS results from activation of large numbers of lymphocytes and subsequent release of inflammatory cytokines. Those authors state that the time course and severity of CRS depends on the inducing agent and magnitude of immune cell activation. Lee et all state that fever is a hallmark and that clinical signs and symptoms can include constitutional symptoms of malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, and headache; skin rash; diarrhea; tachypnea, hypoxemia; cardiovascular symptoms including tachycardia, hypotension, altered cardiac output; coagulation abnormalities; azotemia; transaminitis, hyperbilirubinemia; and neurologic manifestations including headache, mental status changes, confusion, delirium ; hallucinations, tremor, altered gait, and seizures.

I agree with Dr. Mentari that this event was likely due to inotersen and related to cytokine release syndrome, that symptoms must be recognized and therapy started quickly, and that patient and prescriber education regarding this risk is essential.

-Myelopathy

Subject (b) (6) was a 52 y.o. female with Stage 1 hATTR (did not require assistance with ambulation), with a history of pacemaker insertion, positional vertigo, and hypertension, who had an AE of gait disturbance on study day 75 and walking imbalance/myelopathy on Day 226. Inotersen was continued and within approximately 1 month of that, she experienced

[3] "Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)". https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure
[4] Blood 2014 124:188-195; doi: https://doi.org/10.1182/blood-2014-05-552729

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paraparesis with subsequent worsening. On Day 270 she had worsening ataxia and pyramidal signs and was hospitalized with left vestibular neuritis and for evaluation of myelopathy. Examination of CSF and results of MRI did not show an obvious cause. Inotersen was not administered during weeks 40-42 (please see Dr. Mentari's review for details). Exacerbation of paraparesis occurred after inotersen was restarted on weeks 43-45. *I agree with Dr. Mentari's assessment that this event was likely due to inotersen and that it may be consistent with vasculitis (considering the nonclinical findings, class effects of antisense oligonucleotides, and clinical data from this patient).*

- Encephalitis

Subject (b) (6) was a 46 y.o. male with Stage 1 hATTR-PN and cardiomyopathy with NYHA class II heart failure. Dr. Mentari notes that dosing was held on and off in the first 5 months of inotersen because of proteinuria. Approximately 1 month after restarting the subject developed intermittent right-sided lumbar pain that increased over the following days and was associated with anorexia, a 9 kg weight loss, and asthenia, without fever, loss of strength, or radiation. Dosing was held starting approximately day 234 because of SAEs of vomiting and encephalitis. On Day 266 he had lumbar pain, headache, and sudden onset of impaired speech with "trouble finding words" and being "tongue-tied". He had no rigidity in neck or signs of meningeal inflammation. CT of head, spine, chest, abdomen, and pelvis were normal. CSF analyses showed high protein levels and lymphocyte-predominant pleocytosis. Dr. Mentari states that no positive culture results were reported; serum analysis was negative for chronic hepatitis, HIV, and cytomegalovirus. The patient was treated with antibiotics and IV dexamethasone 10 mg four times daily for 4 days. The encephalitis resolved on Day 284. Inotersen was restarted on approximately Day 333, and has continued for approximately 20 months without a recurrence. *I agree with Dr. Mentari that the findings are consistent with central nervous system inflammation, and that given the pro-inflammatory effects of inotersen, this case is possibly related to inotersen. It is possible that the patient had underlying risk factors at one time that contributed to the development of this event, but that did not exist when inotersen was subsequently restarted.*

- ANCA-Positive Systemic Vasculitis

Subject (b) (6) was a 58 y.o. male with Stage 2 hATTR-PN who received inotersen in CS2 and began inotersen in CS3, approximately 3 years after the last dose in CS2. He had 1 dose in CS3 and then went on a vacation to Cuba for 2 weeks. After returning, he reported hand, feet, knee, and shoulder "arteritis" starting during travel, followed by erythematous cutaneous lesions in the lower limbs (with no signs or symptoms of infection while in Cuba, and no additional medications other than paracetamol taken at the start of symptoms), and was diagnosed with PR3-ANCA positive systemic vasculitis with renal, cutaneous, and articular involvement, requiring treatment with prednisolone, cyclophosphamide, and azathioprine. I agree with Dr. Mentari, that in the absence of systemic disease or exposures associated with ANCA-positive vasculitis in this patient, and with the known pro-inflammatory effects of inotersen, this case is likely related to inotersen.

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Hepatic Toxicity

Dr. Mentari notes that the liver is a major site of accumulation of antisense oligonucleotides. She notes that inotersen is deposited in the liver and therefore inotersen has the potential for hepatotoxicity.

Abnormal liver function adverse events were reported for 14/112 (12.5%) of inotersen subjects compared to 4/60 (6.7%) placebo subjects in CS2. These events were generally due to elevated liver enzyme values (including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase,) but also included events of ascites, hypoalbuminemia, INR increased, and prothrombin time prolonged. Dr. Mentari notes that the frequency and type of liver-related adverse events were similar in study CS3.

In CS2, 8% of inotersen patients had an increased ALT at least 3X the upper limit of normal (ULN) compared to 3% of placebo patients. Three percent of inotersen patients had an ALT at least 8X ULN compared to no placebo patients. There was a slight imbalance in total bilirubin at least 2X ULN (2.7% for inotersen vs 1.7% for placebo) but there were no Hy's law cases. Dr. Mentari shows 2 patients for whom elevations resolved while the patient continued on study drug (although in one of those cases there was a second gradual increase in ALT and alkaline phosphatase that did not resolve, with no alternative explanation identified).

Dr. Mentari identified 2 abnormal liver function SAEs from CS3. Subject (b) (6) with *primarily biliary cirrhosis and autoimmune hepatitis* was discussed under deaths. Subject (b) (6) was a 64 y.o. male who received placebo in CS2, had normal results for liver laboratory tests prior to the first dose of inotersen in CS3, and was hospitalized with *cholestatic jaundice* on Study day 464 with no clear etiology, although Dr. Mentari notes that the patient had hilar stricture and that benign hilar strictures can be caused by autoimmune conditions.

I agree with Dr. Mentari's concern that the hepatobiliary effects of inotersen with exposure among larger numbers of patients and over longer treatment durations are unclear. I agree with her recommendation to monitor AST, ALT, and total bilirubin at baseline and during inotersen treatment.

Ocular Toxicity

Dr. Mentari notes that a major function of transthyretin in the plasma is to transport retinol (vitamin A) to tissues. In clinical studies all subjects received vitamin A supplementation. The applicant analyzed ocular treatment-emergent adverse events potentially related to vitamin A deficiency. In CS2 there was not an imbalance of these events for inotersen vs placebo and there did not generally appear to be an increase in events in CS3. Dr. Wiley Chambers, in a review dated September 5, 2018, reviewed the ocular adverse events and noted no specific pattern of ocular adverse events and that ERG data did not demonstrate a pattern of vitamin A deficiencies. Dr. Chambers agreed with the Sponsor's proposal to recommend supplementation with Vitamin A throughout treatment.

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Hemorrhages

Dr. Mentari notes that in CS2, 40 of 112 (35.7%) inotersen subjects had an adverse event in the MedDRA SMQ Hemorrhages compared to 20 of 60 (33.3%) placebo subjects, with 1 severe event of fatal intracranial hemorrhage in the setting of severe thrombocytopenia, discussed above under deaths. She shows other hemorrhage events that she notes were mild and moderate, and similar in CS3 (occurring in 22.8%) as the events in CS2.

Safety Analysis by Demographic Subgroup

Dr. Mentari shows a larger risk difference between inotersen and placebo in subjects 65 years of age and older than observed in subjects less than 65 y.o. for adverse events that she notes are seen frequently within 1 day of administration, such as headache, myalgia, pain in extremity, nausea, and chills, as well as for congestive heart failure.

	< 65 y.o.			> 65 y.o.		
AE	Placebo %	Inotersen %	Risk Difference %	Placebo %	Inotersen %	Risk Difference %
Nausea	17.6	31.3	13.7	3.8	31.3	27.5
Chills	2.9	10.9	8	3.8	27.1	23.3
Myalgia	14.7	9.4	-5.3	3.8	22.9	19.1
Pain in extremity	20.6	4.7	-15.9	3.8	14.6	10.8
Headache	17.6	25	7.4	3.8	20.8	17
Congestive heart failure	2.9	0	-2.9	3.8	12.5	8.7

She also notes larger risk differences between inotersen and placebo in females compared to males for some MedDRA SOCs and for some preferred terms. I note the differences in males and females in placebo, as well, making those differences somewhat difficult to interpret. However, I do note that for vomiting, fatigue, and myalgia, for example, women had a 1.5 to 2x greater frequency of AEs than men. Dr. Mentari proposes that some females may be receiving a higher dose by weight, accounting for these differences.

	Males			Females		
AE	Placebo %	Inotersen %	Risk Difference %	Placebo %	Inotersen %	Risk Difference %
Cardiac Disorders SOC	26.8	20.8	-6	10.5	31.4	20.9
Infections and Infestations SOC	61	53.2	-7.8	63.2	77.1	13.9
Skin and	29.3	33.8	4.5	15.8	34.3	18.5

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Subcutaneous Tissue Disorders SOC						
Diarrhea	24.4	23.4	-1	10.5	25.7	15.2
Vomiting	7.3	11.7	4.4	0	22.9	22.9
Fatigue	24.4	22.1	-2.3	10.5	31.4	20.9
Myalgia	12.2	11.7	-0.5	5.3	22.9	17.6

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Dr. Mentari identified 1 subject with meningioma in CS2 and 4 basal cell carcinoma events (1 subject on inotersen in CS2 and 3 subjects in CS3). I agree with her that the limited data available in clinical studies do not indicate an increased risk of malignancy with inotersen.

Human Reproduction and Pregnancy

There were no pregnancies in the inotersen clinical development program.

Pediatrics and Assessment of Effects on Growth

Inotersen was not evaluated in the pediatric population in this development program.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Dr. Mentari notes no adverse events of overdose in the clinical development program. She found no events of drug abuse and dependence using the MedDRA Drug abuse and dependence SMQ and no adverse events of withdrawal or rebound using the MedDRA Drug withdrawal SMQ.

Concerns identified through U.S. or foreign postmarket experience

There is no previous postmarketing experience. TEGSEDI was approved in Europe in July 2018.

Potential safety issues that could cause concern when considering how the drug may be used in the postmarket setting

I agree with Dr. Mentari that the clinical study findings may not fully represent inotersen clinical safety in the setting of more advanced hATTR-PN; patients with Stage 3 (wheelchair bound) hATTR-PN were not included in the clinical studies. I also agree with her concerns that the frequent laboratory monitoring that is required may be difficult for some patients to maintain in the postmarketing setting, and that may result in differences between the postmarketing and clinical study safety profiles.

9. Advisory Committee Meeting

An advisory committee meeting is not planned.

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10. Pediatrics

This application did not evaluate use in pediatrics.

11. Other Relevant Regulatory Issues

Please refer to the clinical efficacy review.

12. Labeling

Prescribing Information
If inotersen is approved, a boxed warning for thrombocytopenia and glomerulonephritis will be required. I agree with Dr. Mentari's recommendation for additional descriptions of these events as well as stroke and cervicocephalic arterial dissection, inflammatory and immune effects, liver effects, hypersensitivity, uninterpretable platelet counts because a reaction between antiplatelet antibodies and EDTA, and (b) (4)

Other Labeling
A Medication Guide will be an important tool in educating patients and caregivers about the events identified in WARNINGS and PRECAUTIONS and to facilitate prompt recognition and treatment.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
I agree the review team's decision that REMS is required to mitigate the risks of inotersen with respect to the issues of 1) serious bleeding due to severe thrombocytopenia and 2) glomerulonephritis.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
I recommend a postmarketing requirement (PMR) to evaluate pregnancy outcomes, as well as a PMR to characterize thrombocytopenia, glomerulonephritis, and neurologic toxicity (e.g. CNS arterial dissection, stroke, and CNS vasculitis), using data from patients enrolled in the REMS registry. I recommend a PMR to characterize hypersensitivity and cytokine release syndrome occurring within 1 day of inotersen administration.

Recommended Comments to the Applicant
I recommend that a request for enhanced pharmacovigilance with timely reporting and periodic analysis of adverse events of concern (including thrombocytopenia, glomerulonephritis, and neurologic toxicity) be included in the action letter.

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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/

SALLY U YASUDA
10/04/2018

Office of Prescription Drug Promotion

Internal Consults

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Anahita Tavakoli, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Sapna Shah, Regulatory Review Officer, OPDP

CC: Aline Moukhtara, Acting Team Leader, OPDP
Monique Killen, Safety Regulatory Project Manager, OSE
Donna Fitzgerald, Team Leader, DRISK
Robert Pratt, Risk Management Analyst, DRISK
Doris Auth, Associate Director, DRISK
Carole Broadnax, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: October 03, 2018

Re: NDA # 211172
TEGSEDI™ (inotersen) injection, for subcutaneous use (Tegsedi)
Comments on draft Risk Evaluation and Mitigation Strategies (REMS) Materials (Submission date: September 24, 2018)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Tegsedi:

- Healthcare Provider (HCP) REMS Materials:
  - TEGSEDI™ REMS Program Overview
  - TEGSEDI™ REMS Pharmacy Enrollment Form
  - TEGSEDI™ REMS Prescriber Enrollment Form
  - TEGSEDI™ REMS Prescriber Training

- Direct-to-Consumer (Patient) REMS Materials:
  - TEGSEDI™ REMS Patient Enrollment Form
  - TEGSEDI™ REMS Patient Guide
  - TEGSEDI™ REMS Patient Status Form
  - TEGSEDI™ REMS Patient Wallet Card

- TEGSEDI™ REMS Website

The version of the draft REMS materials used in this review were sent from DRISK, Anahita Tavakoli via email on September 24, 2018. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Tegsedi.

General Comment

Please remind the Sponsor that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Healthcare Provider (HCP) REMS Materials:
  - TEGSEDI™ REMS Program Overview
  - TEGSEDI™ REMS Prescriber Training
  - TEGSEDI™ REMS Prescriber Enrollment Form
  - TEGSEDI™ REMS Pharmacy Enrollment Form

- Direct-to-Consumer (Patient) REMS Materials:
  - TEGSEDI™ REMS Patient Enrollment Form
  - TEGSEDI™ REMS Patient Guide
  - TEGSEDI™ REMS Patient Status Form
  - TEGSEDI™ REMS Patient Wallet Card

- TEGSEDI™ REMS Website

Specific Comments

- The proposed REMS materials include statements such as:

  "Report [redacted] (b) (4) serious bleeding [redacted] (b) (4) severe thrombocytopenia and glomerulonephritis to the REMS [redacted] (b) (4)" and "Establish processes and procedures to report [redacted] (b) (4) severe thrombocytopenia, and glomerulonephritis events to the REMS" (TEGSEDI REMS Program Overview)

  "Report events of serious bleeding [redacted] (b) (4) severe thrombocytopenia, and glomerulonephritis. [redacted] (b) (4) " (TEGSEDI REMS Prescriber Enrollment Form [redacted] (b) (4))

- "This pharmacy will establish process and procedures to ensure that adverse events of serious bleeding [redacted] (b) (4) severe thrombocytopenia, and glomerulonephritis are reported to REMS" (TEGSEDI REMS Pharmacy Enrollment Form)

- [redacted] (b) (4) (TEGSEDI REMS Patient Enrollment Form)

- "Report [redacted] (b) (4) to the REMS" (TEGSEDI REMS Prescriber Training)

  - **Risk**
    - Should all adverse events or only REMS specific risks (i.e. severe bleeding due to severe thrombocytopenia and glomerulonephritis) be reported? We defer to DRISK.

      - The Lemtrada REMS Education Program for Healthcare Facilities states (emphasis added):
        - "Report suspected adverse events to Genzyme at Medical Information at 1-800-745-4447 (option 2) or to FDA at 1-800-FDA-1088 or **www.FDA.gov/medwatch**

      - The Myalept REMS Materials states (emphasis added):

- "To report SERIOUS ADVERSE REACTIONS, please call/contact: 1-855-669-2537 and/or FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**"

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- **TEGSEDI™ REMS Program Overview**

  - Page two of the program overview discusses the signs and symptoms of thrombocytopenia.
    - **Risk**
      - We note that the Section 5.2 of the draft PI includes symptoms of thrombocytopenia that have been omitted from this list such as hematoma, hemoptysis, and irregular or heavier than normal menstrual bleeding. We recommend revising this list to be consistent with draft PI.

  - Page two includes the claim, "TEGSEDI may cause glomerulonephritis. The (b) (4) signs and symptoms of glomerulonephritis include. . . [.]"

    - **Risk**
      - (b) (4)

        Furthermore, we note that the draft PI does not include this list of symptoms that are included with this presentation. We defer to DNP as to whether this is an accurate and comprehensive list of signs and symptoms for glomerulonephritis.

  - Page three states, "Assess Patient's platelet count and kidney function." and "Perform ongoing assessments of platelet counts and kidney function." In addition, page four states, "Assess patient's platelet count and kidney function for appropriateness of initiating treatment" and "Assess patient's appropriateness for continuing treatment by monitoring their platelet count and kidney function."

    - **Risk**
      - According to the DOSAGE AND ADMINISTRATION section of the draft PI:

- Assessment Prior to Initiating TEGSEDI

  "Measure platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, and perform urinalysis prior to treatment with TEGSEDI and as directed following treatment initiation. . . [.]"

- Laboratory Testing and Monitoring to Assess Safety after Initiating TEGSEDI

  "Monitor platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin during treatment with TEGSEDI and for 8 weeks following discontinuation of treatment. "

We defer to DNP and DRISK as to whether the above statements should be revised to convey that platelet count, liver and renal function will be monitored (emphasis added).

- Under the "Patient Requirements" section on page five, it says, "The risks associated with TEGSEDI, including serious bleeding and kidney inflammation…" and to "inform your healthcare provider if you have any signs and symptoms of [redacted] (b) (4) and kidney inflammation… [.]" (Emphasis added)
  - **Risk**
    - The phrase "kidney inflammation" omits the following material risk information from the draft Medication Guide (bolded emphasis original, underlined emphasis added):

      kidney inflammation (glomerulonephritis). Your kidneys may stop working properly. Glomerulonephritis can lead to kidney damage and kidney failure that needs dialysis.

      We recommend including this material risk information.

- **TEGSEDI™ REMS Prescriber Enrollment Form**

Risk

- "TEGSEDI is available only through the TEGSEDI REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive TEGSEDI."

    - We recommend including material risk information pertaining to the reasons for the REMS. Specifically, according to the Boxed Warning section of the draft PI (emphasis added):

        - "Because of the risks of serious bleeding due to severe thrombocytopenia and glomerulonephritis, TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program. . . [.]"

- The proposed TEGSEDI REMS Prescriber Enrollment Form includes extensive information pertaining to the type of laboratory tests and frequency for this testing prior to, during, and following treatment discontinuation with Tegsedi. However, we note that some of this information appears to be inconsistent with the draft PI.

  Specifically, according to the Boxed Warning section of the draft PI (in pertinent part) (emphasis added):

  > Prior to starting TEGSEDI, obtain a platelet count [See Dosage and Administration (2.3)]. During treatment, monitor platelet counts [redacted] (b) (4)
  >
  > . . .
  >
  > Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR) and perform a urinalysis [see Dosage and Administration (2.3)]. During treatment monitor serum creatinine [redacted] (b) (4) eGFR [redacted] (b) (4) urinalysis and UPCR every [redacted] (b) (4) weeks.
  >
  > However, we also note that according to the DOSAGE AND ADMINISTRATION section of the draft PI (emphasis added):
  >
  > Assessment Prior to Initiating TEGSEDI
  > Measure platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, and perform

urinalysis prior to treatment with TEGSEDI and as directed following treatment initiation. . . [.]

Laboratory Testing and Monitoring to Assess Safety after Initiating TEGSEDI (emphasis added):

Monitor platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin during treatment with TEGSEDI and for 8 weeks following discontinuation of treatment.

OPDP recommends that the information pertaining laboratory monitoring and frequency for this testing be consistent with the final approved PI.

- **TEGSEDI™ REMS Pharmacy Enrollment Form**
  - "TEGSEDI is available only through the TEGSEDI REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive TEGSEDI."
    - **Risk**
      - We recommend including material risk information pertaining to the reasons for the REMS. Specifically, according to the Boxed Warning section of the draft PI (Emphasis added):
        - "Because of the risks of serious bleeding due to severe thrombocytopenia and glomerulonephritis, TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program. . . [.]"

- **TEGSEDI™ REMS Patient Enrollment Form**
  - "TEGSEDI is available only through the TEGSEDI REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive TEGSEDI."
    - **Risk**
      - We recommend including material risk information pertaining to the reasons for the REMS. Specifically, according to the Boxed Warning section of the draft PI (emphasis added):
        - "Because of the risks of serious bleeding due to severe thrombocytopenia and glomerulonephritis,

TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program. . . [.]"

- By signing below, I attest that prior to prescribing TEGSEDI: I have assessed the patient's platelet count, estimated glomerular filtration rate, urinalysis, and urine protein to creatinine ratio and determined that it is appropriate for this patient to receive TEGSEDI." We recommend that the laboratory monitoring be consistent with the final approved PI.
  - **Risk**
    - According to the Boxed Warning section of the draft PI, platelet counts, <u>serum creatinine</u>, estimated glomerular filtration rate, urine protein to creatinine ratio and urinalysis should be obtained.

    However, we also note that the DOSAGE AND ADMINISTRATION, Assessment Prior to Initiating TEGSEDI section of the draft PI states (emphasis added):

      - "Measure platelet count, <u>serum creatinine</u>, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), <u>alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin</u>, and perform urinalysis prior to treatment with TEGSEDI and as directed following treatment initiation."

- "I have counseled my patient on <u>how to recognize and respond to signs and symptoms of serious bleeding</u> and glomerulonephritis and the need for mandatory ongoing platelet and renal function monitoring" (emphasis added).
  - **Risk**
    - We recommend revising this phrase to read ". . .how to recognize and respond to signs and symptoms of serious bleeding <u>due to severe thrombocytopenia</u> and glomerulonephritis. . . ." in order to adequately convey material risk information from the Boxed Warning section of the draft PI (emphasis added).

- "During treatment every week or more frequently as directed by my healthcare provider, I will: Get a blood test to check my platelet count. During treatment every two weeks, I will: Get a urine test to check my kidneys."
  - **Risk**

        - As previously noted, OPDP recommends that this information be revised, if applicable, to be consistent with the finalized approved PI.

    - "TEGSEDI can cause serious side effects. It can cause low platelet counts that may lead to serious bleeding, and it can cause kidney inflammation and kidney failure."
        - **Risk**
            - To mitigate minimization of risk, we recommend including material risk information from the draft Medication Guide to convey that ". . .serious bleeding <u>could lead to death</u>", and that ". . .Glomerulonephritis can lead to kidney damage and kidney failure <u>that needs dialysis</u>" (emphasis added)

- **TEGSEDI™ REMS Prescriber Training**

    - "TEGSEDI is an antisense oligonucleotide inhibitor for the treatment of human transthyretin (TTR) protein synthesis indicated for treatment of patients with hereditary TTR amyloidosis polyneuropathy (hATTR-PN)."
        - **Indications/Use**
            - This omits the following material information from the INDICATIONS AND USAGE section of the draft PI (emphasis added):

                - TEGSEDI is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis <u>in adults</u>."

            We recommend revising the indication to be consistent with the draft PI.

TEGSEDI REMS Prescriber Training includes very limited information pertaining to the REMS-specific risks of thrombocytopenia and glomerulonephritis. For example, it includes information such as, "Counsel the patient on how to recognize and respond to signs and symptoms of serious bleeding and glomerulonephritis. . . ," "TEGSEDI (b)(4) [redacted] glomerulonephritis," and lists signs and symptoms of thrombocytopenia and glomerulonephritis. However, it omits significant material information associated with the REMS specific risks described in the Boxed Warnings and WARNINGS and PRECAUTIONS sections of the draft PI. OPDP recommends significant revision to mitigate the omission and minimization of risk, and to ensure consistency with the final approved label. For example, we note that Lemtrada REMS Education Program for Prescribers includes extensive information pertaining to the REMS specific risks associated with the drug.

- TEGSEDI must not be initiated in patients with a platelet count less than 100 x 10^9/L. TEGSEDI may cause serious bleeding (b) (4) severe thrombocytopenia" (emphasis added).
  - **Risk**
    - In order to clearly convey this material risk information, we recommend revising this phrase to be consistent with the Boxed Warning draft PI which states, "TEGSEDI is contraindicated in patients with a platelet count. . . [.]" (Emphasis added)

- Page one includes three columns. The first column includes information under the bolded header titled, (b) (4)
  - **Risk**
    - While this information is in Section 5.6 of the draft PI, we note that it is not included with the Boxed Warning and Section 5.1 of the draft PI which discuss the REMS-specific risk of thrombocytopenia. As noted above, we recommend revising this piece to include pertinent material risk information for the REMS-specific risk of thrombocytopenia. For example, according the W&P, thrombocytopenia section of the draft PI:
      - "Three TEGSEDI-treated patients (3%) had sudden severe thrombocytopenia (platelet count below 25 x 109/L), which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage. One patient in a clinical trial experienced a fatal intracranial hemorrhage."
      - "Glucocorticoid therapy is strongly recommended in patients with platelet count (b) (4) 50 x 10^9/L and in patients with suspected immune-mediated thrombocytopenia. Avoid using TEGSEDI in patients for whom glucocorticoid treatment is not advised."

- Page one includes the bolded header titled, "**Thrombocytopenia** (b) (4) (b) (4)" with a list of signs/symptoms of thrombocytopenia
  - **Risk**
    - We note that the Section 5.2 of the draft PI includes symptoms of thrombocytopenia that have been omitted from this list such as hematoma, hemoptysis, irregular or heavier than normal menstrual bleeding. We recommend revising this list to be consistent with draft PI.

- Page one includes the bolded header titled, "**Glomerulonephritis** (b) (4) (b) (4)", the claim "The (b) (4) signs and symptoms of

glomerulonephritis include. . .” with a list of signs/symptoms of glomerulonephritis.

- **Risk**
  - [redacted] (b) (4)

    In addition, we recommend including material risk information from the Boxed Warning section of the draft PI that “If acute glomerulonephritis is confirmed, TEGSDI should be permanently discontinued.”

  - Furthermore, we also note that the draft PI does not include information regarding the signs and symptoms of glomerulonephritis. We defer to DNP as to whether this is an accurate and comprehensive list of signs and symptoms for glomerulonephritis.

- Page one includes information under the bolded header titled, “**What is the TEGSEDI REMS?**” Specifically, under the third bullet, “<u>the need to have platelet count and renal function monitored</u>” (emphasis added).
  - **Risk**
    - According to the DOSAGE AND ADMINISTRATION, Laboratory Testing and Monitoring to Assess Safety after Initiating TEGSEDI of the draft PI:

      - “Monitor platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), <u>alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin</u> during treatment with TEGSEDI and for 8 weeks following discontinuation of treatment.”

    We defer to DNP and DRISK as to whether this should be revised to “The need to have platelet count, <u>hepatic</u> and renal function monitored” (emphasis added).

- Page one includes information under the bolded header titled, “**What is the TEGSEDI REMS?**” Specifically, the forth bullet, “Enrolling all patients in a registry to further <u>support long-term safety</u> and safe use of TEGSEDI” (emphasis added).
  - **Risk**

- This seems promotional in tone and suggests that "long-term safety" has been established with Tegsedi. We defer to DRISK as to whether this phrase can be revised ". . .to evaluate long-term safety. . .[.]"

The proposed TEGSEDI Prescriber Training includes similar claims from the prescriber enrollment form pertaining to specific laboratory tests and frequency for this testing prior to, during, and after treatment discontinuation with Tegsedi. As previously noted, OPDP recommends that this information is revised, if applicable, to be consistent with the final approved PI.

- **TEGSEDI™ REMS Patient Guide**
  - Page one states, [redacted] (b) (4)
    - **Indications/Use**
      - We recommend revising the indication (i.e. abbreviations) to be consistent with the 9/26/2018 version of the draft Med Guide. In addition, it omits material information that safety and efficacy has not been established in pediatrics. Specifically, according to the draft Med Guide, "TEGSEDI is a medicine used to treat polyneuropathy [redacted] (b) (4) with hereditary transthyretin-mediated (hATTR) amyloidosis. It is not known if TEGSEDI is safe and effective in children. (Emphasis added). We recommend revising the indication to be consistent with the medication guide.
  - Page one states, [redacted] (b) (4)
    - **General Comment**
      - This information is promotional in tone and may create a misleading information about the benefits of the drug. We note that this information has been removed from th draft Med Guide. Therefore, OPDP recommends deletion.
  - Page one states, "TEGSEDI can cause serious side effects such as serious bleeding caused by low platelet count (thrombocytopenia) and [redacted] (b) (4). Please talk about these side effects with your doctor" (emphasis added).
    - **Risk**
      - To mitigate minimization of risk, we recommend including material information from the draft Medication Guide to convey that ". . .Glomerulonephritis can lead to kidney damage and kidney failure that needs dialysis" (emphasis added)

In addition, we recommend revising the phrase, (b) (4) [redacted] to "kidney inflammation (glomerulonephritis) and kidney failure" for consistency with the draft Med Guide and to accurately describe this risk.

- Page one states, (b) (4) [redacted]
  - **Risk:**
    - This is promotional in tone and we note that this information has been removed from the draft Med Guide. We recommend deleting these two sentences and revising this information to be consistent with the draft Med Guide, which states, "TEGSEDI may cause the number of platelets in your blood to be reduced."

    - In addition, we recommend including material risk information from the Med Guide that, "This is a (b) (4) [redacted] common side effect of TEGSEDI."

- Page one states, "The signs and symptoms of low platelet count may include:"
  - **Risk**
    - We recommend including material risk information from the draft Medication Guide to "**Call your healthcare provider right away if you have" any of the signs and symptoms listed below** (emphasis original).

- Page one states includes the signs and symptoms of low platelet count.
  - **Risk**
    - We note that the draft Med Guide as well as Section 5.2 in the draft PI includes additional symptoms of thrombocytopenia. (i.e., "vomiting or coughing up blood" and "abnormal or heavy periods (menstrual bleeding)". We recommend adding these additional symptoms to be consistent with the draft Med Guide and draft PI.

- Under the bolded "**Kidney inflammation and kidney failure**" header on page one, it states, "Your kidneys may stop working properly. (b) (4) [redacted]. The (b) (4) [redacted] signs and symptoms of kidney inflammation include:" (emphasis added).
  - **Risk**
    - (b) (4) [redacted]

[redacted] (b) (4)

- Under the bolded "**What is TEGSEDI REMS?**" section on page one, it states, "Because of the risks associated with TEGSEDI…"
  - **Risk**
    - This omits material risk information regarding the reasons for the REMS. Specifically, according to draft Med Guide, "Because of the risk of serious bleeding because of low platelet count and kidney problems, [redacted] (b) (4) …[.]" (Emphasis added) OPDP recommends including this material risk information.

      For example, the Lemtrada REMS Program Overview, it states "Due to serious risks of autoimmune conditions, infusion reactions, and malignancies…[.]"

- Under the bolded "**What is TEGSEDI REMS?**" section on page one, it states, "Both you and your doctor must sign the [redacted] (b) (4) Patient Enrollment Form for you to receive TEGDESI."
  - **Risk**
    - We note that this omits material information from Section 5.3 of the draft PI which states, "Patients must enroll and comply with ongoing monitoring requirement." According to the draft Medication Guide, "You must agree to get your laboratory testing done while you are in the TEGSEDI REMS Program." (Emphasis original) We recommend including this material information pertaining to the REMS requirements.

- On page two, it states, "Your doctor will test your blood and urine to check your platelet count and kidney function before you start TEGSEDI."
  - **Risk**
    - According to the DOSAGE AND ADMINISTRATION, Assessment Prior to Initiating TEGSEDI (Emphasis added):

      - "Measure platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, and perform urinalysis prior to treatment with TEGSEDI and as directed following treatment initiation. . . [.]"

We defer to DNP and DRISK as to whether this should be revised to "Your doctor will test your blood and urine to check your platelet count, kidney and liver function before you start TEGSEDI" (emphasis added).

- **TEGSEDI™ REMS Patient Status Form**

  The TEGSEDI REMS Patient Status Form includes information pertaining to specific laboratory tests and frequency for this testing prior to, during, and after treatment discontinuation with Tegsedi. As previously noted, OPDP recommends that this information is revised, if applicable, to be consistent with the final approved PI.

- **TEGSEDI™ REMS Patient Wallet Card**

  - "Call your doctor or go to the emergency room RIGHT AWAY if you have any of these symptoms…Bleeding into the whites of your eyes…[.]"
    - **Risk**
      - We note that the draft Medication Guide includes additional symptoms of thrombocytopenia. (i.e., "vomiting or coughing up blood" and "abnormal or heavy periods (menstrual bleeding))". We recommend adding these additional symptoms to be consistent with the draft Med Guide.

  - "This patient is receiving TEGSEDI for the treatment of (b) (4)
    - **Indications/Use**
      - This omits material information from the draft PI and Medication Guide that Tegsedi is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. We recommend including this material information regarding the FDA-approved indication.

  - "TEGSEDI has a risk of serious bleeding (b) (4) severe thrombocytopenia and a risk of glomerulonephritis."
    - **Risk**
      - This omits the material risk information from the Boxed Warning section of the draft PI that the severe thrombocytopenia with Tegsedi can be "sudden and unpredictable. . .serious or life-threatening", and that Tegsedi ". . .can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure".

We recommend including this material risk information as the wallet card is intended for healthcare providers who may not be familiar with the REMS-specific risks.

- "Patients treated with TEGSEDI are being regularly monitored for these risks via the following lab results: platelets, estimated glomerular filtration rate (eGFR), urinalysis, and urine protein to creatinine ratio (UPCR)".
  - **Risk**
    - We recommend that this be revised, if applicable, to be consistent with the final approved PI. Specifically, according to the DOSAGE AND ADMINISTRATION, Laboratory Testing and Monitoring to Assess Safety after Initiating TEGSEDI, section of the PI (emphasis added):
      - "Monitor platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis, urine protein to creatinine ratio (UPCR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin during treatment with TEGSEDI and for 8 weeks following discontinuation of treatment."

- **TEGSEDI™ REMS Website**

  - **Risk**
    - The proposed Tegsedi REMS Website includes very limited information pertaining to the REMS-specific risks of thrombocytopenia and glomerulonephritis. In addition, it omits significant material information associated with these risks as described in the Boxed Warnings and WARNINGS and PRECAUTIONS sections of the draft PI. OPDP recommends significant revision to mitigate the omission and minimization of risk, and to ensure consistency with the final approved label.

- Page two presents risk information under the bolded header titled, "**What is the TEGSEDI REMS** (b) (4)? Specifically, (b) (4)
  - **Risk**

- As previously noted, OPDP recommends that this information be revised, if applicable, to be consistent with the final approved PI.

o We also note that the proposed TEGSEDI REMS Website states, (b) (4) [redacted] The term (b) (4) is ambiguous. Should this be revised to convey that adverse reactions should be reported to the Sponsor and/or the FDA? We defer to DRISK.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

SAPNA P SHAH
10/03/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 1, 2018

To: Nick Kozauer
Division of Neurology Products (DNP)

Fannie Choy, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for TEGSEDI (inotersen) injection, for subcutaneous use

NDA: 211172

In response to DNP consult request dated December 5, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for TEGSEDI (inotersen) injection, for subcutaneous use (Tegsedi).

PI: OPDP's comments on the proposed labeling are based on the draft PI retrieved from the DNP Sharepoint on September 28, 2018, and are provided below.

Medication Guide and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on September 26, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 27, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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Reference ID: 4328677

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/

DHARA SHAH
10/01/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 28, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211172
Product Name and Strength:	Tegsedi (inotersen) injection 284 mg/1.5 mL
Applicant/Sponsor Name:	Ionis Pharmaceuticals, Inc.
FDA Received Date:	September 27, 2018
OSE RCM #:	2017-2310-2
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container label and container labeling for Tegsedi (inotersen) injection (Appendix A) to determine if they are acceptable from a medication error perspective. We previously reviewed the draft label and labeling for Tegsedi, submitted to the Agency on April 12, 2018, and found the drafts to be acceptable from a medication error perspective.[a]

2 CONCLUSION

The revised container label and container labeling for Tegsedi (inotersen) injection is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rider B. Label and Labeling Review for Tegsedi (NDA 211172). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 17. RCM No.: 2018-2310-1.

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/s/

BRIANA B RIDER
09/28/2018

LOLITA G WHITE
09/28/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 26, 2018
To:	William Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline Moukhtara, RN, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	TEGSEDI (inotersen)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 211172
Applicant:	Ionis Pharmaceuticals, Inc.

1 INTRODUCTION

On November 6, 2017, Ionis Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application (NDA) for inotersen for the indication of treatment of hereditary transthyretin amylodisos [redacted] (b) (4) This application was granted Fast Track designation and Priority review status due to the seriousness of the treated condition and the significant improvement in effectivenss this product would provide, if approved.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on December 4, 2017, for DMPP and OPDP to review the Applicant's proposed MG and IFU for inotersen.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 17, 2018.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DNP under separate cover.

2 MATERIAL REVIEWED

- Draft TEGSEDI (inotersen) MG and IFU received on August 1, 2018, and received by DMPP and OPDP on September 13, 2018.
- Draft TEGSEDI (inotersen) Prescribing Information (PI) received on November 6, 2017 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 13, 2018.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labelings where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
09/26/2018

ALINE M MOUKHTARA
09/26/2018

LASHAWN M GRIFFITHS
09/26/2018

Ophthalmology Consult Review #2 of NDA 211-172

NDA 211-172
IND 113,968

Submission Date: February 5, 2018
Review completed: September 5, 2018

Name: Tegsedi (inotersen)
Applicant: Ionis Pharmaceutics, Inc.
Class: Antisense oligonucleotide inhibitor of human transthyretin (TTR) protein synthesis

Submitted: Response to Agency Information Request
Ionis Pharmaceuticals, Inc. provided the following information in response to the Agency's request for information pertaining to ophthalmologic assessments.

Reviewer's Comment: *Comments are limited to areas of ophthalmic concern. The Agency's first two questions to the applicant in the Agency Information Request are related to renal function and are not included in this review.*

Question 3: Clarify whether the minimum standards for ERGs set by the International Society for Clinical Electrophysiology of Vision (ISCEV) were followed. Submit a copy of the specific protocol used for ERG testing.

Response: ERGs were collected following the standards set forth by the ISCEV (2008) and as described in the protocol used for the study: ISIS 420915 ERG Qualification and Study Instructions document (Appendix 3).

Reviewer's Comment: *Acceptable.*

Question 4: The definition of vitamin A deficiency is not clear in the protocol. The definition used for the study report should be submitted.

Response: …For monitoring purposes, the protocol used a definition of vitamin A deficiency based on changes in ERG (criteria discussed in Question 7).

For stopping criteria, the protocol used a definition of vitamin A deficiency that relied on both ERG changes and the presence of physical signs in the eye consistent with vitamin A deficiency (Bitot's spots, xerophthalmic ulcers, keratomalacia, or other signs and symptoms of corneal necrosis).

The clinical study reports assessed vitamin A deficiency in 2 ways: (1) based upon ERG findings (criteria discussed in Question 7), and (2) based on an analysis of the adverse event of special interest 'ocular AEs related to vitamin A deficiency'. Because there is no MedDRA SMQ specific to ocular toxicities related to vitamin A deficiency, the analysis of 'ocular AEs

Reference ID: 4315945

related to vitamin A deficiency' was conducted through a broad, concatenated MedDRA search that was defined as: AE within HLT: fat soluble vitamin deficiencies and disorders; PT: vitamin A decreased or vitamin A abnormal. AE within SMQ: optic nerve disorders, corneal disorders, retinal disorders

Reviewer's Comment: *Acceptable.*

Question 5: The criteria used to identify a patient as having a vitamin A deficiency should be submitted.

Response: Please see the response to Question 4.

Reviewer's Comment: *Acceptable.*

Question 6: The specific light stimuli, light adaptation, and portion of the generated waveform used to identify a "change from baseline > 50%" should be submitted.

Response: ISCEV guidelines recommend that several stimulus conditions be used (McCulloch et al. 2015). In this trial, four different ERG stimuli were used to examine rod and cone pathway function. … An ERG was considered to change significantly after treatment started if the amplitude of the a- or b-wave changed by more than 50% from the baseline ERG or the amplitudes decreased to below the labs normal ranges.

Reviewer's Comment: *Acceptable.*

Question 7: The criteria used to identify a vitamin A deficiency on an ERG should be submitted.

Response: The criterion for the clear signs of vitamin A deficiency as assessed by ERG were developed based on published literature. … Based on these published papers, the following criteria were used by the central reader to determine if any change in an ERG could have resulted from a vitamin A deficiency. All 3 conditions must be present to suggest a vitamin A deficiency based solely on the ERG.

1. The a- or b-wave amplitudes must be less than 50% of the baseline ERG values or if the baseline values were normal, subsequent ERGs are below the labs normal ranges.
2. The deficit must be the greatest for the DA 0.01 ERG stimulus condition and the least or not present for the LA 3.0 or LA 3.0 30 Hz flicker stimulus conditions.
3. The ERG changes should be similar in both eyes.

Reviewer's Comment: *Disagree with the definition used to determine if any change in an ERG could have resulted from a vitamin A deficiency. Consequently, each of the ERGs in question was reviewed. Based on a review of the submitted ERGs, while a number of the ERGs were abnormal, I do not believe that any of the patients demonstrated a vitamin A deficiency.*

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Question 8: The ERGs for any patient considered to have an abnormal ERG should be submitted along with identification of why each one was considered abnormal.

Response: All ERG waveforms for any patient with at least 1 abnormal ERG are located in Appendix 4. A listing of CS2 patients with at least one abnormal ERG result is given in Appendix 4. In Part 1, the central readers description of the abnormality is given. A listing of CS3 patients with at least one abnormal ERG result is given in Appendix 4. In Part 1, the central readers description of the abnormality is given.

Reviewer's Comment: *Each of the ERGs in question was reviewed. Based on a review of the submitted ERGs, while a number of the ERGs were abnormal, I do not believe that any of the patients demonstrated a vitamin A deficiency.*

Question 9: The ERG findings of any patient considered to have an ERG showing a vitamin A deficiency should be submitted along with the results of the corresponding ophthalmic examination and the findings of the central reader.

Response: There were 14 patients with at least one ERG finding compatible with vitamin A deficiency as assessed by the central reader (Table 1). A listing of the ERG results for each of these patients is given in Appendix 5. The central readers description of the findings can be found in part 1 of the listings. The corresponding ERG waveforms for each patient are located in Appendix 4. An ophthalmology listing for each of the 14 patients is given in Appendix 5. All but 3 of the ophthalmology examinations corresponding temporally to the ERG examination that was consistent with vitamin A deficiency (Appendix 5).

Reviewer's Comment: *None of the clinical findings demonstrated "classic" findings consistent with vitamin A deficiency. There are a number of patients with dry eye syndrome. It is not possible to distinguish whether the dry eye syndrome is related to the disease being treated, the treatment or another cause.*

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CS2 On-Study Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency (CS2 Safety Set)

	Placebo (N=60)		Inotersen 300 mg (N=112)	
	Subjects, n (%)	Number of	Subjects, n (%)	Number of Events
Ocular TEAEs potentially related to vitamin A	12 (20%)	13	23 (21%)	25
Deficiency				
Corneal disorder	1 (2%)	1	0	0
Deposit eye	1 (2%)	1	2 (2%)	2
Detachment of retinal pigment epithelium	1 (2%)	1	0	0
Dry eye	2 (3%)	2	4 (4%)	4
Dyschromatopsia	1 (2%)	1	0	0
Eye disorder	0	0	1 (1%)	1
Eye irritation	0	0	1 (1%)	2
Foreign body in eye	1 (2%)	1	0	0
Keratitis	2 (3%)	2	0	0
Macular edema	0	0	1 (1%)	1
Ophthalmological examination abnormal	0	0	2 (2%)	2
Photophobia	1 (2%)	1	0	0
Retinal detachment	0	0	1 (1%)	1
Retinal vein occlusion	0	0	1 (1%)	1
Ulcerative keratitis	0	0	1 (1%)	1
Vision blurred	1 (2%)	1	2 (2%)	2
Visual acuity reduced	1 (2%)	1	0	0
Visual field defect	0	0	1 (1%)	1
Visual impairment	0	0	1 (1%)	1
Vitamin D deficiency	0	0	3 (3%)	3
Vitreous disorder	1 (2%)	1	0	0
Vitreous floaters	0	0	3 (3%)	3
Risk difference, %			0.5	
95% CI			-12.1, 13.1	

Source: Table 59, Module 5.3.5.1, CS2 CSR, Table 4.107 and Table 4.114

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

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CS3 On-Study Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency (CS3 Safety Set)

Category Preferred Term	Placebo-Inotersen (N=40)		Inotersen-Inotersen (N=74)		Total (N=114)	
	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events
Ocular TEAEs potentially	4 (10%)	7	6 (8%)	7	10 (9%)	14
related to vitamin A deficiency						
Visual acuity reduced	0	0	2 (3%)	2	2 (2%)	2
Corneal irritation	0	0	1 (1%)	1	1 (1%)	1
Deposit eye	2 (5%)	4	1 (1%)	1	3 (3%)	5
Keratitis	0	0	1 (1%)	1	1 (1%)	1
Retinal hemorrhage	0	0	1 (1%)	1	1 (1%)	1
Vision blurred	0	0	1 (1%)	1	1 (1%)	1
Corneal perforation	1 (2%)	1	0	0	1 (1%)	1
Ulcerative keratitis	1 (2%)	1	0	0	1 (1%)	1
Vitamin D deficiency	1 (2%)	1	0	0	1 (1%)	1

Source: Table 60, Module 5.3.5.2, CS3 CSR, Table 4.99

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

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Longitudinal Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency (Longitudinal Safety Set)

Category Preferred Term	Inotersen 300 mg (N=112)	
	Subjects, n (%)	Number of Events
Ocular TEAEs potentially related to vitamin A deficiency	26 (23%)	32
Dry eye	4 (4%)	4
Deposit eye	3 (3%)	3
Vitamin D deficiency	3 (3%)	3
Vitreous floaters	3 (3%)	3
Vision blurred	2 (2%)	3
Ophthalmological examination abnormal	2 (2%)	2
Visual acuity reduced	2 (2%)	2
Eye irritation	1 (1%)	2
Corneal irritation	1 (1%)	1
Eye disorder	1 (1%)	1
Keratitis	1 (1%)	1
Macular edema	1 (1%)	1
Retinal detachment	1 (1%)	1
Retinal hemorrhage	1 (1%)	1
Retinal vein occlusion	1 (1%)	1
Ulcerative keratitis	1 (1%)	1
Visual field defect	1 (1%)	1
Visual impairment	1 (1%)	1

Source: Table 61, Module 5.3.5.2, CS3 CSR, Table 4.39

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

Reference ID: 4315945

Inotersen Integrated Set Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency

Category Preferred Term	Inotersen 300 mg (N=152)	
	Subjects, n (%)	Number of Events
Ocular TEAEs potentially related to vitamin A deficiency	30 (20%)	39
Deposit eye	5 (3%)	7
Dry eye	4 (3%)	4
Vitamin D deficiency	4 (3%)	4
Vitreous floaters	3 (2%)	3
Vision blurred	2 (1%)	3
Ophthalmological examination abnormal	2 (1%)	3
Ulcerative keratitis	2 (1%)	2
Visual acuity reduced	2 (1%)	2
Eye irritation	1 (1%)	2
Corneal irritation	1 (1%)	1
Corneal perforation	1 (1%)	1
Eye disorder	1 (1%)	1
Keratitis	1 (1%)	1
Macular edema	1 (1%)	1
Retinal detachment	1 (1%)	1
Retinal hemorrhage	1 (1%)	1
Retinal vein occlusion	1 (1%)	1
Visual field defect	1 (1%)	1
Visual impairment	1 (1%)	1

Source: Table 62, Table 2.09

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

Reference ID: 4315945

Response to Original Review Division's Questions:

1. Please evaluate the clinical study adverse event data and electroretinogram (ERG) data for evidence of ocular toxicity related to vitamin A deficiency.

Response: *No specific pattern of ocular adverse events was identified. ERG data did not demonstrate a pattern of vitamin A deficiencies.*

2. Please comment on whether the Sponsor adequately evaluated for ocular toxicity related to vitamin A deficiency in clinical studies of inotersen. If applicable, provide recommendations for further evaluation.

Response: *Yes. The applicant adequately evaluated the potential of ocular vitamin A deficiency. No evidence of vitamin A deficiency was noted on the ocular evaluations.*

3. Please comment on the adequacy of the Sponsor's proposed labeling (b) (4) The Sponsor's labeling (titled "proposed") can be obtained via this link: \\CDSESUB1\evsprod\NDA211172\0001\m1\us\114-label\1141-draft-label

Response: *I agree with the applicant's proposal to recommend that patients take oral supplementation of the recommended daily allowance (RDA) of vitamin A (approximately (b) (4) vitamin A per day) and that Vitamin A supplementation be continued throughout treatment. I agree with the applicant's proposal* (b) (4)

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

Reference ID: 4315945

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/s/

WILEY A CHAMBERS
09/05/2018

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

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Date	3/26/2018
To	Dahlia Walters, RPM OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Center/Office	*CDER/OPQ*
OND Review Division	*DNP*
From	*Jacqueline M Gertz* *CDRH/ODE/DAGRID/GHDB*
Through (Team Lead)	*John McMichael* *CDRH/ODE/DAGRID/GHDB*
Through (Branch Chief)	*CAPT Alan Stevens* *CDRH/ODE/DAGRID/GHDB*
Subject	*Consult for NDA 211172* *ICCR2017-01947* *ICC1700930*
Filing Recommendation	*Recommendation Date:* *Device Constituents Parts of the Combination Product are Acceptable for Filing*
Final Recommendation	*Recommendation Date:* *Device Constituents Parts of the Combination Product are Approvable*

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01947
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=2180
ICC tracking # (Lead)	ICC1700930
Submission Number	NDA 211172
Sponsor	Ionis pharmaceuticals
Drug/Biologic	Inotersen Solution
Indications for Use	Treatment of hereditary transthyretin amyloidosis [redacted] (b) (4)
Device Constituent	Prefilled syringe
Related Files	N/A

Table 2. Review Team		
Were other disciplines consulted?	☐Yes	☒ No

Table 3. Important Dates	
1st round of Information Requests	1/17/2018
Final Lead Device Review Memo Due	4/12/2018
Interim Due Dates	**Due Date**
Filing	12/7/2017
Mid-Cycle	2/15/2018
Internal meeting	4/13/2018
Wrap up meeting	6/1/2018
PDUFA/GDUFA Due Date	7/6/2018

Reference ID: 4332709

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Reference ID: 4332709

2. PURPOSE/BACKGROUND

2.1. Scope

CDER is requesting approval of the Inotersen solution. The device constituent of the combination product is a prefilled glass syringe with a needle safety device.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product on 2/12/2018: OND is requesting a Device consult for the Inotersen solution.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent
- Sterility of the device constituent if applicable

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Device facilities

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

CDRH has no prior interaction with the sponsor. CDER's interactions can be seen in the table below.

Reference ID: 4332709

Table 1 Regulatory History and eCTD Location of Information Addressing FDA's Agreements/Recommendations

Type of Correspondence / Date	Agency Agreements/Recommendations	eCTD Location(s)
Special Protocol Assessment (SPA) – Clinical (March 6, 2013)	Recommendations on the trial design for the pivotal Phase 2/3 study CS2	Module 1.6.3 Type A Meeting Minutes and Clarification
Special Protocol Assessment (SPA) – Carcinogenicity (December 1, 2015)	Recommendations on the study design for a 6-month and 24-month carcinogenicity study.	Module 1.8.2 (SPA) Module 4.2.3.4.2 (6-month study)
Informal Email (October 18, 2016)	A Thorough QT (TQT) Study Waiver was granted for ISIS 420915.	N/A
Type C Meeting -WRO (nonclinical/ clinical) (April 5, 2017)	Concurrence to submit long-term carcinogenicity study post-approval Waiver of the requirements of the Pediatric Research Equity Act (PREA) Presentation/ content of the ISS/ ISE Presentation/ content of the Clinical Summary of Safety (CSS) Dataset format for studies CS1, CS2 and CS3	Module 1.6.3 Type C Meeting Minutes including clarification Module 1.9.1 (PREA) Module 5.3.5.3 (ISS/ISE) Module 2.7.4 (CSS) Module 5.3.4.1 (CS1) Module 5.3.5.1 (CS2) Module 5.3.5.2 (CS3)
Informal Email (May 23, 2017)	Concurrence was received from DMEPA on the design of the protocol for the Human Factors Study.	Module 1.14.1.4 (Human Factors Study – Final Report)
Type C Meeting -WRO (CMC) (July 24, 2017)	Stability data package to be included in the NDA submission/ comparability of synthetic routes used during development	Module 1.6.3 (Meeting Minutes – Written Response)
Informal Call (June 19, 2017)	A Safety Update will be provided 90 days after submission of the initial NDA.	N/A
Pre-Submission Safety Request (July 24, 2017)	Sponsor agreed to provide additional safety-related information requested by the Agency	Module 1.6.3 Annotated document

2.2.1. Related Files

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use

Reference ID: 4332709

Inotersen Solution	Treatment of hereditary transthyretin amyloidosis (b) (4)
Syringe	Delivery of the drug product
Route of Administration	Subcutaneous

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Labeling	1.14.1
Risk evaluation and mitigation strategy supporting document	1.16.2
Common Technical Document Summaries	Module 2
Quality	3.2
Regional	3.2.R
Proposed risk evaluation and mitigation strategy	1.16.1
Pharmaceutical-Development - containclose	3.2.P.2.4
Reg-info.pdf	3.2.r

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The following information was taken from GSR 2.3.P.2 Pharmaceutical Development:

The container closure system for Inotersen (b) (4) Injection is composed of a PFS, which consists of a (b) (4) 2.25 mL, clear glass syringe barrel with a (b) (4) 8 mm staked needle with a rigid needle shield with an (b) (4) The syringe barrel is stoppered with a (b) (4) plunger stopper. The prefilled syringe is assembled into a safety syringe device (SSD), to deliver an injection volume of 1.5 mL (284 mg) per dose.

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Reference ID: 4332709

Instructions for use

(b) (4)

[redacted]

Device Description Stock IR

Device Description Recommendation		
The Sponsor Provided Complete Device Description for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Device Description for the Device Constituent		☐
Device Description Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day Letter IRs - # Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

5. FILING REVIEW

Reference ID: 4332709

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

Filing Review Stock IR

Filing Recommendation		
Filing Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day-letter IRs - #	
The device constituent content in the submission for the combination product is acceptable for filing		☒
The device constituent content in the submission for the combination product is acceptable for filing, CDRH has Information Requests to include in the 74-Day letter, See Section 11.2		☐
The device constituent content in the submission for the combination product is acceptable for filing, See Section 11.1 for Filing Information Requests		☐

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

Table 4: Design Control Documentation Check

Design Control Requirement	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		Reg-info.pdf
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		Reg-info.pdf
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		Pharmaceutical-development-containclos.pdf

Master File Review Instructions

FDA 21 CFR 820.30 - Design Review:
The outputs from the design verification and validation are summarized in formal reports that are distributed to all relevant functions in order that the output is appropriately shared and reviewed.
As part of (b) (4) *review process, technical design reviews are undertaken with key stakeholders to ensure the Safety Syringe Device design is fit for purpose prior to moving to the next development phase. Reviews of design data are undertaken within the medicines process delivery (MPD) project team and within the Department line.*

Master File Stock IR

Reference ID: 4332709

The following design validation information is found in GSR 3.2.P.2.4 Container closure system:
Design input requirements:
4.5.1 Safety Syringe Design Input Requirements

(b) (4)

[redacted]

Design Controls Recommendation		
The Sponsor Provided Complete Design Controls for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Design Controls for the Device Constituent		☐
Design Control Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

Table 5: Summary of Design V&V Attributes

Reference ID: 4332709

The Sponsor submitted this information in Pharmaceutical-Development -containclose: 3.2.P.2.4

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		X		
To-be-marketed device was used in the pivotal clinical trial?				X
Selectable dose range on device matches the labeled dose range for the medication?				X
Verification methods relevant to specific use conditions as described in design documents and labeling		X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		X		
Traceability demonstrated for specifications to performance data			X	
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	X		
	ISO 11608-2:2012 – Needles	X DMF		
	ISO 11608-5:2012 – Automated Functions	X		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		X		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility - ISO 10993 sections 4, 5, 10, 11	X		
	Sterility	X		

Referenced Standards and Guidance Documents

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
Iso 11040-4	Glass barrel for injectables	X	
[redacted] (b) (4)		X	
ISO 10993 part 1, 4, 5, 7, 10, 11, 18	Biological evaluation of medical devices	X	
[redacted] (b) (4)		X	
ISO 7864	Sterile hypodermic needles for single use	X	
[redacted] (b) (4)		X	

7.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device	X		

The following design input information is found in GSR section 3.2.R.3.1:

Reference ID: 4332709

3 DESIGN INPUT

(b) (4)

[redacted]

The following device supplier information is found in GSR section 3.2.R.4.5 SSD Material Selection

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Reference ID: 4332709

The purpose of design validation is to demonstrate that the developed SSD conforms to the defined user needs and intended uses. Since the SSD employs the same injection technique as the Phase 3 syringe, design validation for the safety syringe involved human factors validation through simulated use. A summary of the human factors validation study is provided below.

Design changes:

During the development of the [redacted] (b) (4)

The cause of the failure was identified as a combination of the following areas:

• *The potential for the safety shield failing to activate if the plunger rod is not fully depressed. (The user misinterprets an audible click as the end of stroke)*

• *The device handling for users with reduced manual dexterity had to be fully allowed.*

The following areas were proposed as design options that could target those failure modes:

• *Minimising the activation time by* [redacted] (b) (4).

• *Reducing actuation force* [redacted] (b) (4)

• *Reduce impact of unintentional actuation*

[redacted] (b) (4) *identified the root cause of this issue, and identified an engineering solution to address it. With the engineering solution in place, it was shown through in vitro testing* [redacted] (b) (4) *and formative human factors testing* [redacted] (b) (4) *that the issue had been mitigated.*

Reviewer Comment: DMEPA completed a review of the Human factors testing and identified that the safety needle locking mechanism failed repeated. The Sponsor cites the [redacted] (b) (4) as the cause and states that they have mitigated this problem [redacted] (b) (4), but did not perform an additional human factors study to verify this mitigation.

IR response received 1/29/2018 – additional studies were conducted with the devices with [redacted] (b) (4) The safety needle locking mechanism failed on those with [redacted] (b) (4) and those with [redacted] (b) (4) passed. Additionally, samples of both devices were sent to FDA. Those with [redacted] (b) (4) activated the safety needle correctly. DMEPA also reviewed this problem and has found it acceptable.

All submitted documents state the design input requirements citing standards and guidances and a complete design history file.

Clinical Validation Stock IR

Reference ID: 4332709

Design Validation Recommendation		
The Sponsor Provided Complete Design Validation for the Device Constituent		☐
The Sponsor **DID NOT** Provide Complete Design Validation for the Device Constituent		☐
Design Validation Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☒
There are Complete Response Deficiencies, See Section 12		☐

Reference ID: 4332709

7.3. Design Verification Review

7.3.1. Design Verification Testing Summary

Essential Functional Requirements						
	N/A	**Acceptance Criteria**	**Method Acceptable**	**Results/ Deviations**	**Adequate**	
					Yes	**No**
Dose Accuracy		(b) (4) [redacted]	ISO 11608	1.5 – 1.6 mL	X	
Break Loose Force			(b) (4) [redacted]	7-9.5N	X	
Glide Force				5.25-6.13N	X	
Visual/Audible Feedback					X	
Device Requirements						
	N/A	**Acceptance Criteria**	**Method Acceptable**	**Results/ Deviations**	**Adequate**	
					Yes	**No**
Injection Depth		(b) (4) [redacted]	Entire needle	8mm	x	
Injection time					X	
Needle Connection Type	X					
Needle Resistance to Bend/Fracture			(b) (4) [redacted]		x	
Seal Integrity Testing[1]			(b) (4) [redacted]	All units tested had absorbance results less than the system sensitivity absorbance obtained in the same run, which denotes that the seal integrity of the units were intact	x	
Separation Force	X					

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Unscrewing Torque	X					
Ease of Assembly	X					
Resistance to Overriding	X					
Stress Cracking	X					
Validation of Graduation Markings	X					
Dead Space	X			Only for insulin		
Coring Needle Test			(b) (4)		X	
Anti-Needle Stick Performance testing[2]		(b) (4) to activate	Bench testing and simulated clinical use testing	No failures	X	
Connectivity to other devices necessary for use[3]	X					
Tip cap removal force		(b) (4)		(b) (4)	x	
Piston seal blowback[4]	X					
Sterility		(b) (4)		(b) (4)	X	

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				[redacted] (b) (4)		

[1]to assess liquid leakage, air ingress, and dye ingress once the syringe is filled with the drug or biologica [redacted] connecting device. The sensitivity of the selected test method should be specified and validated. System integrity should be demonstrated throughout the product shelf-life.
[2]of an anti-needlestick mechanism with a glass syringe to demonstrate safety and effectiveness as recommended in FDA's guidance document, "Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features " (August 2005).
[3] [redacted] (b) (4)
[4]

7.3.2. Environmental Conditioning Testing

All Essential Functional Requirements Evaluated under normal and stressed conditioning				
		Adequate	Inadequate	N/A
Normal/Anticipated Conditions	In-Use atmosphere	pass		
	Last-Dose Accuracy	Single use		
	Life-Cycle Testing			X
Challenge/Stressed Conditions	Free-Fall	ISO 11608		
	Dry heat/cold storage	Pass		
	Damp Heat	Pass		
	Cyclical			X
	Vibration			X

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	Transportation, storage, handling	Shelf life 18 months at 2-8C, 6 weeks at 30C No adverse effect with (b) (4) (b) (4)		

Reference ID: 4332709

7.3.3. Biocompatibility Review

Biocompatibility Review Instructions

Biocompatibility Evaluation		
Materials List	Plunger	(b) (4) [redacted]
	Syringe Body	
	Needle	
	Accessories	
Additives/Colorants	None	
Device Characteristics		
Category	☐ External communicating device	
Contact Type	☒ Blood path, indirect ☐ CSF contacting[1] [1]consult biocompatibility consultant	
Contact Duration	☒ ≤24h (limited) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), and Material-mediated Pyrogenicity ☐ >24h to 30 days (prolonged) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, and Subchronic systemic toxicity ☐ >30 days (permanent) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, Subchronic systemic toxicity, and Genotoxicity *Notes:* *The endpoints included in the biocompatibility evaluation of the needle are dependent on the type and duration of contact. Below are the recommended endpoints for blood path, indirect, which are applicable for both subcutaneous and intramuscular injections. If the needle is CSF contacting, information may be needed to support the evaluation of the neurotoxicity endpoint.*	
Testing Performed	☒ Cytotoxicity ☒ Sensitization ☒ Irritation or Intracutaneous Reactivity ☒ Acute System Toxicity ☒ Material-Mediated Pyrogenicity	☐ Subacute/Subchronic Toxicity ☐ Genotoxicity ☒ Hemocompatibility ☐ Carcinogenicity

Did the Sponsor provide a written justification in lieu of biocompatibility testing	☐ **Yes**	☐ **No**	☒ **N/A**
IS the written justification acceptable?	☐ **Yes**	☐ **No**	☒ **N/A**

Reference ID: 4332709

Did the Sponsor perform the appropriate testing?	☒ Yes	☐ No	☐ N/A
Review of Biocompatibility Testing The Sponsor submitted the required testing for a limited contact duration product checked above: cytotoxicity, sensitization, irritation, acute system toxicity, material mediated pyrogenicity, and hemocompatibility. The studies were conducted in agreement with ISO 10993 sections 4, 5, 10, 11 with passing results.			

The following biocompatibility information was found in STMT-QE2018315-47510510-IONIS received 1/25/2018.

(b) (4)

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(b) (4)

Biocompatibility Stock IR

Design Verification Recommendation		
The Sponsor Provided Complete Design Verification for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Design Verification for the Device Constituent		☐
Design Verification Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Summary

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		

8.2. Summary of Risk Analysis

Drug Risk analysis:

Ionis Pharmaceuticals, Inc. is proposing a Risk Evaluation and Mitigation Strategy (REMS) to address and manage the serious risks of <<TRADENAME>>. Distribution and dispensing will be restricted to ensure that the appropriate patients and or caregivers receive the product, and that there is ongoing data collection and educational communications beyond what would be achieved with labeling and routine pharmacovigilance. The specific risks to be managed are thrombocytopenia and glomerulonephritis. To mitigate these risks, laboratory

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testing of blood (platelet count, and eGFR) and urine (protein/creatinine ratio [UPCR]) is required prior to initiation of <<TRADENAME>>. Testing of platelet count and UPCR is required at regular intervals thereafter, based on product labeling. Both prescribers and patients will be educated about the importance of concurrent monitoring for signs and symptoms that may indicate thrombocytopenia and glomerulonephritis. Early recognition and response to symptoms or signs of these risks is critically important.

The REMS is designed to follow the (FDA March 2005 Guidance Document, 2005), Development and Use of Risk Minimization Action Plans (RiskMAP) and principles of Risk Evaluation and Mitigation Strategies as described in the (FDA Amendments Act of 2007, 2007) and the (September 2009 Draft Guidance Document, 2019), Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications.

The goal of the <<TRADENAME>> (inotersen) REMS is to mitigate the risks of thrombocytopenia and glomerulonephritis associated with the use of <<TRADENAME>> by:

• Educating prescribers and pharmacists about the risks of thrombocytopenia and glomerulonephritis and appropriate monitoring requirements

• Informing patients about the risks, signs and symptoms of thrombocytopenia and glomerulonephritis, and appropriate monitoring requirements

• Educate prescribers and patients on the monitoring schedule for platelets and renal function prior to dispensing <<TRADENAME>> and during treatment

• Establishing long-term safety and safe use of <<TRADENAME>> by documentation of safe use conditions.

Device Risk analysis:

As part of the development of the ISSD, an overarching risk management program was established by (b) (4) *in line with ISO 14971. The risk management program was intended to identify, evaluate, and mitigate risks associated with the design, manufacture, and use of the ISSD. The program provided a framework that allowed individual parties to conduct risk management activities within their areas of responsibility using their procedures.*

Risks associated with the device that were identified as being above the threshold of acceptability were collected and addressed with control measures designed to mitigate risk. The control measures included modifications to the design (device and process equipment) and, where design changes could not mitigate risk, instructions for use (IFU) and training were optimized with appropriate control measures. Evidence of the effectiveness of the control measures is provided through design verification and validation activities (Section 6 and 7) and the syringe functionality results collected during stability studies (CTD Section 3.2.P.8.3).

Table 3 provides a summary of the key risks associated with device use, along with the corresponding control measures, including device design changes and revisions to the IFU. The final IFU was based on user Human Factors and risk assessments and are provided in the proposed labelling.

The residual risks of the ISSD were weighed against the benefits of the drug product and the benefits of the ISSD were concluded to outweigh the residual risks. Therefore, it was concluded that no additional risk mitigation measures are required.
Details of the risk assessments, control measures, and risk/benefit analysis are provided in the Inotersen DHF.

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Table 3 Summary of Key Risks Associated with ISSD Use

Potential Use Risk	Potential Harm	Control Measure
Storage of product at elevated temperatures thereby potentially impacting product quality	Exposure to degraded product with unknown therapeutic consequences	IFU provides instructions related to product storage [redacted] (b) (4) along with further direction to use the product within a specified time limit after removing it from the refrigerator
Prolonged exposure to light	Exposure to degraded product with unknown therapeutic consequences	IFU storage instructions state to protect from light [redacted] (b) (4)
Use of expired product	Exposure to degraded product with unknown therapeutic consequences	IFU instructs user to check the expiration date [redacted] (b) (4) prior to use [redacted] (b) (4) do not use if expiration date has passed")
Removal of cap a significantly long time before injection	Possible drying of product and clogging of needle resulting in a slower delivery (or no delivery) – reduction in dose and efficacy of treatment	IFU states for user to remove cap immediately prior to injection ("Do not remove cap until [redacted] (b) (4)
Injection into area of the body other than approved injection site (abdomen and thigh)	Increased pain and possible impact to drug absorption	IFU includes diagram of injection sites
Patient or caregiver/health care professional fails to pinch injection site prior to needle insertion	Potential intramuscular injection resulting in potential increased pain	IFU contains diagram of pinching skin during needle insertion
Injection angle/depth too shallow or remove needle before delivery completed	Reduction in dose and efficacy of treatment	IFU states for user to insert entire needle and provides diagram of angle; illustrations show complete delivery of drug before removal of needle
Accidental contact with needle before/after use	Needle stick injury	Design of device has needle shielding feature before and after use IFU instructs user to dispose of product in Sharps container and includes illustration
Failure to dispose of used device in Sharps container	Potential needle stick by someone in household or waste stream including cross-contamination of infectious disease	Design of device has needle shielding feature after use IFU states to dispose of product in Sharps container and includes illustration

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Reviewer's comment: DMEPA completed a review of the Human factors testing and identified that the safety needle locking mechanism failed repeated. The Sponsor cites the label location as the cause and states that they have mitigated this problem by moving the label, but did not perform an additional human factors study to verify this mitigation.

IR response received 1/29/2018 – additional studies were conducted with the devices (b) (4) The safety needle locking mechanism failed on those (b) (4) (b) (4) and those (b) (4) passed. Additionally, samples of both devices were sent to FDA. Those with the (b) (4) activated the safety needle correctly. DMEPA also reviewed this problem and has found it acceptable.

Risk Analysis Stock IR

Risk Analysis Recommendation		
The Sponsor provided complete Risk Analysis for the Device Constituent		☒
The Sponsor **DID NOT** provide There are Complete Response Deficiencies, See Section 13 Risk Analysis for the Device Constituent		☐
Risk Analysis Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

9. LABELING

Pre-Filled Syringe Labeling Checklist

Attribute		Present		
		Yes	**No**	**N/A**
Device Type	Type	X		
	Syringe Size(s)	X		
	Needle Gauge		X	
	Needle Length		X	
	Quantity	X		
Prescription Statement under 801.109(b)(1), except for insulin syringes		X		
Special requirements for insulin syringes as described in 801.403 about mixing insulin, including "For use with U100 insulin only" on the barrel and gradations on the barrel in units;				X
Any instructions for using specialized syringes such as the anti-needlestick devices and cartridge syringes;		X		
Any specific drug or biologic use;		X		
Instructions on how to clean and sterilize any reusable components.				X

9.1. Device Labels

Reference ID: 4332709

Inner package label found in GSR Section 1.14.1.1 – Draft labeling:

Outer Carton label found in GSR Section 1.14.1.1 – Draft labeling:

Reference ID: 4332709

(b) (4)

[redacted]

Reviewer Comment: The carton and inner package label are acceptable. It includes the required Rx statement, manufacturer contact information, lot number, expiration date, single use only.

9.2. Instructional Labeling

The following instructions for use information is found in GSR Section 1.14.1.1 Draft instructions for use, including the warnings statements.

Reference ID: 4332709

(b) (4)

[redacted]

Reference ID: 4332709

Reviewer Comment: The instructions for use are acceptable. The instructions provided in the package inserts are clear and concise and include all steps necessary to use the device as intended and activate the device's needle safety shield.

9.3. Warnings/Precautions/Contraindications

None of the warnings found in the insert, carton, or immediate container pertain to the device.

Reviewer Comment: The warning statement are acceptable.

Labeling Recommendation		
The Sponsor provided complete Labeling for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Labeling for the Device Constituent		☐
Labeling Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

10.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

Release Specifications

Attribute	Specification	Test Method
Dose Accuracy	(b) (4)	Iso 11608
Audible / Visual information on injection status		Click
Break Loose/Glide Force	Break loose: less than (b) (4) Glide force: less than (b) (4)	Iso (b) (4) Iso

The following design transfer information is included in GSR section 3.2.R.8

GSK declined to license Inotersen (b) (4) Injection; therefore, Ionis will be the Sponsor of the New Drug Application. As part of the transitional activities, the DHF in its entirety was transferred to Ionis by GSK.

The following information is included in Container-closure-system.pdf GSR section 3.2.P.7

(b) (4)

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Reviewer Comment: The applicant has provided stability studies room temperature, and refrigerated temperature stored in a vertical and horizontal position. Breakout force, gliding force and leakage testing are all within the device specifications.

The design transfer is acceptable.

Release Specification Stock IR

Release Specifications Recommendation		
The Sponsor provided complete Release Specifications for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Release Specifications for the Device Constituent		☐
Release Specifications Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

11.INTERACTIVE REVIEW

11.1. Filing Information Requests

Are there filing review information requests? ☒ No ☐ Yes

This section is not applicable

11.2. 74-Day letter Information Requests

Are there 74-Day Letter information requests? ☒ No ☐ Yes

This section is not applicable

11.3. Mid-Cycle Information Requests

Are there Mid-Cycle review information requests? ☐ No ☒ Yes

IR sent 1/17/2018

(b) (4)

(b) (4)

Reference ID: 4332709

(b) (4)

(b) (4)

Reviewer's comment: Supplied test report are acceptable

11.4. Interactive Review

Are there other interactive review information requests? ☒ No ☐ Yes

This section is not applicable

12.COMPLETE RESPONSE DEFICIENCIES

There are no outstanding unresolved information requests, therefore CDRH does not have any deficiencies for a CR Letter.

13.RECOMMENDATION

13.1. Recommendation to CDER/OPQ

CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

14.Appendix

This section is not applicable

Reference ID: 4332709

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

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Date	3/26/2018
To	Dahlia Walters, RPM OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Center/Office	*CDER/OPQ*
OND Review Division	*DNP*
From	*Jacqueline M Gertz* *CDRH/ODE/DAGRID/GHDB*
Through (Team Lead)	*John McMichael* *CDRH/ODE/DAGRID/GHDB*
Through (Branch Chief)	*CAPT Alan Stevens* *CDRH/ODE/DAGRID/GHDB*
Subject	*Consult for NDA 211172* *ICCR2017-01947* *ICC1700930*
Filing **Recommendation**	*Recommendation Date:* *Device Constituents Parts of the Combination Product are Acceptable for Filing*
Final **Recommendation**	*Recommendation Date:* *Device Constituents Parts of the Combination Product are Approvable*

Digital Signature Concurrence Table	
Reviewer	Jacqueline Gertz -S Digitally signed by Jacqueline Gertz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001948760, cn=Jacqueline Gertz -S Date: 2018.03.26 17:05:14 -04'00'
Team Lead	John C. Mcmichael -S 2018.03.27 11:19:52 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.03.27 14:41:40 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01947
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=2180
ICC tracking # (Lead)	ICC1700930
Submission Number	NDA 211172
Sponsor	Ionis pharmaceuticals
Drug/Biologic	Inotersen Solution
Indications for Use	Treatment of hereditary transthyretin amyloidosis to [redacted] (b) (4)
Device Constituent	Prefilled syringe
Related Files	N/A

Table 2. Review Team		
Were other disciplines consulted?	☐Yes	☒ No

Table 3. Important Dates	
1st round of Information Requests	1/17/2018
Final Lead Device Review Memo Due	4/12/2018
Interim Due Dates	**Due Date**
Filing	12/7/2017
Mid-Cycle	2/15/2018
Internal meeting	4/13/2018
Wrap up meeting	6/1/2018
PDUFA/GDUFA Due Date	7/6/2018

Reference ID: 4332709

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2. PURPOSE/BACKGROUND

2.1. Scope

CDER is requesting approval of the Inotersen solution. The device constituent of the combination product is a prefilled glass syringe with a needle safety device.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product on 2/12/2018: OND is requesting a Device consult for the Inotersen solution.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent
- Sterility of the device constituent if applicable

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Device facilities

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

CDRH has no prior interaction with the sponsor. CDER's interactions can be seen in the table below.

Reference ID: 4332709

Table 1 Regulatory History and eCTD Location of Information Addressing FDA's Agreements/Recommendations

Type of Correspondence / Date	Agency Agreements/Recommendations	eCTD Location(s)
Special Protocol Assessment (SPA) – Clinical (March 6, 2013)	Recommendations on the trial design for the pivotal Phase 2/3 study CS2	Module 1.6.3 Type A Meeting Minutes and Clarification
Special Protocol Assessment (SPA) – Carcinogenicity (December 1, 2015)	Recommendations on the study design for a 6-month and 24-month carcinogenicity study.	Module 1.8.2 (SPA) Module 4.2.3.4.2 (6-month study)
Informal Email (October 18, 2016)	A Thorough QT (TQT) Study Waiver was granted for ISIS 420915.	N/A
Type C Meeting -WRO (nonclinical/ clinical) (April 5, 2017)	Concurrence to submit long-term carcinogenicity study post-approval Waiver of the requirements of the Pediatric Research Equity Act (PREA) Presentation/ content of the ISS/ ISE Presentation/ content of the Clinical Summary of Safety (CSS) Dataset format for studies CS1, CS2 and CS3	Module 1.6.3 Type C Meeting Minutes including clarification Module 1.9.1 (PREA) Module 5.3.5.3 (ISS/ISE) Module 2.7.4 (CSS) Module 5.3.4.1 (CS1) Module 5.3.5.1 (CS2) Module 5.3.5.2 (CS3)
Informal Email (May 23, 2017)	Concurrence was received from DMEPA on the design of the protocol for the Human Factors Study.	Module 1.14.1.4 (Human Factors Study – Final Report)
Type C Meeting -WRO (CMC) (July 24, 2017)	Stability data package to be included in the NDA submission/ comparability of synthetic routes used during development	Module 1.6.3 (Meeting Minutes – Written Response)
Informal Call (June 19, 2017)	A Safety Update will be provided 90 days after submission of the initial NDA.	N/A
Pre-Submission Safety Request (July 24, 2017)	Sponsor agreed to provide additional safety-related information requested by the Agency	Module 1.6.3 Annotated document

2.2.1. Related Files

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use

Reference ID: 4332709

Inotersen Solution	Treatment of hereditary transthyretin amyloidosis [redacted] (b) (4)
Syringe	Delivery of the drug product
Route of Administration	Subcutaneous

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Labeling	1.14.1
Risk evaluation and mitigation strategy supporting document	1.16.2
Common Technical Document Summaries	Module 2
Quality	3.2
Regional	3.2.R
Proposed risk evaluation and mitigation strategy	1.16.1
Pharmaceutical-Development - containclose	3.2.P.2.4
Reg-info.pdf	3.2.r

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The following information was taken from GSR 2.3.P.2 Pharmaceutical Development:

The container closure system for Inotersen [redacted] (b) (4) Injection is composed of a PFS, which consists of a [redacted] (b) (4) 2.25 mL, clear glass syringe barrel with a [redacted] (b) (4)), 8 mm staked needle with a rigid needle shield with an [redacted] (b) (4) liner. The syringe barrel is stoppered with a [redacted] (b) (4) plunger stopper. The prefilled syringe is assembled into a safety syringe device (SSD), to deliver an injection volume of 1.5 mL (284 mg) per dose.

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Reference ID: 4332709

Instructions for use

(b) (4)

[redacted]

Device Description Stock IR

Device Description Recommendation		
The Sponsor Provided Complete Device Description for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Device Description for the Device Constituent		☐
Device Description Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day Letter IRs - # Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

5. FILING REVIEW

Reference ID: 4332709

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

Filing Review Stock IR

Filing Recommendation		
Filing Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day-letter IRs - #	
The device constituent content in the submission for the combination product is acceptable for filing		☒
The device constituent content in the submission for the combination product is acceptable for filing, CDRH has Information Requests to include in the 74-Day letter, See Section 11.2		☐
The device constituent content in the submission for the combination product is acceptable for filing, See Section 11.1 for Filing Information Requests		☐

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

Table 4: Design Control Documentation Check

Design Control Requirement	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		Reg-info.pdf
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		Reg-info.pdf
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		Pharmaceutical-development-containclos.pdf

Master File Review Instructions

FDA 21 CFR 820.30 - Design Review:
The outputs from the design verification and validation are summarized in formal reports that are distributed to all relevant functions in order that the output is appropriately shared and reviewed.
As part of (b) (4) *review process, technical design reviews are undertaken with key stakeholders to ensure the Safety Syringe Device design is fit for purpose prior to moving to the next development phase. Reviews of design data are undertaken within the medicines process delivery (MPD) project team and within the Department line.*

Master File Stock IR

Reference ID: 4332709

The following design validation information is found in GSR 3.2.P.2.4 Container closure system:
Design input requirements:
4.5.1 Safety Syringe Design Input Requirements

(b) (4)

[redacted]

Table 10 Functional Parameter Criteria

Functional Parameter	Criteria	Basis for Requirement
[redacted]		

(b) (4)

Design Controls Recommendation		
The Sponsor Provided Complete Design Controls for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Design Controls for the Device Constituent		☐
Design Control Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

Table 5: Summary of Design V&V Attributes

Reference ID: 4332709

The Sponsor submitted this information in Pharmaceutical-Development -containclose: 3.2.P.2.4

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		X		
To-be-marketed device was used in the pivotal clinical trial?				X
Selectable dose range on device matches the labeled dose range for the medication?				X
Verification methods relevant to specific use conditions as described in design documents and labeling		X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		X		
Traceability demonstrated for specifications to performance data			X	
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	X		
	ISO 11608-2:2012 – Needles	X DMF		
	ISO 11608-5:2012 – Automated Functions	X		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		X		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility - ISO 10993 sections 4, 5, 10, 11	X		
	Sterility	X		

Referenced Standards and Guidance Documents

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
Iso 11040-4	Glass barrel for injectables	X	
(b) (4)		X	
ISO 10993 part 1, 4, 5, 7, 10, 11, 18	Biological evaluation of medical devices	X	
(b) (4)		X	
ISO 7864	Sterile hypodermic needles for single use	X	
(b) (4)		X	

7.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device	X		

The following design input information is found in GSR section 3.2.R.3.1:

Reference ID: 4332709

3 DESIGN INPUT

(b) (4)

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Reference ID: 4332709

The purpose of design validation is to demonstrate that the developed SSD conforms to the defined user needs and intended uses. Since the SSD employs the same injection technique as the Phase 3 syringe, design validation for the safety syringe involved human factors validation through simulated use. A summary of the human factors validation study is provided below.

Design changes:

During the development of the Nemera 2.25mL (b) (4)

The cause of the failure was identified as a combination of the following areas:

• *The potential for the safety shield failing to activate if the plunger rod is not fully depressed. (The user misinterprets an audible click as the end of stroke)*

• *The device handling for users with reduced manual dexterity had to be fully allowed.*

The following areas were proposed as design options that could target those failure modes:

• *Minimising the activation time* (b) (4)

• *Reducing actuation force* (b) (4)

• *Reduce impact of unintentional actuation*

(b) (4) *identified the root cause of this issue, and identified an engineering solution to address it. With the engineering solution in place, it was shown through in vitro testing* (b) (4) *) and formative human factors testing* (b) (4) *) that the issue had been mitigated.*

Reviewer Comment: DMEPA completed a review of the Human factors testing and identified that the safety needle locking mechanism failed repeated. The Sponsor cites the (b) (4) as the cause and states that they have mitigated this problem by (b) (4), but did not perform an additional human factors study to verify this mitigation.

IR response received 1/29/2018 – additional studies were conducted with the devices with (b) (4) The safety needle locking mechanism failed on those with (b) (4) and those with (b) (4) passed. Additionally, samples of both devices were sent to FDA. Those with (b) (4) activated the safety needle correctly. DMEPA also reviewed this problem and has found it acceptable.

All submitted documents state the design input requirements citing standards and guidances and a complete design history file.

Clinical Validation Stock IR

Reference ID: 4332709

Design Validation Recommendation		
The Sponsor Provided Complete Design Validation for the Device Constituent		☐
The Sponsor **DID NOT** Provide Complete Design Validation for the Device Constituent		☐
Design Validation Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☒
There are Complete Response Deficiencies, See Section 12		☐

Reference ID: 4332709

7.3. Design Verification Review

7.3.1. Design Verification Testing Summary

Essential Functional Requirements						
	N/A	**Acceptance Criteria**	**Method Acceptable**	**Results/ Deviations**	**Adequate**	
					Yes	**No**
Dose Accuracy		(b) (4) [redacted]	ISO 11608	1.5 – 1.6 mL	X	
Break Loose Force			(b) (4) [redacted]	7-9.5N	X	
Glide Force				5.25-6.13N	X	
Visual/Audible Feedback					X	
Device Requirements						
	N/A	**Acceptance Criteria**	**Method Acceptable**	**Results/ Deviations**	**Adequate**	
					Yes	**No**
Injection Depth		(b) (4) [redacted]	Entire needle	8mm	x	
Injection time					X	
Needle Connection Type	X					
Needle Resistance to Bend/Fracture			(b) (4) [redacted]		x	
Seal Integrity Testing[1]			(b) (4) [redacted]	All units tested had absorbance results less than the system sensitivity absorbance obtained in the same run, which denotes that the seal integrity of the units were intact	x	
Separation Force	X					

Reference ID: 4332709

Unscrewing Torque	X					
Ease of Assembly	X					
Resistance to Overriding	X					
Stress Cracking	X					
Validation of Graduation Markings	X					
Dead Space	X			Only for insulin		
Coring Needle Test			(b) (4)		X	
Anti-Needle Stick Performance testing[2]		(b) (4) to activate	Bench testing and simulated clinical use testing	No failures	X	
Connectivity to other devices necessary for use[3]	X					
Tip cap removal force		(b) (4)		(b) (4)	x	
Piston seal blowback[4]	X					
Sterility		(b) (4)		(b) (4)	X	

Reference ID: 4332709

				(b) (4)		

[1]to assess liquid leakage, air ingress, and dye ingress once the syringe is filled with the drug or biological product as intended and when connected to a connecting device. The sensitivity of the selected test method should be specified and validated. System integrity should be demonstrated throughout the product shelf-life.
[2]of an anti-needlestick mechanism with a glass syringe to demonstrate safety and effectiveness as recommended in FDA's guidance document, "Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features " (August 2005).
[3] (b) (4)
[4]

7.3.2. Environmental Conditioning Testing

All Essential Functional Requirements Evaluated under normal and stressed conditioning				
		Adequate	Inadequate	N/A
Normal/Anticipated Conditions	In-Use atmosphere	pass		
	Last-Dose Accuracy	Single use		
	Life-Cycle Testing			X
Challenge/Stressed Conditions	Free-Fall	ISO 11608		
	Dry heat/cold storage	Pass		
	Damp Heat	Pass		
	Cyclical			X
	Vibration			X

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	Transportation, storage, handling	Shelf life 18 months at 2-8C, 6 weeks at 30C No adverse effect with (b) (4) (b) (4)		

Reference ID: 4332709

7.3.3. Biocompatibility Review

Biocompatibility Review Instructions

Biocompatibility Evaluation		
Materials List	Plunger	(b) (4) [redacted]
	Syringe Body	
	Needle	
	Accessories	
Additives/Colorants	None	
Device Characteristics		
Category	☐ External communicating device	
Contact Type	☒ Blood path, indirect ☐ CSF contacting[1] [1]consult biocompatibility consultant	
Contact Duration	☒ ≤24h (limited) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), and Material-mediated Pyrogenicity ☐ >24h to 30 days (prolonged) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, and Subchronic systemic toxicity ☐ >30 days (permanent) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, Subchronic systemic toxicity, and Genotoxicity *Notes:* *The endpoints included in the biocompatibility evaluation of the needle are dependent on the type and duration of contact. Below are the recommended endpoints for blood path, indirect, which are applicable for both subcutaneous and intramuscular injections. If the needle is CSF contacting, information may be needed to support the evaluation of the neurotoxicity endpoint.*	
Testing Performed	☒ Cytotoxicity ☒ Sensitization ☒ Irritation or Intracutaneous Reactivity ☒ Acute System Toxicity ☒ Material-Mediated Pyrogenicity	☐ Subacute/Subchronic Toxicity ☐ Genotoxicity ☒ Hemocompatibility ☐ Carcinogenicity

Did the Sponsor provide a written justification in lieu of biocompatibility testing	☐ **Yes**	☐ **No**	☒ **N/A**
IS the written justification acceptable?	☐ **Yes**	☐ **No**	☒ **N/A**

Reference ID: 4332709

Did the Sponsor perform the appropriate testing?	☒ Yes	☐ No	☐ N/A
Review of Biocompatibility Testing The Sponsor submitted the required testing for a limited contact duration product checked above: cytotoxicity, sensitization, irritation, acute system toxicity, material mediated pyrogenicity, and hemocompatibility. The studies were conducted in agreement with ISO 10993 sections 4, 5, 10, 11 with passing results.			

The following biocompatibility information was found in STMT-QE2018315-47510510-IONIS received 1/25/2018.

(b) (4)

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(b) (4)

[redacted]

Biocompatibility Stock IR

Design Verification Recommendation		
The Sponsor Provided Complete Design Verification for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Design Verification for the Device Constituent		☐
Design Verification Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Summary

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		

8.2. Summary of Risk Analysis

Drug Risk analysis:

Ionis Pharmaceuticals, Inc. is proposing a Risk Evaluation and Mitigation Strategy (REMS) to address and manage the serious risks of <<TRADENAME>>. Distribution and dispensing will be restricted to ensure that the appropriate patients and or caregivers receive the product, and that there is ongoing data collection and educational communications beyond what would be achieved with labeling and routine pharmacovigilance. The specific risks to be managed are thrombocytopenia and glomerulonephritis. To mitigate these risks, laboratory

Reference ID: 4332709

testing of blood (platelet count, and eGFR) and urine (protein/creatinine ratio [UPCR]) is required prior to initiation of <<TRADENAME>>. Testing of platelet count and UPCR is required at regular intervals thereafter, based on product labeling. Both prescribers and patients will be educated about the importance of concurrent monitoring for signs and symptoms that may indicate thrombocytopenia and glomerulonephritis. Early recognition and response to symptoms or signs of these risks is critically important.

The REMS is designed to follow the (FDA March 2005 Guidance Document, 2005), Development and Use of Risk Minimization Action Plans (RiskMAP) and principles of Risk Evaluation and Mitigation Strategies as described in the (FDA Amendments Act of 2007, 2007) and the (September 2009 Draft Guidance Document, 2019), Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications.

The goal of the <<TRADENAME>> (inotersen) REMS is to mitigate the risks of thrombocytopenia and glomerulonephritis associated with the use of <<TRADENAME>> by:

• Educating prescribers and pharmacists about the risks of thrombocytopenia and glomerulonephritis and appropriate monitoring requirements

• Informing patients about the risks, signs and symptoms of thrombocytopenia and glomerulonephritis, and appropriate monitoring requirements

• Educate prescribers and patients on the monitoring schedule for platelets and renal function prior to dispensing <<TRADENAME>> and during treatment

• Establishing long-term safety and safe use of <<TRADENAME>> by documentation of safe use conditions.

Device Risk analysis:

As part of the development of the ISSD, an overarching risk management program was established by (b) (4) *in line with ISO 14971. The risk management program was intended to identify, evaluate, and mitigate risks associated with the design, manufacture, and use of the ISSD. The program provided a framework that allowed individual parties to conduct risk management activities within their areas of responsibility using their procedures.*

Risks associated with the device that were identified as being above the threshold of acceptability were collected and addressed with control measures designed to mitigate risk. The control measures included modifications to the design (device and process equipment) and, where design changes could not mitigate risk, instructions for use (IFU) and training were optimized with appropriate control measures. Evidence of the effectiveness of the control measures is provided through design verification and validation activities (Section 6 and 7) and the syringe functionality results collected during stability studies (CTD Section 3.2.P.8.3).

Table 3 provides a summary of the key risks associated with device use, along with the corresponding control measures, including device design changes and revisions to the IFU. The final IFU was based on user Human Factors and risk assessments and are provided in the proposed labelling.

The residual risks of the ISSD were weighed against the benefits of the drug product and the benefits of the ISSD were concluded to outweigh the residual risks. Therefore, it was concluded that no additional risk mitigation measures are required.
Details of the risk assessments, control measures, and risk/benefit analysis are provided in the Inotersen DHF.

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Table 3 Summary of Key Risks Associated with ISSD Use

Potential Use Risk	Potential Harm	Control Measure
Storage of product at elevated temperatures thereby potentially impacting product quality	Exposure to degraded product with unknown therapeutic consequences	IFU provides instructions related to product storage (b) (4) (b) (4) along with further direction to use the product within a specified time limit after removing it from the refrigerator
Prolonged exposure to light	Exposure to degraded product with unknown therapeutic consequences	IFU storage instructions state to protect from light (b) (4)
Use of expired product	Exposure to degraded product with unknown therapeutic consequences	IFU instructs user to check the expiration date (b) (4) prior to use (b) (4) (b) (4) do not use if expiration date has passed")
Removal of cap a significantly long time before injection	Possible drying of product and clogging of needle resulting in a slower delivery (or no delivery) – reduction in dose and efficacy of treatment	IFU states for user to remove cap immediately prior to injection ("Do not remove cap until (b) (4) (b) (4)
Injection into area of the body other than approved injection site (abdomen and thigh)	Increased pain and possible impact to drug absorption	IFU includes diagram of injection sites
Patient or caregiver/health care professional fails to pinch injection site prior to needle insertion	Potential intramuscular injection resulting in potential increased pain	IFU contains diagram of pinching skin during needle insertion
Injection angle/depth too shallow or remove needle before delivery completed	Reduction in dose and efficacy of treatment	IFU states for user to insert entire needle and provides diagram of angle; illustrations show complete delivery of drug before removal of needle
Accidental contact with needle before/after use	Needle stick injury	Design of device has needle shielding feature before and after use IFU instructs user to dispose of product in Sharps container and includes illustration
Failure to dispose of used device in Sharps container	Potential needle stick by someone in household or waste stream including cross-contamination of infectious disease	Design of device has needle shielding feature after use IFU states to dispose of product in Sharps container and includes illustration

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Reviewer's comment: DMEPA completed a review of the Human factors testing and identified that the safety needle locking mechanism failed repeated. The Sponsor cites the label location as the cause and states that they have mitigated this problem by moving the label, but did not perform an additional human factors study to verify this mitigation.

IR response received 1/29/2018 – additional studies were conducted with the devices (b) (4) The safety needle locking mechanism failed on those (b) (4) (b) (4) and those (b) (4) passed. Additionally, samples of both devices were sent to FDA. Those with the (b) (4) activated the safety needle correctly. DMEPA also reviewed this problem and has found it acceptable.

Risk Analysis Stock IR

Risk Analysis Recommendation		
The Sponsor provided complete Risk Analysis for the Device Constituent		☒
The Sponsor **DID NOT** provide There are Complete Response Deficiencies, See Section 13 Risk Analysis for the Device Constituent		☐
Risk Analysis Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

9. LABELING

Pre-Filled Syringe Labeling Checklist

Attribute		Present		
		Yes	**No**	**N/A**
Device Type	Type	X		
	Syringe Size(s)	X		
	Needle Gauge		X	
	Needle Length		X	
	Quantity	X		
Prescription Statement under 801.109(b)(1), except for insulin syringes		X		
Special requirements for insulin syringes as described in 801.403 about mixing insulin, including "For use with U100 insulin only" on the barrel and gradations on the barrel in units;				X
Any instructions for using specialized syringes such as the anti-needlestick devices and cartridge syringes;		X		
Any specific drug or biologic use;		X		
Instructions on how to clean and sterilize any reusable components.				X

9.1. Device Labels

Reference ID: 4332709

Inner package label found in GSR Section 1.14.1.1 – Draft labeling:

Outer Carton label found in GSR Section 1.14.1.1 – Draft labeling:

Reference ID: 4332709

(b) (4)

[redacted]

Reviewer Comment: The carton and inner package label are acceptable. It includes the required Rx statement, manufacturer contact information, lot number, expiration date, single use only.

9.2. Instructional Labeling

The following instructions for use information is found in GSR Section 1.14.1.1 Draft instructions for use, including the warnings statements.

Reference ID: 4332709

(b) (4)

[redacted]

Reference ID: 4332709

Reviewer Comment: The instructions for use are acceptable. The instructions provided in the package inserts are clear and concise and include all steps necessary to use the device as intended and activate the device's needle safety shield.

9.3. Warnings/Precautions/Contraindications

None of the warnings found in the insert, carton, or immediate container pertain to the device.

Reviewer Comment: The warning statement are acceptable.

Labeling Recommendation		
The Sponsor provided complete Labeling for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Labeling for the Device Constituent		☐
Labeling Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

10.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

Release Specifications

Attribute	Specification	Test Method
Dose Accuracy	(b) (4)	Iso 11608
Audible / Visual information on injection status		Click
Break Loose/Glide Force	Break loose: less than (b) (4) Glide force: less than (b) (4)	(b) (4)

The following design transfer information is included in GSR section 3.2.R.8

GSK declined to license Inotersen (b) (4) Injection; therefore, Ionis will be the Sponsor of the New Drug Application. As part of the transitional activities, the DHF in its entirety was transferred to Ionis by GSK.

The following information is included in Container-closure-system.pdf GSR section 3.2.P.7

(b) (4)

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Reviewer Comment: The applicant has provided stability studies room temperature, and refrigerated temperature stored in a vertical and horizontal position. Breakout force, gliding force and leakage testing are all within the device specifications.

The design transfer is acceptable.

Release Specification Stock IR

Release Specifications Recommendation		
The Sponsor provided complete Release Specifications for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Release Specifications for the Device Constituent		☐
Release Specifications Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

11.INTERACTIVE REVIEW

11.1. Filing Information Requests

Are there filing review information requests? ☒ No ☐ Yes

This section is not applicable

11.2. 74-Day letter Information Requests

Are there 74-Day Letter information requests? ☒ No ☐ Yes

This section is not applicable

11.3. Mid-Cycle Information Requests

Are there Mid-Cycle review information requests? ☐ No ☒ Yes

IR sent 1/17/2018

(b) (4)

Reference ID: 4332709

(b) (4)

[redacted]

Reviewer's comment: Supplied test report are acceptable

11.4. Interactive Review

Are there other interactive review information requests? ☒ No ☐ Yes

This section is not applicable

12.COMPLETE RESPONSE DEFICIENCIES

There are no outstanding unresolved information requests, therefore CDRH does not have any deficiencies for a CR Letter.

13.RECOMMENDATION

13.1. Recommendation to CDER/OPQ

CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

14.Appendix

This section is not applicable

Reference ID: 4332709

Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 6/07/2018 12:37:18PM
GUID: 50816dbc000085595ca3284bbca465a8

Clinical Inspection Summary

Date	June 4, 2018
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Nick Kozauer, M.D., Clinical Team Leader Chris Breder, M.D., Ph.D., Clinical Reviewer Evelyn Mentari, M.D., Clinical Reviewer Fannie Choy, Regulatory Project Manager Division of Neurology Products
NDA#	211172
Applicant	Ionis Pharmaceuticals Inc.
Drug	Inotersen
NME	Yes
Review Priority	Priority
Proposed Indication	Treatment of patients with hereditary transthyretin amyloidosis with polyneuropathy (b) (4)
Consultation Request Date	December 6, 2017
Summary Goal Date	June 15, 2018
Action Goal Date	July 6, 2018
PDUFA Date	July 6, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Coelho, Cruz, and Gertz were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. 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).

II. BACKGROUND

The Applicant submitted this NDA to support the use of inotersen in the treatment of patients with hereditary transthyretin amyloidosis with polyneuropathy (b) (4)

Inspections were requested for the following protocol in support of this application:

Protocol 420915-CS2, "A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Subjects with Familial Amyloid Polyneuropathy"

This study was conducted at 24 study sites in 10 countries enrolling 173 subjects.

The primary objective of this study was to evaluate the efficacy of inotersen compared to placebo when administered for 65 weeks as measured by the change from Baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire total score in subjects with hereditary transthyretin (TTR) amyloidosis with polyneuropathy (hATTR-PN). The primary efficacy endpoints were the change from Baseline to Week 66 in the mNIS+7 score and in the Norfolk QoL-DN questionnaire total score.

Secondary efficacy endpoints of particular interest as identified by the reviewing medical officer included:

- Change from baseline to Week 66 in the Norfolk QOL-DN questionnaire symptoms domain score (Stage 1 patients only) and the Norfolk QOL-DN questionnaire physical functioning/large fiber neuropathy domain score (Stage 2 patients only)
- Change from baseline to Week 65 in the Modified Body Mass Index (mBMI)
- Change from baseline to Week 65 in the Body Mass Index (BMI)
- Change in GLS by ECHO from baseline to Week 65 in the Randomized Set, ECHO subgroup and in the CM-ECHO Set

Rationale for Site Selection

The clinical sites of Drs. Coelho, Cruz, and Gertz were selected for inspection because of their relatively large enrollments and their effects on efficacy.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site # 1817 **Teresa Coelho, M.D.** Unidade Clinica de Paramiloidose Largo Professor Abel Salazar Porto, N/A 499-001 Portugal	420915-CS2 Subjects: 21	29 Jan-2 Feb 2018	NAI
Site# 1863 **Marcia Waddington Cruz, M.D.** Professor Rodolpho Paulo Rocco, 225 Street Rio de Janeiro, N/A 21941-913	420915-CS2 Subjects: 15	5-9 May 2018	NAI
Site # 1824 **Morie Gertz, M.D.** 200 First Street SW Rochester, MN 55905	420915-CS2 Subjects: 14	5-9 May 2018	VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

(b) (4) . Therefore, certified copies of CNA booklets from all study sites other than those inspected for this application were requested from the sponsor. The NIS scores from randomly selected CNA booklets were then calculated by this reviewer and compared with the line listings. The NIS scores at Baseline and at Week 66 were consistent with the data listings for twelve subjects across eight sites (one-third of all sites).

1. Teresa Coelho, M.D.

At this site for Protocol 420915-CS2, 22 subjects were screened, 21 subjects were enrolled in the study, and 15 subjects completed the study, with 14 subjects continuing on to the open label extension study.

The study records of all 21 enrolled subjects were partially reviewed, with the records of 16 subjects reviewed in more detail. Informed consent was obtained appropriately from all 21 enrolled subjects. Other records reviewed included, but were not limited to, ethics committee approvals, financial disclosures, diagnoses and other eligibility criteria, ophthalmology records, medical histories, protocol deviations, progress notes, laboratory reports, electrocardiogram reports, subject Quality of Life assessments, neurophysiological assessments, treatment records, concomitant medications, and drug accountability. Source documents were a combination of hand-written documents, worksheets, and printed electronic records.

NIS and +7 scores were transmitted to the (b) (4) for the determination of the mNIS+7 primary endpoint. NIS scores for 16 subjects were recalculated on site and were consistent with those in the data listings. The field investigator provided copies of NIS worksheets for three additional subjects to this reviewer, who determined that the NIS scores for these subjects were also consistent with the data listings.

2. Marcia Waddington Cruz, M.D.

At this site for Protocol 420915-CS2, 17 subjects were screened and 16 subjects were enrolled in the study, with one subject being transferred to another site. The ethics committee approved the initial protocol and subsequent protocol amendments. All subjects signed the initial informed consent forms prior to any study procedures.

The study records of eight subjects were reviewed. The source documentation for the Norfolk QoL surveys at baseline and Week 66 were compared with the data listings. Similarly, the mNIS+7 scores at Baseline (assessment 1 and 2) and Week 66 (assessment 1 and 2) were compared with data listings. Some very minor discrepancies were noted that were isolated in nature and unlikely to have impacted the overall efficacy results of the study.

Other records reviewed included ethics committee correspondence and approvals, monitoring correspondence, financial disclosure forms, study protocol and amendments, informed consent forms, inclusion/exclusion criteria, source documentation, primary and secondary efficacy endpoints, adverse events, electronic subject data, and drug accountability and storage records.

Protocol-required creatinine clearances based on 24-hour urines were not always calculated in cases of unscheduled visits (though the 24-hour urines were obtained), apparently because of a lack of linkage between the requisitions for the 24-hour urine collection and the serum creatinine. Subject numbers (b) (6) did not have creatinine clearances calculated for unscheduled visits. This issue was communicated to the reviewing medical officer, who noted that the estimated glomerular filtration rates based on serum creatinine provided sufficient safety information with respect to renal safety monitoring.

3. Morie Gertz, M.D.

At this site for Protocol 420915-CS2, 24 subjects were screened, 14 subjects were enrolled in the study, one subject died, and 13 subjects completed the study, with 12 subjects continuing on to the open label extension study. All subjects signed the initial informed consent forms prior to any study procedures.

The records for all 14 enrolled subjects were reviewed. Records reviewed included subjects' source records (which were compared to the line listings), sponsor, monitor, and IRB correspondence, study staff training, primary efficacy endpoints, protocol deviations, adverse events, and test article accountability and storage. The NIS Component and Subcomponent Results and Norfolk QOL-DN Scores were reviewed for Subjects #s (b) (6) and (b) (6). Spot checks of the NIS scores at Baseline and Week 66 were reviewed for all other subjects. No discrepancies were noted.

A Form FDA 483 was issued at the completion of the inspection noting 14 examples of unreported non-serious adverse events:

Subject Randomization #	Study Treatment	Adverse Event	Date
(b) (6)	420915	Injection sites reddened and itching bilateral abdomen	(b) (6)
	Placebo	Edema	
	Placebo	Left leg numbness now goes to the knee	
	420915	dizzy and lightheaded	
	420915	Increased abdominal and testicular pain	
	420915	Fainting episode (2)	
	420915	Abdominal fullness	
	420915	Bruising – right knee	
	420915	Bruising – right eye	
	420915	Nail discoloration	
	420915	Dizziness	
	420915	Amnesia	
	420915	Loss of consciousness	
	Placebo	Weight loss	

Dr. Gertz adequately responded to the inspection findings in a letter dated March 22, 2018. He noted that "left leg numbness now goes to the knee" for Subject # (b) (6) and "testicular pain" for Subject # (b) (6) were pre-existing documented conditions and, as they did not worsen during the course of the study, he disagreed with the need to report them as adverse events. The review division may wish to consider the effect, if any, of the unreported non-serious adverse events on the overall safety results of this study.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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{See appended electronic signature page}

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Susan D. Thompson, M.D., Team Leader
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cc:
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DNP\Team Leader\Nick Kozauer
DNP\Medical Officer\Chris Breder
DNP\Medical Officer\Evelyn Mentari
DNP\Project Manager\Fannie Choy
OSI\DCCE\Division Director\Ni Khin
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OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
06/04/2018

PHILLIP D KRONSTEIN
06/04/2018

SUSAN D THOMPSON
06/04/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 17, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211172
Product Name and Strength:	Tegsedi (inotersen) injection 284 mg/1.5 mL
Applicant/Sponsor Name:	Ionis Pharmaceuticals, Inc.
FDA Received Date:	April 12, 2018
OSE RCM #:	2017-2310-1
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container label and container labeling for Tegsedi (inotersen) injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and container labeling for Tegsedi (inotersen) injection is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rider B. Label and Labeling Review for Tegsedi (NDA 211172). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 23. RCM No.: 2018-2310.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BRIANA B RIDER
04/17/2018

LOLITA G WHITE
04/17/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 11, 2018

From: Laurel A. Menapace, M.D.
Medical Officer
Division of Hematology Products

Through: Andrew Dmytrijuk, M.D.
Medical Officer Team Leader (Acting)
Division of Hematology Products

R. Angelo de Claro, M.D.
Deputy Division Director (Acting)
Division of Hematology Products

Subject: Consult Request regarding Inotersen
NDA 211172

To: Evelyn Mentari, MD, MS
Safety Clinical Reviewer
Division of Neurology

Request:

Dr. Evelyn Mentari from the Division of Neurology Products (DNP), requests the Division of Hematology Products (DHP) clinical opinion regarding the development of thrombocytopenia associated with inotersen treatment as well as laboratory monitoring and mitigation practices proposed by the sponsor. The Request for Consultation from DNP to DHP is shown in Appendix 1 of this review for reference.

Materials reviewed:

- DNP Request for Consultation (Appendix 1)
- DNP Preliminary Clinical Review of NDA 211172 (received March 8, 2018) by Dr. Evelyn Mentari in the Division of Neurology Products (DNP)
- The Sponsor's Analysis of Thrombocytopenia (NDA 211172 Summary of Clinical Safety, pages 126-140)
- Sponsor's Responses to Information Requests submitted to NDA 211172 on January 8, 2018 and February 12, 2018
- The Sponsor's Proposed Label for Inotersen

Reference ID: 4247193

Background:

On November 6, 2017, NDA 211172 (original application) for inotersen to treat patients with hereditary transthyretin amyloidosis (hATTR) was received by the Division of Neurology Products (DNP). Inotersen is a 2′-O-(2-methoxyethyl) [2′-MOE] antisense oligonucleotide (ASO) drug that targets human transthyretin (TTR) messenger ribonucleic acid (mRNA). Hybridization to the cognate TTR mRNA results in the RNase H1-mediated degradation of the transthyretin mRNA preventing production of the transthyretin protein. Thrombocytopenia has been described with several drugs in the antisense oligonucletide class. Pivotal clinical studies of inotersen in hATTR subjects submitted in support of NDA 211172 included a placebo-controlled study, CS2 and an open label extension study, CS3. The clinical studies are summarized in the section Summary of Studies CS2 and CS3 in this review. The Request for Consultation from DNP to DHP is shown in Appendix 1 of this review for reference. The DHP responses to DNP questions are in the section Discussion in this review.

Hereditary transthyretin-mediated (hATTR) amyloidosis, caused by misfolding of the TTR protein, is a progressive, degenerative, multisystemic, life-threatening disease. The worldwide prevalence is approximately 50,000 individuals, although this is likely an underestimate given potential for misdiagnosis or failure to diagnose given the rare and insidious nature of the disease. The protein TTR is synthesized and secreted by the liver and transports thyroxine (T4) and retinol. Mutations in TTR lead to amino acid substitutions in the TTR protein that render the tertiary structure prone to misfolding, resulting in the formation of insoluble amyloid fibrils. Approximately 120 different points of single or double mutations, or deletions in the TTR gene have been reported in the literature with resultant variable penetrance and phenotypic manifestations of the disease.

Patients with hATTR typically develop amyloid cardiomyopathy as manifested by conduction abnormalities, arrhythmias or heart failure, proteinuria or renal failure secondary to glomerular involvement, as well as progressive sensory-motor polyneuropathy due to deposition of TTR amyloid in the endoneurium and surrounding neuron vasculature. Other significant clinical manifestations of the disease include autonomic dysfunction with resultant orthostatic hypotension, impaired gastrointestinal motility, urinary retention, and sexual dysfunction. Ocular disease results in vitreous opacification and glaucoma. Gastrointestinal symptoms including early satiety accompanied by weight loss, nausea, vomiting, as well as alternating diarrhea and constipation are frequently reported in patients with hATTR.

As the disease progresses, symptoms increase in severity, leading to significant disability, decreased quality of life, and untimely death. hATTR amyloidosis can lead to mortality within 2 to 15 years from initial diagnosis. There are no approved treatments for hATTR amyloidosis in the US, although orthotopic liver transplant is offered to a select group of patients and can reduce the amount of TTR protein made in the body. However, liver transplantation has failed to successfully eradicate disease in hATTR patients or result in improved quality of life or overall survival.

Reference ID: 4247193

Summary of Studies CS2 and CS3

CS2 was a Phase 2/3 multicenter, double-blind, randomized, stratified, placebo-controlled study of inotersen in Stage 1 and 2 subjects with hereditary ATTR with polyneuropathy (hATTR-PN) with a Neuropathy Impairment Score (NIS) ≥10 and ≤130. Approximately 135 subjects were randomized 2:1 to 300 mg inotersen or placebo. The study was conducted at 24 centers in 10 countries.

CS3 is an ongoing, multicenter, open label extension study. Eligible subjects who have satisfactorily completed CS2 are eligible to receive 300 mg inotersen once weekly for up to 260 weeks (5 years) in CS3. There are 22 study centers in 9 countries.

The following table (Table 1) and figure (Figure 1) provide the key design features of the CS2 and CS3 studies and depict the overall study schema.

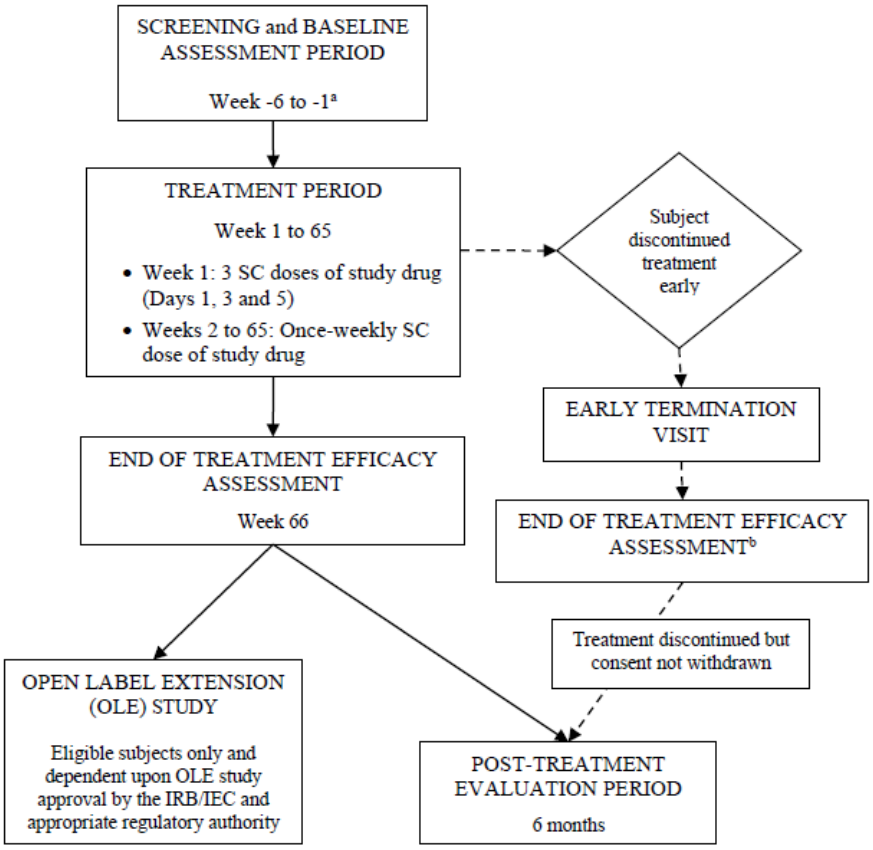
Table 1: Summary of Studies Contributing to Evidence of Safety

Study ID	**Study CS2 (ISIS 420915-CS2)**	**Study CS3 (ISIS 420915-CS3)**
Phase	Phase 2/3	Phase 3
Critical design features	Multicenter, double-blind, placebo-controlled	Multicenter, OLE
Study population	Stage 1 and 2 subjects with hATTR-PN with an NIS ≥10 and ≤130 at CS2 Baseline	
Number of subjects planned	135, approximately 50% Stage 1 and 50% Stage 2 subjects	Eligible subjects who had satisfactorily completed Study CS2[a]
Number of subjects randomized/enrolled and dosed	Randomized: 173; Dosed: 172[b] 67.4% Stage 1 and 32.6% Stage 2 by eCRF	Enrolled and Dosed: 114 received inotersen (at interim analysis)
Median Duration of Study Drug Exposure	449.0 days in CS2	386.0 days in CS3
Treatment regimen[c]	300 mg inotersen or placebo SC injection Week 1: (Days 1, 3, and 5) Weeks 2 to 65: once-weekly (for a total of 67 doses)	300 mg inotersen once-weekly SC injection
Sites (locations)[d]	Argentina, Brazil, France, Germany, Italy, New Zealand, Portugal, Spain, United Kingdom, and United States	Argentina, Brazil, France, Germany, Italy, Portugal, Spain, United Kingdom, and United States

Source: Sponsor's Summary of Clinical Efficacy, November 6, 2017 submission to NDA 211172

Reference ID: 4247193

Figure 1: Overall Study Design and Treatment Schema



Source: Sponsor's Summary of Clinical Efficacy, November 6, 2017 submission to NDA 211172

During the course of the clinical development program, reductions in platelet counts were observed and thrombocytopenia was therefore identified as a risk of treatment with inotersen. In the original CS2 protocol, platelet measurements were scheduled 2-6 weeks apart. After a fatal bleeding event occurred in the setting of Grade 4 thrombocytopenia during study CS2, the CS2 and CS3 protocols were amended to include weekly platelet measurements

The following text describes high level overall findings from studies CS2 and CS3 in regard to reported adverse events of thrombocytopenia and their clinical impact in the studied patient population.

The sponsor definition of a confirmed platelet count for purposes of adverse event reporting is as follows "An initial laboratory value was confirmed by the next available laboratory result performed on a different day and within 7 days of the initial value. If there was no retest within 7 days, then the initial value was presumed confirmed."

Reference ID: 4247193

The following table highlights the number of patients who experienced thrombocytopenia in studies CS2 and CS3.

Table 2: Subjects with Decreased Platelet Counts (Central and Local Laboratory Values) in 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=40)	Inotersen-Inotersen (N=74)	Inotersen 300 mg (N=152)
Confirmed value, n (%)					
≥30% decrease from Baseline/Inotersen Baseline	3 (5.0)	79 (70.5)	25 (62.5)	53 (71.6)	111 (73.0)
≥50% decrease from Baseline/Inotersen Baseline	1 (1.7)	20 (17.9)	10 (25.0)	21 (28.4)	44 (28.9)
<140 x 10^9/L	8 (13.3)	60 (53.6)	19 (47.5)	43 (58.1)	86 (56.6)
<100 x 10^9/L	1 (1.7)	26 (23.2)	13 (32.5)	23 (31.1)	48 (31.6)
<75 x 10^9/L	0	12 (10.7)	3 (7.5)	8 (10.8)	20 (13.2)
<50 x 10^9/L	0	3 (2.7)	0	1 (1.4)	4 (2.6)
<25 x 10^9/L	0	3 (2.7)	0	0	3 (2.0)

Source: Sponsor's Summary of Clinical Safety, Table 69, November 6, 2017 submission to NDA 211172

Study CS2

In CS2, there was a 22.4% higher (95% CI: 13.9, 31.0) incidence rate of on-study AESIs of thrombocytopenia in the inotersen group compared with the placebo group. Most TEAEs of thrombocytopenia or decreased platelet count were mild or moderate in severity.

Table 3: CS2 On-Study Thrombocytopenia Treatment-Emergent Adverse Events (CS2 Safety Population)

Category Preferred Term	Placebo (N=60)		Inotersen 300 mg (N=112)	
	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events
Thrombocytopenia	1 (1.7)	2	27 (24.1)	35
Platelet count decreased	0	0	12 (10.7)	14
Thrombocytopenia	1 (1.7)	2	15 (13.4)	21
Risk difference, % 95% CI			22.4 13.9, 31.0	

Source: Module 5.3.5.1, CS2 CSR, Table 4.107 and Table 4.114

Source: Sponsor's Summary of Clinical Safety, Table 64, November 6, 2017 submission to NDA 211172

In Study CS2, platelet counts <100 x 10^9/L occurred in 26 of 112 (23.2%) of inotersen treated subjects as compared to 1 out of 60 (1.6%) of placebo patients. Twelve subjects out of 112 (10.7%) inotersen treated subjects had a platelet measurement at any given time point < 75 x 10^9/L, compared to 0 of 60 placebo subjects. Three inotersen subjects (2.7%) had a platelet measurement at any time point <25 x 10^9/L (Grade 4), including one subject (b) (6) who died from intracranial hemorrhage. Two subjects with platelet counts ≤10 x 10^9/ L had

Reference ID: 4247193

uninterpretable platelet results just prior to the low count result. These subjects may have had EDTA-related pseudothrombocytopenia with platelet clumping. All 3 subjects who developed Grade 4 thrombocytopenia had treatment-emergent anti-platelet IgG antibodies detected shortly before, or at the time of, the severe reduction in platelet count (Refer to the sponsor's Summary of Clinical Safety, page 140).

The original CS2 study protocol included CBC measurements that were scheduled 3-6 weeks apart. After Subject (b) (6) had severe thrombocytopenia and died of intracranial hemorrhage, platelets were monitored weekly.

No difference between treatment groups was observed in the incidence of bleeding events during the study.

Study CS3

In CS3, a higher proportion of subjects in the placebo-inotersen group reported AESIs of thrombocytopenia than subjects in the inotersen-inotersen group during the on-study period (Table 4). It is presumed by the sponsor that subjects in the placebo-inotersen group first experienced a decrease in platelets in CS3 after first exposure to inotersen, while subjects in the inotersen-inotersen group may have already experienced a decrease in platelets in CS2 that stabilized before CS3.

Table 4: CS3 On-Study Thrombocytopenia Treatment-Emergent Adverse Events (CS3 Safety Population)

Category Preferred Term	Placebo-Inotersen (N=40)		Inotersen-Inotersen (N=74)		Total (N=114)	
	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events
Thrombocytopenia	9 (22.5)	9	10 (13.5)	11	19 (16.7)	20
Thrombocytopenia	8 (20.0)	8	8 (10.8)	8	16 (14.0)	16
Platelet count decreased	1 (2.5)	1	3 (4.1)	3	4 (3.5)	4

Source: Module 5.3.5.2, CS3 CSR, Table 4.99
Source: Sponsor's Summary of Clinical Safety, Table 65, November 6, 2017 submission to NDA 211172

Four subjects in Study CS3 had nadir platelet counts <50 x 10^9/L, which were considered unconfirmed by the sponsor and were not included in Table 2. While one subject's nadir was consistent with a laboratory error, 3 subjects had nadir platelet counts, ranging from 33-41 x 10^9/L, that were not consistent with laboratory errors:

- All of the subjects (n=3) had similar decreases in platelet count on other dates.
- The post-nadir platelet increases in the confirmatory platelet counts occurred in the setting of inotersen dose cessation or dose reduction (n=3).

Reference ID: 4247193

- One subject (out of the 3 subjects with unconfirmed nadir platelet counts <50 x 10^9/L) received corticosteroids in response to the nadir platelet count, which contributed to the increased confirmatory platelet count.

None of the thrombocytopenia AESIs reported during the on-study period were severe.

Longitudinal Safety Set

The longitudinal safety analysis was based on data collected from the first dose of inotersen received in CS2 until the subject's last contact in CS2 or CS3. In the longitudinal safety set, 31.3% of subjects had 48 AESIs of thrombocytopenia (Table 4). As previously discussed, a total of 3 subjects experienced severe Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 TEAEs of thrombocytopenia in CS2 and 1 subject with severe Grade 4 thrombocytopenia (Subject (b) (6)) had a treatment-emergent SAE of intracranial hemorrhage that was fatal.

No severe treatment emergent adverse events (TEAEs) of thrombocytopenia were reported by the sponsor in CS3. However, DNP clinical review identified 3 cases of thrombocytopenia less than 50 x 10^9/L which were defined as unconfirmed. One subject in the inotersen-inotersen group had a confirmed CTCAE Grade 3 thrombocytopenia on laboratory testing.

In total, 6 subjects (5.4%) discontinued study drug due to thrombocytopenia on studies CS2 and CS3. Table 5 provides further information regarding these discontinuation events and nadir platelet counts.

Table 5: Longitudinal Thrombocytopenia Treatment-Emergent Adverse Events (Longitudinal Safety Set)

Category Preferred Term	Inotersen 300 mg (N=112)	
	Subjects, n (%)	Number of Events
Thrombocytopenia	35 (31.3)	48
Thrombocytopenia	23 (20.5)	31
Platelet count decreased	14 (12.5)	17

Source: Module 5.3.5.2, CS3 CSR, Table 4.39

Source: Sponsor's Summary of Clinical Safety, Table 66, November 6, 2017 submission to NDA 211172

Table 6: Longitudinal Safety Set Listing of Subjects Who Discontinued Treatment Due to Platelet-Related Adverse Events

Reference ID: 4247193

Subject (Study Discontinued)	Preferred Term	Study D1 (Platelet Value)	Date of Last Dose	Date of Platelet Nadir (Platelet Value)	End of Follow-Up or Last Platelet Value On-Study (Platelet Value)	Comments
(b) (6)	Thrombocytopenia	(b) (6) 191 x 10^9/L	(b) (6)	5 x 10^9/L	(b) (6) 175 x 10^9/L	Treated with i.v. methylprednisolone; AE outcome=resolved
	Thrombocytopenia	(b) (6) 187 x 10^9/L		9 x 10^9/L	(b) (6) 227 x 10^9/L	Treated with oral prednisone; AE outcome=resolved
	Haemorrhage intracranial	(b) (6) 222 x 10^9/L		(b) (6) <10 x 10^9/L	NA	Intracranial hemorrhage; AE outcome=fatal
	Platelet Count Decreased	(b) (6) 126 x 10^9/L		60 x 10^9/L	(b) (6) 134 x 10^9/L	No treatment; AE outcome=not resolved
	Thrombocytopenia	(b) (6) 108 x 10^9/L		55 x 10^9/L (additional same day count 83 x 10^9/L from local laboratory)	(b) (6) 130 x 10^9/L	No treatment; AE outcome=not resolved
	Platelet Count Decreased	(b) (6) 194 x 10^9/L		81 x 10^9/L	(b) (6) 120 x 10^9/L	No treatment; AE outcome=resolved

Source: Module 5.3.5.1, CS2 CSR, Appendix 16.2.5, Listing 13; Module 5.3.5.1, CS2 CSR, Appendix 16.2.7, Listing 46; Module 5.3.5.1, CS2 CSR, Appendix 16.2.8, Listing 50; Module 5.3.5.2, CS3 CSR, Appendix 16.2.5, Listing 9; Module 5.3.5.2, CS3 CSR, Appendix 16.2.7, Listing 38; and Module 5.3.5.2, CS3 CSR, Appendix 16.2.8, Listing 41

Source: Sponsor's Summary of Clinical Safety, Table 67, November 6, 2017 submission to NDA 211172

Table 7 shows the proportion of patients with thrombocytopenia events by grade, decreased from baseline and toxicity in the CS2, CS3, longitudinal and integrated safety populations.

Table 7: Subjects with Platelet Abnormalities (Central and Local Laboratory Values)

	CS2 (On-Study) (CS2 Safety Set)		CS3 (On-Study) (CS3 Safety Set)		Longitudinal (Longitudinal Safety Set)	Inotersen Integrated Set
	Placebo (N=60)	Inotersen 300 mg (N=112)	Placebo-Inotersen (N=40)	Inotersen-Inotersen (N=74)	Inotersen 300 mg (N=112)	Inotersen 300 mg (N=152)
Any value <140 x 10^9/L, n (%)	**10 (16.7)**	**62 (55.4)**	**21 (52.5)**	**47 (63.5)**	**72 (64.3)**	**93 (61.2)**
Confirmed platelet count decrease, n (%)						
Grade 1a (≥100 x 10^9/L to <140 x 10^9/L)	8 (13.3)	59 (52.7)	19 (47.5)	43 (58.1)	66 (58.9)	85 (55.9)
Grade 1b (≥75 x 10^9/L to <100 x 10^9/L)	1 (1.7)	24 (21.4)	13 (32.5)	23 (31.1)	33 (29.5)	46 (30.3)
Grade 2 (≥50 x 10^9/L to <75 x 10^9/L)	0	11 (9.8)	3 (7.5)	8 (10.8)	16 (14.3)	19 (12.5)
Grade 3 (≥25 x 10^9/L to <50 x 10^9/L)	0	2 (1.8)	0	1 (1.4)	3 (2.7)	3 (2.0)
Grade 4 (<25 x 10^9/L)	0	3 (2.7)	0	0	3 (2.7)	3 (2.0)
Confirmed value, n (%)						
≥30% decrease from Baseline/Inotersen Baseline	3 (5.0)	79 (70.5)	25 (62.5)	53 (71.6)	86 (76.8)	111 (73.0)
≥50% decrease from Baseline/Inotersen Baseline	1 (1.7)	20 (17.9)	10 (25.0)	21 (28.4)	34 (30.4)	44 (28.9)
<140 x 10^9/L	8 (13.3)	60 (53.6)	19 (47.5)	43 (58.1)	67 (59.8)	86 (56.6)
<100 x 10^9/L	1 (1.7)	26 (23.2)	13 (32.5)	23 (31.1)	35 (31.3)	48 (31.6)
<75 x 10^9/L	0	12 (10.7)	3 (7.5)	8 (10.8)	17 (15.2)	20 (13.2)
<50 x 10^9/L	0	3 (2.7)	0	1 (1.4)	4 (3.6)	4 (2.6)
<25 x 10^9/L	0	3 (2.7)	0	0	3 (2.7)	3 (2.0)
Confirmed maximum toxicity grade, n (%)						
Grade 1a	7 (11.7)	34 (30.4)	6 (15.0)	20 (27.0)	32 (28.6)	38 (25.0)
Grade 1b	1 (1.7)	14 (12.5)	10 (25.0)	15 (20.3)	18 (16.1)	28 (18.4)
Grade 2	0	9 (8.0)	3 (7.5)	7 (9.5)	13 (11.6)	16 (10.5)
Grade 3	0	0	0	1 (1.4)	1 (0.9)	1 (0.7)
Grade 4	0	3 (2.7)	0	0	3 (2.7)	3 (2.0)

Source: Sponsor's Summary of Clinical Safety, Table 69, November 6, 2017 submission to NDA 211172

Reference ID: 4247193

Clinical Narratives (Reproduced from DNP Clinical Safety Review for NDA 211172)

Study CS2 Subject (b) (6)

At enrollment, this 35 year old male from Argentina had Stage 2 hATTR. Platelet counts were normal at baseline. All interpretable platelet counts prior to the onset of severe thrombocytopenia were normal (see table 8 below). Three months after the first inotersen dose (Day 87) he developed treatment-emergent IgG antiplatelet antibodies, and the platelet count was not interpretable because of clumping. There were no reported symptoms of thrombocytopenia until Study Day 121, when he suddenly lost consciousness and began bleeding from the mouth. Upon hospitalization, his platelet count was <10 x 10^9/L, and he was diagnosed with intracranial hemorrhage. His neurological function rapidly deteriorated, and he died on Study Day 122 after receiving a total of 19 doses of inotersen. The patient's last inotersen dose was administered on Study Day 115.

Figure 2: Subject (b) (6) Summary of Events.[1]

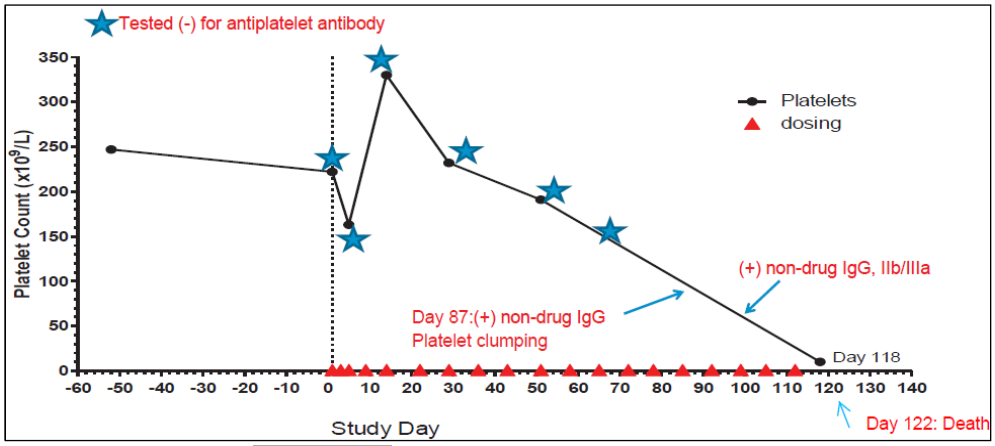


Table 8. Subject (b) (6) Platelet counts.[2]

Date (Study Day)	On/Off Inotersen	Platelet count (NR 140-400 x10^9/L)
(b) (6) (Screening)	Off	247
(Study Day 1)	Off	222
(Study Day 5)	On	163
(Study Day 15)	On	330
(Study Day 30)	On	232
(Study Day 52)	On	191
(Study Day 87)	On	Platelet clumps (estimate appears normal)
(Study Day 121)	On	<10

NR = Normal range

[1] P. 1066 Sponsor response to FDA pre-submission safety requests. Module 1 November 6, 2017 NDA 211172
[2] Narrative p. 3758 Study CS2 Clinical Study Report. Module 5 November 6, 2017 submission to NDA 211172

Reference ID: 4247193

Study CS2 Subject (b) (6)

At enrollment, this 45 year old female from Italy had Stage 1 hATTR. Platelet counts were normal at baseline and on Study Day 15. During Study Days 27-49, she reported symptoms of thrombocytopenia (including heavy menstruation, hematomas, and gingival bleeding) at multiple time points (see table below). On Study Day 31 the platelet count was not interpretable because of clumping. Because of gingival bleeding reported at Week 8 (Study Day 52), treatment was stopped. Platelet count from the Week 8 visit was 9 x 10^9/L, and IgG antiplatelet antibody test was positive. The subject was hospitalized and received platelet transfusions (x2) and glucocorticoids (methylprednisolone followed by prednisone). The subject was "relatively refractory to platelet transfusions in the first few days of thrombocytopenia suggesting rapid removal of transfused platelets from the circulation, probably due to destruction of platelets by antiplatelet antibodies."[3] Inotersen was permanently discontinued, with the subject receiving a total of 9 inotersen doses. The last inotersen dose was administered on Study Day 45. Platelet counts improved after inotersen discontinuation and glucocorticoid treatment.

Figure 3. Subject (b) (6) Summary of Events[4]

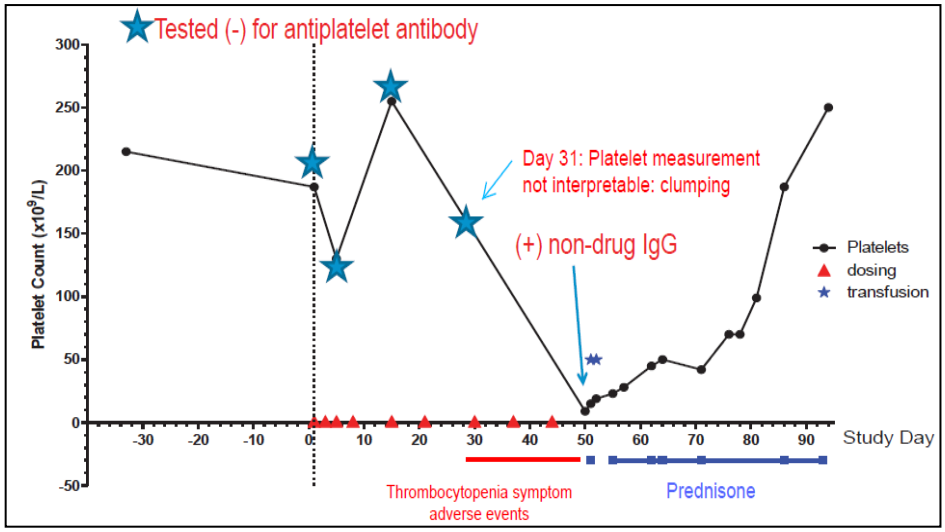


Table 9: Subject (b) (6) Platelet Counts[4]

Date (Study Day)		On/Off Inotersen	Platelet count (NR 140-400 x10^9/L) Adverse events
(b) (6)	(Screening)	Off	215
	(Study Day 1)	Off	187
	(Study Day 5)	On	130
	(Study Day 15)	On	255
	Study Day 27)	On	Heavy menstruation

[3] P. 21 Study Report 420915-CR02
[4] P. 1065 Sponsor response to FDA pre-submission safety requests. Module 1 November 6, 2017 NDA 211172

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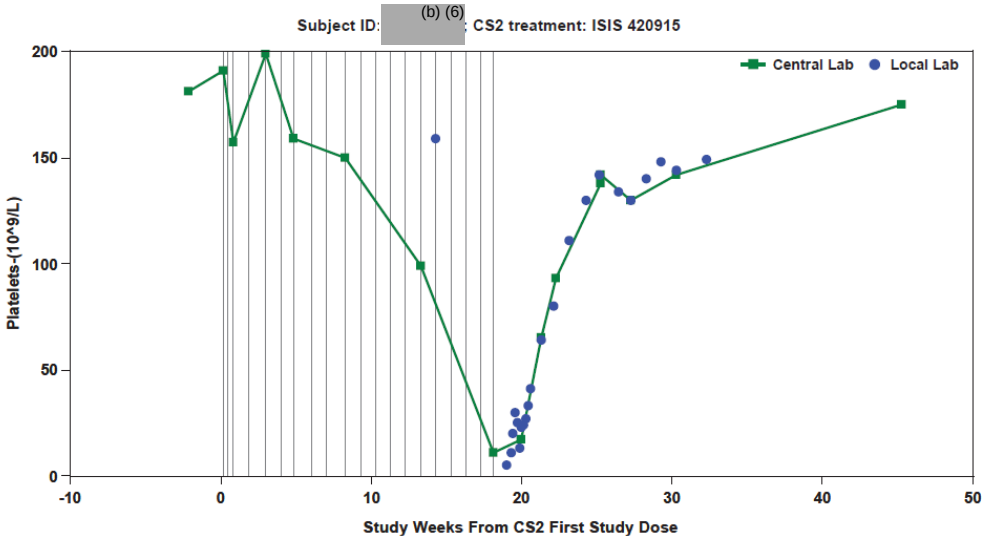
(b) (6)	Study Day 30)	On	Lower limb hematomas
	Study Day 31)	On	Platelet count uninterpretable: clumping
	Study Day 44)	On	Hematoma finger left hand
	Study Day 49)	On	Gingival bleeding
	(Study Day 52)	Off	9
	(Study Day 61)	Off	24
	(Study Day 68)	Off	66
	(Study Day 73)	Off	42
	(Study Day 79)	Off	72
	(Study Day 87)	Off	187
	(Study Day 95)	Off	250
	(Study Day 156)	Off	227

NR = Normal range

Study CS2 Subject (b) (6)

At enrollment, this 69 year old male from Brazil had Stage 1 hATTR. Platelet counts were normal at baseline. Platelet counts were generally normal (see graph and table below) until 4 months after the first dose of inotersen (Study Day 127), when he had a platelet count of 11 x 10^9/L and tested positive for IgG antiplatelet antibodies. He reported bruising with minor trauma on Study Day 127. He received his last inotersen dose on Study Day 127 after receiving a total of 20 doses. On Day 133, he reached a nadir platelet count of 5 x 10^9/L, and he was hospitalized. He was treated with intravenous methylprednisolone, and his platelet count improved.

Figure 4: Subject (b) (6) Summary of Platelet Counts [5]



Grey vertical lines represent the dosing records from CS2 study.

[5] Source: Sponsor's Integrated Summary of Safety, page 2901

Reference ID: 4247193

Table 10: Subject (b) (6) Summary of dosing and platelet counts.[6]

Date (Study Day)	On/Off Inotersen	Platelet count (NR 140-400 x10^9/L)
(b) (6) (Screening)	Off	181
(Study Day 1)	Off	191
(Study Day 6)	On	157
(Study Day 58)	On	150
(Study Day 93)	On	99
(Study Day 100)[a]	On	159
(Study Day 127)	On	11
(Study Day 129)[a]	On	11 (NR not provided)
(Study Day 131)[a]	On	10 (NR not provided)
(Study Day 133)[a]	On	5 (NR 150-450)
(Study Day 135)[a]	Off	11 (NR 150-450)
(Study Day 136)[a]	Off	20 (NR 150-450)
(Study Day 137)[a]	Off	30 (NR 150-450)
(Study Day 140)	Off	17 23[a] (NR 150-450)
(Study Day 144)[a]	Off	41 (NR 150-450)
(Study Day 149)	Off	65 64[a] (NR 150-450)
(Study Day 156)	Off	93
(Study Day 162)[a]	Off	111
Study Day 176)	Off	142
Study Day 177)	Off	142 138
Study Day 191)	Off	130
Study Day 317)	Off	175

[a] Local laboratory results
NR = Normal range

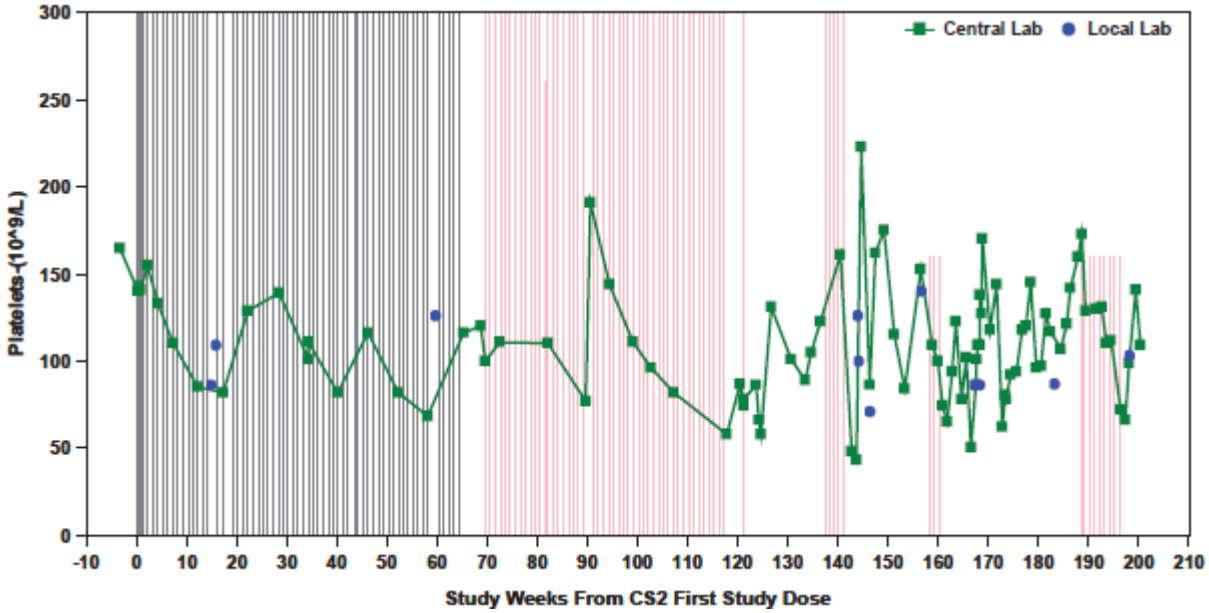
Study CS2/CS3 Subject (b) (6)

At enrollment, this 55 year old male from the United States had Stage 1 hATTR. Platelet counts were normal at baseline. He experienced a gradual decline in platelet count with multiple inotersen dose pauses. The subject had fluctuating platelet counts, including platelet increases with cessation of inotersen dose and platelet decreases with reinitiation of inotersen (see table below). The subject tested positive for treatment-emergent antiplatelet antibodies (indirect assay) on Study Day 848. The last full dose (inotersen 300 mg) was administered on Study Day 988, and then treatment was held because of low platelet counts. He reached a nadir platelet count of 43 x 10^9/L 2 years and 9 months after his first inotersen dose (Study Day 1005). He received prednisolone 20 mg daily for 31 days starting on Study Day 1193 for treatment of thrombocytopenia. In the last 60 weeks of Study CS3, the subject received a total of 12 reduced inotersen doses (160 mg weekly) in between dose pauses for thrombocytopenia.

[6] Narrative p. 3809-3812 CS2 clinical study report.

Reference ID: 4247193

Figure 1. Subject (b) (6) Summary of Dosing and Platelet Counts



Source: Sponsor's Integrated Summary of Safety, Page 2848

Grey and pink lines represent the dosing records from CS2 and CS3 studies, respectively. Solid and dash lines represent the dosing records for inotersen and placebo, respectively. When the dose amount was less than the full dose, the length of the line was proportional the amount administered.

Table 11: Subject (b) (6) Summary of Dosing and Platelet Counts.[7]

Date (Study Day)	On/Off Inotersen	Platelet count (NR 140-400 x10^9/L)
(b) (6) (Screening)	Off	165
(Study Day 1)	Off	140
(Study Day 29)	On	133
Study Day 85)	On	85 (NR 140-400)
(Study Day 103) [a]	On	86 (NR 150-450)
(Study Day 110) [a]	Off	109 (NR 150-450)
Study Day 407)	On	68 (NR 140-400)
Study Day 417) [a]	Off	126 (NR 150-450)
Study Day 457)	Off	116 (NR 140-400)
(Study Day 480)	Off	120 (NR 140-400)
(Study Day 487)	Off	100 (NR 140-400)
(Study Day 575)	On	110 (NR 140-400)
Study Day 627)	On	77 (NR 140-400)
Study Day 634)	Off	191 (NR 140-400)
(Study Day 750)	On	82 (NR 140-400)
Study Day 824)	On	58 (NR 140-400)
(Study Day 848)	Off	78(NR 140-400) 74 (NR 140-400)
(Study Day 872)	Off	58 (NR 140-400)

[7] P. 2966-2967 CS3 Clinical Study Report

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(b) (6)	(Study Day 956)	Off	123 (NR 140-400)
	(Study Day 983)	On	161 (NR 140-400)
	Study Day 999)	Off	48 (NR 140-400)
	Study Day 1005)	Off	43 (NR 140-400)
	Study Day 1044)	Off	175 (NR 140-400)
	(Study Day 1096)	Off	153 (NR 140-400)
	(Study Day 1111)	On (160 mg)*	109 (NR 140-400)
	(Study Day 1119)	On (160 mg)*	100 (NR 140-400)
	(Study Day 1126)	On (160 mg)*	74 x109/L (NR 140-400)
	Study Day 1166)	Off	50 (NR 140-400)
	(Study Day 1320)	Off	173 (NR 140-400)
	(Study Day 1326)	On (160 mg)*	129 (NR 140-400)
	Study Day 1361)	On (160 mg)*	112 (NR 140-400)
	Study Day 1368)	On (160 mg)*	Platelet clumps (NR 140-400)
	Study Day 1403)	Off	109 (NR 140-400)

NR = Normal range

* Dose reduced due to thrombocytopenia

Concomitant Glucocorticoid Administration

High dose glucocorticoids were administered to two of the three subjects that developed CTCAE Grade 4 thrombocytopenia in Study CS2 (Subjects (b) (6) and one additional subject in CS2 (Subject (b) (6); this subject commenced oral prednisolone at the end of CS2 and completed prednisolone treatment in CS3) and 7 additional subjects in Study CS3 (Subjects (b) (6) received lower dose prednisolone for treatment of lesser degrees of thrombocytopenia/platelet count reduction.

The subjects who received glucocorticoids for treatment of Grade 4 thrombocytopenia responded as follows:

- Subject (b) (6) had a platelet count of $5x10^9$/L on Study Day 133 from start of inotersen treatment. Methylprednisolone 1 g per day for 3 days was initiated the same day and the subject and experienced a robust and sustained platelet response, with platelets rising to > $50x10^9$/L after approximately 22 Days and >$100x10^9$/L after approximately 46 days.

- Subject (b) (6) had a platelet count of $9x10^9$/L and $15x10^9$/L on Study Days 53 and 54 respectively from start of inotersen treatment. Platelet transfusion (one transfusion per day on two successive days; number of units unknown) in tandem with a two doses of IV methylprednisolone 20 mg (during each transfusion) was initiated on Study Day 54. Prednisolone 50 mg per day (for 10 days) orally was initiated a few days after the last platelet transfusion and then tapered to 25 and then 18.5 mg for 2 days and 7 days.

The subjects that received lower doses of oral glucocorticoids for treatment of lesser degrees of platelet count reduction responded less consistently:

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- Subject (b) (6) received inotersen in CS2 and CS3 and initiated oral prednisone 50 mg per day at the end of CS2 (on Study Day 443 from start of inotersen treatment) for treatment of petechia, which was associated with thrombocytopenia. The prednisolone was tapered slowly throughout CS2 and CS3. The response to glucocorticoid treatment resulted in platelet count for this subject increasing from $83x10^9$/L (value in CS2, 2 days prior to initiation of prednisolone) to 143x109/L (value in CS3) over a period of approximately 15 days.

- Subject (b) (6) who received inotersen in CS2 and CS3, was found to have a platelet count of $33x10^9$/L on central lab report at Day 533 from start of inotersen treatment. Oral prednisolone 60 mg per day was initiated by the investigator on Study Day 535. A local lab platelet count performed the same day showed a value of $68x10^9$/L and glucocorticoids were subsequently discontinued after three days of treatment. On initiation of prednisolone the platelet count increased to $181x10^9$/L after 5 days but fell back to $77x10^9$/L approximately 2 weeks after prednisolone was discontinued.

- Subject (b) (6) received inotersen in both CS2 and CS3 and had a platelet count of $101x10^9$/L on Study Day 639 from the start of inotersen treatment. Oral prednisolone 20 mg per day was initiated on Study Day 641. Prednisolone dosing was continued for 31 days. After 19 days of prednisolone the platelet count had fallen to 64x109/L. After 26 days of prednisolone the platelet count was $162x10^9$/L. Ten days after discontinuing the prednisolone the platelet count was $99x10^9$/L.

- Subject (b) (6) received inotersen in both CS2 and CS3 and had a platelet count of $114x10^9$/L on Study Day 719 from the start of inotersen treatment. Oral prednisolone 20 mg per day was initiated on Study Day 725. Prednisolone dosing was continued for 31 days. Platelet count varied between 113 and $122x10^9$/L during dosing with prednisolone.

- Subject (b) (6) received inotersen in both CS2 and CS3 and had a platelet count of $106x10^9$/L on Study Day 954 after initiation of inotersen treatment. Oral prednisolone 20 mg per day was initiated on Study Day 954. Prednisolone dosing was continued for 31 days. Platelet count varied between 10^9 and $119x10^9$/L during dosing with prednisolone.

- Subject (b) (6) received placebo in CS2 and inotersen in CS3 and had a platelet count of $143x10^9$/L at the time of initiation of oral prednisolone 20 mg per day on Study Day 543 from the start of inotersen treatment. Prednisolone dosing was continued for 31 days. Platelet count increased to 175 $x10^9$/L after two weeks of prednisolone but fell back to 118x109/L by the end of treatment with prednisolone.

- Subject (b) (6) received inotersen in both CS2 and CS3 and had a platelet count of $76x10^9$/L on Study Day 1059 from the start of inotersen treatment. Oral prednisolone 20 mg per day was initiated on Study Day 1063. Prednisolone dosing was continued for 31 days. Platelet count varied between 82 and $95x10^9$/L during dosing with prednisolone.

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Bleeding

In CS2, the percentage of patients who experienced hemorrhagic events during the study was similar between treatment groups (23.3% [14/60 subjects] and 21.4% [24/112 subjects] in the placebo and inotersen arms respectively). Actual bleeds were reported more frequently at sites other than the injection site. Hematomas were reported at a similar incidence (1.7% [1/60 subjects] and 2.7% [3/112 subjects] in the placebo and inotersen arms respectively) at the injection site and at sites other than the injection site in both treatment groups. The majority of TEAEs of hemorrhage were mild or moderate in severity in both treatment groups. There was 1 severe bleeding SAE of intracranial hemorrhage that occurred in association with CTCAE Grade 4 thrombocytopenia in CS2. There were no cases of disseminated intravascular coagulation (DIC) or thrombotic thrombocytopenic purpura (TTP) reported in CS2.

An analysis of TEAEs of hemorrhage by platelet count category showed that of the 40 inotersen-treated subjects who had a hemorrhage TEAE, 29 of 40 subjects (73%) experienced 37 of 63 events (59%) while their platelet counts were within the normal range ($\geq 140 \times 10^9$/L). A total of 14 of 40 subjects (35%) experienced 26 out of 63 events (41%) at the time of a low platelet count.

In CS3, the percentage of patients who experienced hemorrhagic events during the study was similar between the placebo-inotersen and inotersen-inotersen groups (15% [6/40 subjects] and 9.5% [7/71 subjects] respectively). The most commonly experienced hemorrhage preferred term was injection site bruising. All of the hemorrhage TEAEs were mild or moderate in severity. There were no cases of DIC or TTP reported in CS3.

Analysis of the bleeding events by platelet count for the total subjects group in CS3 showed that, of the 31 subjects who had a bleeding event (31 events), 14/31 (45%) subjects experienced 14/31 (45%) of the bleeding events at the time of normal platelet count (≥140,000/mm3) and 17/31 (55%) subjects experienced 17/31 (55%) of bleeding events at the time of a low platelet count. No subject experienced more than 1 bleeding event.

Reference ID: 4247193

Table 12: CS2 On-Study Hemorrhages Treatment-Emergent Adverse Events (CS2 Safety Set)

	Placebo (N=60)		Inotersen 300 mg (N=112)	
	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events
Haemorrhages	20 (33.3)	26	40 (35.7)	63
Actual bleeds	14 (23.3)	17	24 (21.4)	32
At injection site	1 (1.7)	1	4 (3.6)	5
Injection site haemorrhage	1 (1.7)	1	4 (3.6)	5
Not at injection site	13 (21.7)	16	20 (17.9)	27
Conjunctival haemorrhage	3 (5.0)	3	2 (1.8)	3
Diarrhoea haemorrhagic	0	0	1 (0.9)	1
Ecchymosis	4 (6.7)	4	5 (4.5)	7
Epistaxis	0	0	1 (0.9)	1
Gastrointestinal haemorrhage	0	0	1 (0.9)	1
Gingival bleeding	1 (1.7)	1	1 (0.9)	1
Haematuria	5 (8.3)	7	5 (4.5)	5
Haemorrhage intracranial	0	0	1 (0.9)	1
Menorrhagia	0	0	1 (0.9)	1
Metrorrhagia	0	0	1 (0.9)	1
Periorbital haemorrhage	1 (1.7)	1	3 (2.7)	3
Scleral haemorrhage	0	0	1 (0.9)	1
Vessel puncture site haemorrhage	0	0	1 (0.9)	1
Hematomas/subdermal bleeds	7 (11.7)	7	23 (20.5)	27
At injection site	3 (5.0)	3	11 (9.8)	11
Injection site bruising	2 (3.3)	2	8 (7.1)	8
Injection site haematoma	1 (1.7)	1	3 (2.7)	3
Not at injection site	4 (6.7)	4	14 (12.5)	16
Blood urine present	1 (1.7)	1	0	0
Contusion	1 (1.7)	1	8 (7.1)	9
Haematoma	1 (1.7)	1	4 (3.6)	5
Petechiae	0	0	1 (0.9)	1
Purpura	0	0	1 (0.9)	1
Purpura non-thrombocytopenic	1 (1.7)	1	0	0
Investigations SOC (test results)	1 (1.7)	2	2 (1.8)	4
Haematocrit decreased	0	0	1 (0.9)	1
Haemoglobin decreased	0	0	2 (1.8)	2
International normalised ratio increased	1 (1.7)	1	0	0
Prothrombin time prolonged	1 (1.7)	1	0	0
Red blood cell count decreased	0	0	1 (0.9)	1
Risk difference, % 95% CI			2.4 -12.5, 17.2	

Source: Module 5.3.5.1, CS2 CSR, Table 4.109 and Table 4.116

Source: Sponsor's Summary of Clinical Safety, Table 98, November 6, 2017 submission to NDA 211172

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Table 13: CS3 On-Study Hemorrhages Treatment-Emergent Adverse Events (CS3 Safety Set)

Category Preferred term	Placebo-Inotersen (N=40)		Inotersen-Inotersen (N=74)		Total (N=114)	
	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events
Haemorrhages	11 (27.5)	12	15 (20.3)	19	26 (22.8)	31
Actual bleeds	6 (15.0)	6	7 (9.5)	8	13 (11.4)	14
At injection site	1 (2.5)	1	1 (1.4)	1	2 (1.8)	2
Injection site haemorrhage	1 (2.5)	1	1 (1.4)	1	2 (1.8)	2
Not at injection site	5 (12.5)	5	6 (8.1)	7	11 (9.6)	12
Haematuria	2 (5.0)	2	3 (4.1)	3	5 (4.4)	5
Ecchymosis	1 (2.5)	1	1 (1.4)	1	2 (1.8)	2
Gingival bleeding	0	0	1 (1.4)	1	1 (0.9)	1
Haemorrhage	0	0	1 (1.4)	1	1 (0.9)	1
Retinal haemorrhage	0	0	1 (1.4)	1	1 (0.9)	1
Haemoptysis	1 (2.5)	1	0	0	1 (0.9)	1
Rectal haemorrhage	1 (2.5)	1	0	0	1 (0.9)	1
Hematomas/subdermal bleeds	5 (12.5)	5	9 (12.2)	10	14 (12.3)	15
At injection site	2 (5.0)	2	5 (6.8)	5	7 (6.1)	7
Injection site bruising	2 (5.0)	2	4 (5.4)	4	6 (5.3)	6
Injection site haematoma	0	0	1 (1.4)	1	1 (0.9)	1
Not at injection site	3 (7.5)	3	4 (5.4)	5	7 (6.1)	8
Contusion	1 (2.5)	1	2 (2.7)	3	3 (2.6)	4
Haematoma	1 (2.5)	1	1 (1.4)	1	2 (1.8)	2
Increased tendency to bruise	0	0	1 (1.4)	1	1 (0.9)	1
Purpura	1 (2.5)	1	0	0	1 (0.9)	1
Investigations SOC (test results)	1 (2.5)	1	1 (1.4)	1	2 (1.8)	2
International normalised ratio increased	0	0	1 (1.4)	1	1 (0.9)	1
Haemoglobin decreased	1 (2.5)	1	0	0	1 (0.9)	1

Source: Module 5.3.5.2, CS3 CSR, Table 4.100
Source: Sponsor's Summary of Clinical Safety, Table 99, November 6, 2017 submission to NDA 211172

Evaluation of Mechanism of Platelet Count Declines

An extensive investigation to evaluate the cause of the observed platelet count changes in the Inotersen Phase 3 program has been conducted by the sponsor.

The following conclusions were provided by the sponsor in the Summary of Clinical Safety (Section 2.7.4, page 139):

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- There is no evidence of an effect on megakaryocyte function as demonstrated by bone marrow biopsy and rapid recovery of platelet count following discontinuation of study drug.
- There is no evidence of thrombotic microangiopathy, disseminated intravascular coagulation (DIC), or thrombotic thrombocytopenic purpura (TTP) as demonstrated by fibrinogen and d-dimer levels, and coagulation parameters.
- There is no evidence that inotersen causes platelet activation as demonstrated by incubating human platelets at inotersen concentrations that are 2 times the anticipated maximum serum concentration (Cmax) at the 300 mg SC dose.
- A classical heparin-induced thrombocytopenia (HIT) type mechanism has been excluded based on absence of immunoglobulin G (IgG) anti-PF4 antibodies and negative serotonin release assay in inotersen-treated subjects with thrombocytopenia.
- Systemic complement activation is unlikely to be a general contributor based on the results of testing serum complement factor levels in a subset of subjects.
- An effect on platelet function is unlikely based on lack of increased risk or severity of bleeding in (a) thrombocytopenic subjects as compared with subjects with normal platelet count, and (b) subjects receiving antiplatelet and/or antithrombotic agents as compared with those who did not receive these drugs.

Analyses of two ATTR natural history databases by the sponsor suggest that platelet reductions below 50,000 are not part of the natural history of subjects with hATTR. However, decreases in the range of 75 to 99,000 may occur in 7% to 17% of patients with hATTR although the mechanism by which this occurs is not known and there is limited data in the literature.

Platelet immunology testing performed at [redacted] (b) (4) demonstrated that antiplatelet antibodies (IgG and IgM) and anti-platelet factor 4 [anti-PF4] antibodies (IgM only) were present prior to treatment in the serum of some subjects enrolled in CS2.

Treatment-emergent antiplatelet antibodies (IgG and IgM) and anti-PF4 antibodies (IgG, IgM, and IgA) were seen both in subjects receiving inotersen (~29% of inotersen-treated in CS2 and >53% of subjects in CS3 where all subjects received inotersen) and in subjects receiving placebo (~6% of subjects in the placebo group in CS2).

Anti-PF4 IgG antibodies were seen in two subjects, but neither subject had thrombocytopenia, And in both cases the serotonin release assay was negative, thereby excluding a classical HIT like mechanism.

The presence of antiplatelet antibodies in inotersen-treated subjects did not discriminate well between thrombocytopenic and non-thrombocytopenic subjects since antiplatelet antibodies were seen in both of these groups. However, all three subjects who developed Grade 4 thrombocytopenia had a treatment-emergent anti-platelet IgG detected shortly before, or at the time of the severe reduction in platelet count. It is plausible that the more severe thrombocytopenia observed in a small number of subjects in CS2 is immune mediated. Further,

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one of these subjects was relatively refractory to platelet transfusions in the first few days of thrombocytopenia, suggesting rapid removal of transfused platelets from the circulation, consistent with an immune thrombocytopenia. The sponsor noted that Grade 4 cases also responded well to corticosteroid administration, which is consistent with an immune-mediated thrombocytopenic mechanism. However, discontinuation of study drug often coincided with start glucocorticoid treatment so it is difficult to isolate the response to steroids alone. In 2 of the cases of severe thrombocytopenia, the platelet epitope was GPIIb/IIIa, which is a common target for antiplatelet antibodies in immune thrombocytopenia.

In the third Grade 4 thrombocytopenia case, no epitope was identified. However, most subjects who developed antiplatelet IgG did not develop severe thrombocytopenia (and some did not develop thrombocytopenia at all) and, in the Grade 4 cases, emergence of the antiplatelet IgG antibodies occurred very close to or at the time of the severe platelet count decline, so it is unlikely that testing for antiplatelet IgG is a feasible screening tool for risk stratification purposes.

It is important to note that some antiplatelet antibody test results showed evidence of drug dependence as shown in Table 14 below.

Table 14: Study CS2 Summary of Antiplatelet Antibody Test Results and Changes in Platelet Count

	Nadir platelet count **Median (Range)**	**Largest percent decrease in platelets from baseline** **Median (Range)**
Inotersen subjects (N=37)		
No positive antiplatelet antibody test (N=22)	91 (54 to 236)	-46 (-61 to -14)
Treatment-emergent positive antiplatelet antibody test (N=9)	65 (5 to 108)	-68 (-97 to -45)
Antiplatelet antibody test positive at baseline (N=6)	89 (68 to 204)	-58 (-65 to -10)
Placebo subjects (N=18)		
No positive antiplatelet antibody test (N=17)	177 (128 to 285)	-16 (-24 to -16)
Treatment-emergent positive antiplatelet antibody test (N=0)	-	-
Antiplatelet antibody test positive at baseline (N=1)	149	-11

Platelet count normal range (central laboratory): 140 – 400 x 10^9/L
Sources: Submissions to NDA 211172 on November 6, 1017 (dataset ADLB) and February 12, 2018.

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Table 15: Subjects with nadir platelet counts <75 x 10^9/L and treatment-emergent positive antiplatelet antibody measurement. Studies CS2 and CS3

Study	Site ID	Subject ID	Nadir Platelet Count	Antibody Type(s)	Antiplatelet antibody positive shortly before or at a time of platelet decline	Antiplatelet antibody positive at baseline
CS2	(b) (6)	(b) (6)	5	Antiplatelet IgG - Drug Independent/* Anti- GPIIb/IIIa#	Yes	No
CS2			9	Antiplatelet IgG - Drug Independent	Yes	No
CS2			10	Antiplatelet IgG - Drug Independent Anti- GPIIb/IIIa#	Yes	No
CS3			33	Antiplatelet IgM - Drug Dependent/ Antiplatelet IgG - Drug Dependent/ Antiplatelet IgG - Drug Independent/ *	Yes	No
CS3			41	Antiplatelet IgG - Drug Dependent	Yes	No
CS3			43	Platelet Antibodies, Indirect	Yes	No
CS3			50	Antiplatelet IgM - Drug Dependent/ Antiplatelet IgG - Drug Independent/*	Yes	No
CS3			56	Platelet Antibodies, Indirect	Yes	No
CS2			58	Platelet Antibodies, Indirect	Yes	No
CS3			59	Antiplatelet IgM - Drug Dependent/ Antiplatelet IgG - Drug Dependent/ Antiplatelet IgG - Drug Independent	Yes	No
CS2			62	Antiplatelet IgG - Drug Independent/*	Yes	No
CS3			66	Antiplatelet IgG - Drug Dependent	Yes	No
CS3			69	Platelet Antibodies, Indirect	Yes	No

Source: Responses to FDA information request submitted to NDA 211172 on January 8, 2018 and February 12, 2018.

Reference ID: 4247193

Discussion:

DNP Question to DHP

1. In the Sponsor's proposed label, are the instructions regarding frequency of platelet monitoring acceptable?

DHP Response:

The following table outlines the sponsor's proposed labeling for patients who experience thrombocytopenia while being treated with inotersen.

(b) (4)

[redacted]

No, the outlined platelet monitoring guidelines as presented in the Sponsor's proposed labeling do not appear adequate based on all available data from the CS2 and CS3 clinical studies. Refer to the following bulleted items for further description of key safety issues that DHP considers important and relevant to platelet monitoring.

Statements denoted by quotations could be incorporated into the draft labeling language for inotersen:

- *It should be discussed in the labeling that "if a platelet count is uninterpretable and/or there is suspicion of EDTA mediated platelet clumping, a repeat platelet count should be collected in a sodium citrate tube as soon as possible." This is standard of care; however, it is important to inform the prescriber population (neurologists) of the appropriate follow up testing in this setting.*

- *"If a patient develops of platelet count ≤ 10 x 10^9/L, they should be transferred to an inpatient setting for frequent monitoring of platelet count (at least daily) and to expedite*

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consultation with a hematologist, administration of platelet transfusions as well as glucocorticoids if deemed necessary."

- *"If a patient develops severe thrombocytopenia (defined as a platelet count ≤ 50 x 10^9/L at any time point during treatment with inotersen), it should be advised that consultation with a hematologist is highly recommended for further discussion of the risk benefit of inotersen treatment and to exclude other etiologies of thrombocytopenia."*

- *"If there is suspicion for immune mediated thrombocytopenia with acute onset of severe thrombocytopenia, the drug should be immediately discontinued. Consultation with a hematologist is also recommended. Antibody testing should only be sent for confirmatory purposes."*

- *"Patients should be educated to immediately contact a provider or seek medical attention with any signs or symptoms of bleeding, including: epistaxis, gingival bleeding, easy bruising, petechia or purpura, hematoma, hematuria, hematochezia or melena."*

- *It should be addressed in the labeling that "if a patient is receiving full dose systemic anticoagulation or thromboprophylaxis they are at increased risk for clinically significant bleeding in the setting of thrombocytopenia, particularly if severe thrombocytopenia occurs (platelet count less than 50 x 109/L). Discontinuation of anticoagulant therapy in the setting of severe thrombocytopenia should be recommended."*

While moderate and severe thrombocytopenia are both associated with an increased risk of clinically significant bleeding, the degree of thrombocytopenia is not necessarily predictive of an individual's bleeding risk. Furthermore, unpredicted, acute and severe reductions in platelet counts were observed in subjects treated on the CS2 study (2.7%, 3 out of 112 inotersen treated subjects). While increased frequency of platelet count monitoring is certainly advised, it may not necessarily mitigate the risk of severe thrombocytopenia in the setting of inotersen treatment.

DNP Question to DHP

2a. In patients who had thrombocytopenia after inotersen treatment, [redacted] (b) (4) an acceptable option?

DHP Response: *Please refer to the table in Question 1 for the sponsor's proposed labeling.*

Response to 2a: *From the data provided by the sponsor, DHP cannot explicitly state which patients should be deemed safe to undergo rechallenge with the drug in the case that significant thrombocytopenia occurs. We agree with the sponsor's proposal to permanently discontinue inotersen if the platelet count decreased beyond 25 x 10^9/L* [redacted] (b) (4)

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The decision to rechallenge other select patients with [redacted] (b) (4) *inotersen should be made on a case by case basis after careful consideration by the treating neurologist as well as consultation with a hematologist. The severity of and duration of resultant thrombocytopenia, associated major and minor clinical bleeding symptoms, and platelet response to drug discontinuation or glucocorticoid administration should be evaluated.*

Given that hATTR is a life threatening, progressive disease with no approved treatment options in the US, the risk versus benefit of inotersen therapy will need to be weighed by treating providers and communicated to patients. While the risks associated with this treatment are significant, the potential for improvement in neuropathy symptoms and overall quality of life in this patient population should be considered.

[redacted] (b) (4)

As per the sponsor's response dated January 8, 2018 to the information request issued by DNP regarding thrombocytopenia in the study population, at the time of the database lock for the NDA submission, all patients that required a reduced dose for management of thrombocytopenia had their weekly dose reduced by 50% (changed from 284 mg SC weekly to 142 mg SC weekly.

However, the effect of dose reduction in CS2/CS3 patients cannot be accurately assessed given multiple confounding variables including the following:

- *The onset and severity of thrombocytopenia in subjects treated with inotersen did not occur in a consistent pattern. Refer to the previous clinical narratives for subjects who experienced Grade 4 thrombocytopenia (pages 9-15 of the background) as well as Tables 16 and 17.*
- *Glucocorticoids of varying doses and duration were administered to select patients who developed severe thrombocytopenia while on study.*
- *Subjects had drug held intermittently for varying lengths of time ("dose pauses") throughout the study period.*

The following text will describe dose pauses in both studies, a description of concomitant glucocorticoid administration in the CS2 and CS3 studies is located in pages 15-16 of the background.

Analysis of Dose Pauses in CS2 and CS3

In CS2, 11 (9.8%) subjects paused dosing due to platelet count falling below 75 x 10^9/L (the dose pause threshold), and dosing of inotersen remained paused until the platelet count had recovered to at least 100 x 10^9/L (the 3 subjects who experienced Grade 4 thrombocytopenia permanently discontinued dosing and were not included in this total). Inotersen was successfully reinitiated following dose pauses in all except one of these subjects (Subject [redacted] (b) (6)*, although a switch*

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to a reduced dose was required to maintain platelet counts above 75 x 10^9/L in 2 subjects. The mean duration of dose pause in subjects who reinitiated dosing was 4.5 weeks (range: 1 to 10 weeks).

In CS3, 10 (8.8%) subjects paused dosing due to platelet count falling below the dose pause threshold. Of these, 4 subjects had previously paused dosing for platelet count less than 75 x 10^9/L in CS2. Inotersen was reinitiated after dose pause for all but one of these subjects (Subject (b) (6)), although a switch to a reduced dose was required to maintain platelet counts above 75 x 109/L in more than half of the subjects. The mean duration of dose pause in subjects who reinitiated dosing was 7.8 weeks (range: 1 to 19 weeks).

The following tables provided by the sponsor highlight the subjects who paused dosing in study CS2 and CS3 for platelet counts less than 75 x 10^9/L.

Table 16: CS2 Subjects Who Paused Dosing Due to Platelet Count <75 x 10^9/L

Subject Number[a]	Number of Dose Pauses	Week Number for Dose Pauses	Length of Pause (Weeks)	Dosing Reinitiated (Yes/No)/ Dose on Reinitiation[b]
(b) (6)	1	18-29	12	No
	1	19-21	3	Yes/Full Dose
	4	31-35 37-40 56-58 61-63	5 4 3 3	Yes/Full Dose
	2	28-31 35-41	4 7	Yes/Reduced Dose
	2	22-28 55-64	7 10	Yes/Reduced Dose
	2	48-54 62-65	7 4	Yes/Full Dose
	1	17-19	3	Yes/Full Dose
	1	43-46	4	Yes/Full Dose
	1	58-62	5	Yes/Full Dose
	3	30-31 36 44	2 1 1	Yes/Full Dose
	1	60	1	Yes/Full Dose

Source: Module 5.3.5.1, CS2 CSR, Appendix 16.2.5, Listing 13 and Listing 15
a. The 3 subjects who permanently discontinued study drug due to CTCAE Grade 4 thrombocytopenia were not included.
b. Reduced dose was 150 mg/week.

Source: Responses to FDA information request submitted to NDA 211172 on January 8, 2018 and February 12, 2018.

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Table 17: CS3 Subjects Who Paused Dosing Due to Platelet Count <75 x 10^9/L

Subject Number	Number of Dose Pauses	Week Number for Dose Pauses	Length of Pause (Weeks)	Dosing Reinitiated (Yes/No)/ Dose on Reinitiation[a]
(b) (6)	1	46-52	7	No
	1	31-44	14	Yes/Reduced Dose
	3	17 86-87 105	1 2 1	Yes/Reduced Dose
	3	7-16 20-24 44-57	10 5 14	Yes/Reduced Dose
	2	16 18-27	1 10	Yes/Full Dose
	3	48-51 55-58 101-119	4 4 19	Yes/Reduced Dose
	1	13-16	4	Yes/Full Dose
	1	29-37	9	Yes/Full Dose
	2	51-68 87-103	18 17	Yes/Reduced Dose
	6	50-52 54-63 74-81 93-100 105-109 129-133	3 10 8 8 5 5	Yes/Reduced Dose

Source: Module 5.3.5.2, CS3 CSR, Appendix 16.2.5, Listing 9 and Listing 11
a. Reduced dose was 150 mg/week (Subject (b) (6) received 150 mg every 2 weeks).
b. Subject was also dose paused for platelet count <75 x 10^9/L in CS2.

Source: Responses to FDA information request submitted to NDA 211172 on January 8, 2018 and February 12, 2018.

DNP Question to DHP

2b. Please comment on the Sponsor's proposals (b) (4)

The Sponsor provides additional information (b) (4) in clinical studies on p. 3 of the IR response located at this link: \\CDSESUB1\evsprod\NDA211172\0007\m1\us\12-cover-letter.

DHP Response to 2b: (b) (4)

The half life of inotersen is long (approximately 4 weeks) and the sponsor claims (b) (4)

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[redacted] (b) (4) *(refer to Population Pharmacodynamic Analyses Report Addendum 1). DNP consultation with Pharmacology will be required to adequately assess the sponsor's population PK/PD modeling for* [redacted] (b) (4)

DHP cannot address whether [redacted] (b) (4) *There is a paucity of clinical and efficacy data in subjects treated with this regimen and the sponsor's PK/PD population model will need to be reviewed by a clinical pharmacology reviewer to determine its acceptability for the purpose* [redacted] (b) (4).

DNP Question to DHP

2c. If a patient does undergo rechallenge, are there additional precautions that should be performed?

DHP Response to 2c: *Beyond continued frequent monitoring of the platelet count, DHP has no additional suggestions in patients undergoing rechallenge* [redacted] (b) (4)

DNP Question to DHP

3. We are concerned about severe thrombocytopenia with rechallenge. Which patients should avoid retreatment with inotersen?

DHP Response to 3: *Patients who develop acute onset of severe thrombocytopenia (platelet count less than 25 x 10^9/L) appear to be at greatest risk for clinically significant bleeding events.*

We agree with the sponsor's proposal to permanently discontinue inotersen in patients who develop a platelet count less than 25 x 10^9/L. These patients should not be rechallenged with inotersen even if platelet counts improve or normalize. The decision to rechallenge patients whose platelet count nadirs are above the aforementioned threshold should be made on a case by case basis with careful consideration of the risk versus benefit of continuing treatment [redacted] (b) (4)

DNP Question to DHP

4. Is there a role for testing for anti-platelet antibodies in patients treated with inotersen?

DHP Response to 4: *Based on the data provided by the sponsor and discussed in pages 20-22 of this consult, the presence of antiplatelet antibodies in inotersen-treated subjects did not discriminate well between thrombocytopenic and non-thrombocytopenic subjects since antiplatelet antibodies were seen in both groups. In CS2, a very small proportion of placebo and inotersen treated hATTR patients also had evidence of antiplatelet antibodies at baseline (1 out of 18 placebo subjects and 6 out of 37 inotersen subjects respectively). However, all 3 subjects*

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who developed Grade 4 thrombocytopenia had treatment-emergent anti-platelet IgG detected shortly before, or at the time of the severe reduction in platelet count.

Only a small proportion of subjects were selected for antiplatelet antibody testing at the discretion of the sponsor although this occurred in a blinded fashion (n=55). Therefore, recommendations regarding testing for screening or diagnostic purposes are not conclusive. Results from subjects who underwent antiplatelet antibody testing may not be generalizable to all subjects treated on study.

DHP does not believe there is a role for antiplatelet antibody testing during the initiation of inotersen treatment for the purposes of screening given that results may not accurately predict which hATTR patients will develop thrombocytopenia.

DHP does not recommend testing for antiplatelet antibodies in patients who develop severe thrombocytopenia in an effort to diagnose immune mediated thrombocytopenia or DITP. If there is suspicion for immune mediated thrombocytopenia with acute onset of severe thrombocytopenia, the drug should be immediately discontinued. Consultation with a hematologist is also recommended. Antibody testing should only be sent for confirmatory purposes.

The rationale for this is three-fold:

(1) Such testing is not widely available and requires substantial time to process, therefore it is not feasible to wait for test results before deciding whether to discontinue the potential causative drug.

(2) Patients with immune-mediated thrombocytopenia may have unpredictable, acute, and significant reductions in platelet count which makes it unsafe to wait for antiplatelet antibody testing results.

(3) Tests for drug-dependent antibodies can be negative in patients with probable immune mediated thrombocytopenia because assay methods may be insufficiently sensitive to detect some antibodies, some drugs are relatively insoluble in water and are difficult to incorporate into in vitro assays, and a metabolite formed in vivo, rather than the primary drug, may be responsible for the thrombocytopenia.

DNP Question to DHP

5. If you have any other recommendations on thrombocytopenia-related sections of the prescribing information, please let us know.

DHP Response to 5: *Please refer to the responses to Question 1 and 2. There are no additional recommendations regarding thrombocytopenia-related sections of the prescribing information.*

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Additional DHP Comments:

It is recommended that the sponsor be requested to provide analysis of concomitant medications in studies CS2 and CS3 to exclude other etiologies of observed thrombocytopenic events. There are multiple medications known to cause drug induced immune thrombocytopenia (DITP).

In addition, if feasible, the sponsor should conduct an analysis of subjects exposed to heparin products (low molecular weight heparins and unfractionated heparins) given PF4 positivity observed in a small proportion of patients (n=2) on the study.

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Reference ID: 4247193

COMMENTS / SPECIAL INSTRUCTIONS:

The Sponsor's labeling (titled "proposed-v2") can be obtained via this link and is also attached:
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Additional documents referenced in this document will be sent with the consult request. If the hematology reviewer has not received them, please email Evelyn Mentari:
evelyn.mentari@fda.hhs.gov

We have the following requests and questions:

1. In the Sponsor's proposed label, are the instructions regarding frequency of platelet monitoring acceptable? For your reference, we have sent the Study CS2 and CS3 rules for platelet monitoring and dose stopping.

2. In patients who had thrombocytopenia after inotersen treatment, for which patients is rechallenge (b) (4) an acceptable option? Please comment on the Sponsor's proposals regarding (b) (4) in Table 1 of the proposed label. If a patient does undergo rechallenge, are there additional precautions that should be performed? The Sponsor provides additional information regarding (b) (4) in clinical studies on p. 3 of the IR response located at this link:
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3. We are concerned about severe thrombocytopenia with rechallenge. Which patients should avoid retreatment with inotersen?

4. In the proposed label Table 1 footnote, the Sponsor recommends glucocorticoid therapy in patients with a platelet count <25 x 10^9/ L. Please let us know of any changes that you recommend to this language.
The Sponsor provides a summary of experience with treatment of post-inotersen thrombocytopenia with glucocorticoids on p. 5 of the IR response located at this link:
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4. Is there a role for testing for anti-platelet antibodies in patients treated with inotersen?

5. If you have any other recommendations on thrombocytopenia-related sections of the prescribing information, please let us know.

Thank you for your assistance. Please let us know if any additional information may be helpful, including any additional requests to the Sponsor.

Reference ID: 4216506

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAUREL A MENAPACE
04/11/2018

ANDREW DMYTRIJUK
04/11/2018

ROMEO A DE CLARO
04/11/2018

Center for Drug Evaluation and Research
Office of Biotechnology Products
Division of Biotechnology Review and Research IV
Silver Spring, MD

Memorandum of Review: Immunogenicity assay Consult

STN:	NDA211172
Subject:	Immunogenicity assay Consult Review
Consult Date:	February 9, 2018
Review/Revision Date:	March 23, 2018
Primary Reviewer:	Haoheng Yan, MD, PhD Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Reviewer:	Bazarragchaa Damdinsuren, MD, PhD Team Leader, OPQ/OBP/DBRR IV
Tertiary Reviewer:	Christopher Downey, PhD Review Chief, OPQ/OBP/DBRR IV
Applicant:	Ionis Pharmaceuticals
Product:	Tegsedi (inotersen, ISIS 420915), antisense oligonucleotide
Indications:	hATTR-polyneuropathy
Action Due Date:	July 6, 2018

I. Recommendation:

The anti-drug antibody assay is appropriately validated and suitable for detecting anti-inotersen antibodies in patient plasma samples from the clinical studies in this NDA submission.

II. Assay Validation Review Summary

Inotersen is a 2′-O-(2-methoxyethyl) (2′-MOE) antisense oligonucleotide inhibitor of both mutant and wild-type human transthyretin (TTR) production, and proposed for treatment of hATTR-polyneuropathy. The proposed regime is 300mg weekly subcutaneous injection. To evaluate the immunogenicity of inotersen, the sponsor developed an anti-drug antibody (ADA) assay, which includes screening, confirmatory and titer assays. The ADA assay uses a direct ELISA format (uses protein A/G as detection agent).

Overall, the ADA assay is appropriately validated and is adequate for its intended use. The following two aspects of the assay are communicated with the clinical pharmacology team:

1) Due to the binding characteristic of Protein A/G, the assay can detect predominantly IgG isotypes, but is weaker on detecting other Ig isotypes such as IgM. Theoretically, the IgG is likely the main component of sustained immune response based on the long-term, chronic dosing of this drug. This is based on our understanding for protein products, but we are unaware of evidence that humoral immune response to foreign oligonucleotides is different from the

response to protein therapeutics. The likelihood that the assay is weak on detecting non-IgG isotypes (e.g., IgM) might not significantly affect the ability to evaluate the immunogenicity of this drug, unless the clinical and clinical pharmacology team conclude that early onset (<1month) of ADA is important in the evaluation.

2) The ADA assay is relatively sensitive; thus the sponsor should use ADA titer to stratify patients when analyzing the ADA impact on safety and efficacy.

III. Review

- Unless otherwise noted, figures and tables in the review were adapted or copied directly from the submission.
- The review sequence of the individual aspects of the assay validation may not follow the exact sequence in the submission.
- Reviewer's comments are shown in italic font.
- The "guidance" cited in the review refer to "FDA Draft Guidance to Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins, April 2016" http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf

Background and Consult Request

On November 6, 2017, Ionis Pharmaceuticals submitted an original NDA 211172 for Tegsedi (inotersen). Inotersen is a 2′-O-(2-methoxyethyl) (2′-MOE) antisense oligonucleotide (ASO) inhibitor of both mutant and wild-type human transthyretin (TTR) production. Inotersen was designed to bind to human TTR mRNA and prevent secretion of TTR protein by the liver.

DNP has submitted a consult to OBP to review the adequacy of ADA assay with respect to sensitivity, specificity, and isotype detection so that Office of Clinical Pharmacology can determine their impact on exposure-response analysis.

Reviewer's Comment:

Note that the NDA does not include neutralizing antibody (NAb) assay (and NAb assessment). Generally, the NAb assessment is not required for oligonucleotide products, instead we consider that all ADAs to oligonucleotides are neutralizing. This is due to small size of the oligonucleotides in comparison to the ADAs (immunoglobulins), where the oligonucleotides bound to ADA typically are not capable to bind to their targets.

5.3.1.4. Validation Report for Anti-Drug Antibody Binding Assay (420915-MV07)

The sponsor uses a three tiered strategy to detect ADAs. Clinical samples are first tested in an ADA binding screening assay. Samples that screened positive are tested by a confirmatory assay to assess the specificity. Confirmed positive sample are tested for titer.

Reference ID: 4240723

The screening assay is an enzyme-linked immunosorbent assay (ELISA)-based assay. Serum samples and positive controls (PCs) are added to 96-well microtiter plates coated with inotersen. Anti-inotersen antibodies bind to the immobilized inotersen on the plate and can subsequently be detected by Protein A/G-horseradish peroxidase (HRP) conjugate. Plates are washed and the immune complex is visualized with addition of TMB substrate. The plates are read at OD 450nM, where the color intensity is proportional to amount of bound ADA.

Samples tested equal to or above the screening cut-point are analyzed in a confirmatory assay using the same ELISA platform using cold-competition of 50µg/mL inotersen.

Confirmed positive samples are tested in the titer assay, in which the samples are 2-fold serially diluted before testing in the screening assay.

Reviewer's Comment:

The Sponsor uses a tiered approach to evaluate ADA as recommended in the guidance.

Essential Reagents and Concentrations:

Positive Control (PC): Rabbit Anti- ISIS 420915 Rabbit IgG, Affinity Purified

Low Positive Control (LPC): 8.23 ng/mL PC spiked into human plasma

Medium Positive Control (MPC): 100 ng/mL PC spiked into human plasma

High Positive Control (HPC): 5000 ng/mL PC spiked into human plasma

Negative Control (NC): Pooled human plasma

Minimum required dilution (MRD): 1:50 (2% plasma)

Screening Cut Point (SCP) and Titer Cut Point (TCP) Determination

Fifty (50) individual normal human plasma samples with no prior exposure to the drug were used to determine the SCP. Samples were analyzed in over 3 days by two analysts (for a total of six results per sample). A floating cut point was determined using a statistical method which includes log transformation, outlier removal and distribution analysis.

SCP factor was determined to be 1.09 which corresponds to 5% false positive rate.

Plate Specific SCP = Mean of NC OD values for a given run × 1.09

TCP was determined with the same dataset, at 0.1% false positive rate.

Plate Specific TCP = Mean of NC OD values for a given run × 1.18

The sponsor compared the distributions (mean and SD) of 20 normal human plasma vs 20 diseased treatment naïve plasma. The sponsor concluded that the assay readouts are comparable between the two populations, thus the cut points determined using normal human plasma are appropriate for in study samples.

Reviewer's Comment:

I also verified the SCP using pre-dose samples included in the report "Evaluation by ELISA of Anti-ISIS 420915 Antibodies in Human K2EDTA Plasma Samples from Ionis Study ISIS 420915-CS2" (section 5.3.5.1). The positive rate for pre-dose samples from the screening assay

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is ~8%. Therefore, the SCP determined using normal human plasma is considered suitable for to be used as in study SCP. The TCP is also acceptable.

Confirmatory Cut Point (CCP) Determination

A confirmatory (specificity) cut point was determined using 50 normal human plasma samples. All samples were pre-treated with 7.5ng/mL PC with or without 50µg/mL inotersen. The results were used to calculate the %Inhibition.

%Inhibition = 100 × [1 - (OD with drug/OD without drug)]

Statistical analysis to determine CCP was conducted using %Inhibition from the dataset targeting 1% false positive rate.

CCP = mean %inhibition – 2.33 × SD = 16.5%

The %inhibitions for LPC (150ng/ml) and for HPC (5000ng/mL) are, on average, 86.8% and 98.6%, respectively.

Reviewer's Comment:

(b) (4)

The CCP of 16.5% is quite low (which might lead to higher false positivity) based on my experience. However, only one pre-dose sample (out of 100+ subjects) were confirmed as positive in the CS2 report cited above, which suggests the false positive is acceptable.

Intra-Assay Precision

The intra-assay precision was determined using OD results from 6 sets of PCs per concentration (6.27ng/mL, 8.23ng/mL, 100ng/mL and 5000ng/mL) and 3 sets of NCs (duplicate measurements), performed by two analysts. All %CV are less than 8.3%.

Inter-Assay Precision

The inter-assay precision was determined using OD results from all accepted runs. The results for inter-assay precision of NCs and PCs were respectively 13.8% and 5.4% to 23.6% (12.0%, 10.8%, 23.6% and 5.4% for the 4 PCs listed in the intra-assay precision section).

Reviewer's Comment:

The assay precisions are acceptable.

Assay Sensitivity

The assay sensitivity was calculated using the interpolated value (at SCP) from multiple serial dilution curves from HPC (5000ng/mL to 1.22ng/mL). The estimated assay sensitivity is 6.28 ng/mL.

Reviewer's Comments: *The assay sensitivity is acceptable (meets the guidance recommendation).*

Reference ID: 4240723

Assay Selectivity

The matrix selectivity was performed by analyzing 10 lots of normal human K2EDTA plasma (from 5 male and 5 female individuals) and NC spiked with and without LPC, MPC and HPC (8.23 ng/mL, 100 ng/mL, and 5000 ng/mL).

In addition, assay interference was studied in hemolyzed plasma samples. This test was performed by analyzing aliquots of control samples (NC and the PC at 8.23 ng/mL, 100 ng/mL, and 5000 ng/mL) with 1, 2, and 5% hemolyzed samples.

Reviewer's Comments: *All 10 individual plasma lots showed recovery between 90%-105% at each PC spike level. The % recovery in hemolyzed samples are between 94.5%-118.8%. Based on these results no matrix interference is detected.*

Drug Tolerance

NC and PCs (8.23, 100, 250, and 5000 ng/mL) were pre-incubated for at least 1 hour at room temperature in the presence of the drug at different concentrations (0, 1, 4, 8 and 16 µg/mL, then were tested in the screening assay (results are in Table 13). The OD values in bold font are the highest tolerable drug concentration for each corresponding PC level. The results show that 100ng/mL PC is still detectable with 16 µg/mL drug in the screening assay.

TABLE 13. Drug Tolerance for the Anti-ISIS 420915 Antibody Detection Assay in Human K_2EDTA Plasma

	Optical Density (OD)									
			Rabbit Polyclonal Ab to ISIS 420915							
ISIS 420915 (µg/mL)	Negative Control	%CV	LPC1 (8.23 ng/mL)	%CV	LPC2 (100 ng/mL)	%CV	250 ng/mL	%CV	HPC (5000 ng/mL)	%CV
0	0.0338	0.8	**0.0518**	1.9	0.2219	1.8	0.4596	0.1	2.921	2.0
1	0.0357	1.8	0.0356	0.4	0.0669	3.6	0.1065	3.0	0.7069	0.2
4	0.0348	2.2	0.0400	10.4	0.0494	0.9	0.0740	6.4	0.4806	0.0
8	0.0353	0.6	0.0363	1.0	0.0474	0.6	0.0612	0.0	0.3702	1.7
16	0.0351	1.8	0.0366	2.5	**0.0456**	13.0	**0.0523**	0.4	**0.2924**	2.1

Note: OD values in bold font correlate to highest tolerable ISIS 420915 concentration (maximum ISIS 420915 concentration with positive control OD still ≥ plate cut point) for each respective positive control level.
Run ID: 140219-2471301-HUPL-MM-1A-031
Plate cut point = 0.0396

Reviewer's Comments:

According to clinical pharmacology reviewer - Dr. Mariam Ahmed, the Cmax of drug in the clinical study is 12.1 µg/mL. Therefore, the drug tolerance of the assay is acceptable.

Specificity

Specificity of the assay was evaluated by its ability to exclusively detect an antibody response specific for the anti-ISIS 420915 (inotersen) antibody. Assay specificity was assessed by binding inhibition of PCs (8.23, 100 and 5000 ng/mL) in the presence and absence of 50 µg/mL ISIS 420915.

Additionally, binding inhibition was also tested with two related molecules (b) (4)

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The %inhibitions for the PCs are similar between samples containing ISIS 420915 and ISIS (b) (4)

The sponsor concluded that "these data suggest the positive control antibody cross-reacts with (b) (4) but weakly recognize the oligonucleotide sequence."

Reviewer's Comment

The assay specificity is acceptable.

Stability

Sample stability was assessed using 8.23ng/mL and 100ng/mL PCs as surrogates. The testing conditions include room temperature and 4°C for 26hrs, respectively, and 6 freeze/thaw cycles. The results are presented in Tables 16-18 in the report.

Reviewer's Comment:

The % recovery (OD) of the stored samples (compared to fresh prepared samples) are >90% Sample stability is appropriately assessed. Samples are stable for up to 26hrs in the assessed conditions and for up to 6 freeze/thaw cycles.

Titer Assay

Precisions of the titer assay were assessed using 2-fold serial dilutions of the PC (concentration between 5000ng/mL and 1.22ng/mL). Intra-assay precision and inter-assay precision were determined using the analysis runs for assay sensitivity determination. The assays were run by two analysts. The OD levels for the 12 dilution curves were reported.

Reviewer's Comment:

The results show that the titer values for all 12 dilutions are within 2 fold. The titer assay precisions are acceptable.

System Suitability Controls:

- All runs utilize NCs in triplicates, three levels of PCs in duplicates per level.
- For NCs and PCs, the %CV from duplicate measurements are not greater than 25% unless both measurements are below the plate cut point. Otherwise, the data are not reportable.
- Mean OD of NC for each run has to be between 0.0257 and 0.0627.
- PC s (5000, 100 amd 8.23ng/mL)/ NC (mean) ratios for each run have to range from 33.6 to 110, 2.27 to 8.89, and 1.08 to 1.64, respectively.
- For the plate to be accepted, at least two-thirds of NCs, 50% of the PCs (at each level), and at least two-thirds of all PCs should be reportable.
- The OD values of the controls meet the following order: NC < LPC < MPC < HPC.

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The ranges of PC/NC ratios were calculated using all the applicable assay validation runs with the lower and upper limit as (mean PC) / (mean NC) ratio ± $t_{0.005}$,df × SD, which assumes 1% failure with respect to the lower and upper extremes.

Reviewer's Comment:

The system suitability controls seem acceptable for this binding ADA assay.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAOHENG N YAN
03/28/2018

BAZARRAGCHAA DAMDINSUREN
03/28/2018

CHRISTOPHER D DOWNEY
03/28/2018

HUMAN FACTORS RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 23, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211172
Product Name and Strength:	Tegsedi (inotersen) injection 284 mg/1.5 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ionis Pharmaceuticals, Inc.
Submission Date:	November 6, 2017
OSE RCM #:	2017-2310
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

Reference ID: 4238846

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) requested a Human Factors consultative review of a human factors validation study report submitted under NDA 211172 for Tegsedi (inotersen) pre-filled syringe (PFS). In addition, we provide a review of the Instructions for Use (IFU), container labels, carton labeling, and prescribing information (PI) to determine if they are acceptable from a medication error perspective.

1.1 PRODUCT INFORMATION

Tegsedi (inotersen) injection is an antisense oligonucleotide inhibitor of human transthyretin (TTR) protein synthesis indicated for treatment of adult patients with hereditary TTR amyloidosis with polyneuropathy (hATTR-PN) (b) (4) This is a combination product with a proposed pre-filled syringe (PFS) device constituent part that delivers a 284 mg dose of inotersen. Tegsedi is administered by subcutaneous injection once every week (b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH) and FDA/Sponsor Interactions	B
Human Factors Study Report	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Requests Issued During the Review	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

3.1 HUMAN FACTORS VALIDATION STUDY RESULTS AND ANALYSIS

Sixty-six representative users of the product (34 patients and 32 caregivers) participated in the simulated use HF validation study. Failures observed in the HF validation study involved three Sponsor-identified critical tasks. Of those three tasks, we do not agree that the task to check

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the expiration date prior to use should be categorized as critical. To better inform our re-categorization of the task from critical to essential, we consulted the chemistry reviewer and the medical officer to determine if there is any unique circumstance that would cause us to have concern for the failure to check the expiration date prior to use specifically for this particular product. There were no concerns identified. As such, we find the task to check expiration date to be an essential task that we will not analyze further.

In addition, during the HF validation study, it was observed that the needle safety mechanism failed to activate. To verify the delayed engagement of the safety feature on the PFS from the Human Factors Validation Study, a laboratory study (DCR-999) was performed at Ionis to verify the issue, and then to confirm that proper placement of labels (b) (4) We confirmed the results of laboratory study DCR-999 with the CDRH, General Hospital Device Branch (GHDB). (b) (4) We find this mitigation to be acceptable (see Appendix E).

We evaluated the use errors and difficulties pertaining to the other essential tasks for risk of medication error. We agree with the Sponsor that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable. Details for these essential task failures may be found in the submission. (See Appendix C)

Tables 2 and 3 below provides a summary and analysis of the study results. There were 8 failures that occurred with the following critical tasks[a].

Table 2: Summary of Critical Tasks Use Errors

Critical Task	Use Errors
Keep refrigerated until use	4
Push the plunger all the way down	4

[a] Critical task: Step required for the safe and effective use of the product.

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Table 3: Summary and Analysis of Critical Tasks Use Errors					
Critical Task Description and Number of Use Errors	**Evaluation Method**	**Description of Use Errors and Participant Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Mitigation Strategies or Justification for No Additional Mitigations**	**DMEPA's Analysis and Recommendation**
Keep refrigerated until use (n = 4)	**Knowledge Test** – Where would you store the syringe before using it?	The following four participants incorrectly answered the Knowledge question. Specifically, **P32** – One patient state they would have stored the medication in a kitchen cupboard. **P46** – One patient states they would store the PFS in the linen closet. **P53** – One patient states they would store the PFS in the medicine cabinet. **CG54** – One caregiver suggests a very cold cupboard is OK, even after reading out loud	Study artifact, comprehension lapse, memory lapse, current regimes, and insufficient review of the IFU.	IFU test and acceptable stability data at 30°C during the length of monthly dose supply. Storage temperature on carton and device label.	According to the Sponsor, failure to keep the product refrigerated could result in injection of degraded product depending on how long the product is stored outside of the recommended temperature range (36°F - 46°F; 2°C - 8°C). We confirmed with the medical officer the potential clinical consequence associated with this use error. That is, drug degradation due to improper storage could result in reduced drug efficacy (compromised medical care) potentially leading to disease progression and decreased quality of life for the patient. According to the proposed labeling, the product can be stored at room temperature for up to 6 weeks. Therefore, a patient or caregiver could store a one-month supply of the product (4-count carton) at room temperature without risk of degradation. The risk of administration of degraded product resulting from failure to keep the product refrigerated increases as the quantity of product dispensed (e.g., 90-day supply; three 4-count cartons) increases. However, due to the risk of thrombocytopenia and glomerulonephritis associated with use of the product which requires frequent laboratory monitoring (platelet count should be monitored every 2

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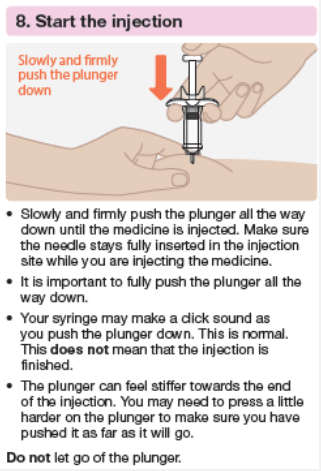
		the temperature stated in the IFU. "In a cold cupboard. Depending in instructions", then checks IFU. "2-8 degrees"			weeks during treatment), we do not anticipate that patients will be dispensed greater than a one month supply of product. Thus, the limited quantity of product dispensed will help mitigate the risk of the product being stored at room temperature beyond 6 weeks. Our review of the instructions for use (IFU) find that the storage instructions are prominent and clearly state to store the product in the refrigerator. Our review of the carton labeling finds that the storage instructions lack clarity and prominence. **We provide specific recommendations to address this concern in section 4.2 recommendation A.2.**
Push the plunger all the way down (n=4)	**Simulated Use**	**First Injection:** (n = 3) **P31 –**One participant does not push plunger all the way down during first simulated injection. The participant pushed plunger down until a click was heard. Does not attempt to during second simulated injection. **P60 –** One participant did not	Comprehension lapse, memory lapse, alternative verification method and insufficient review of the IFU	P31 had significant difficulty pushing plunger down, due to condition of hands. It is concluded that P31 would be very unlikely to administer their own medication in reality and is more likely to rely on the support of a caregiver. Visually plunger appeared to be at bottom of travel. Demonstration session prior to handling and dosing.	According to the Sponsor, the possible risks associated with failure to push the plunger all the way down are: 1) underdose and 2) needle stick injury. Pressing the plunger all the way down is required to administer the full dose and actuate the needle safety mechanism. A needle stick injury resulting from failure to actuate the needle safety mechanism could result in serious harm to the user. For example, infection with transmissible disease could result if the patient has a transmissible disease and the user (e.g., caregiver, healthcare professional) sustains a needle stick injury. All four participants who experienced difficulty during the HF validation study successfully administered the full dose. Our review of the study results did not identify any instances

		push plunger all the way down during the first simulated injection, but realized error and corrected behavior during the second simulation, following further review of instructions. “I was expecting needle to retract, as I’d read in instructions.” Pressed to the end of the dose, but did not activate safety feature on first injection. “I think what I read is that the needle would go in? I felt like I did as it said to press it all the way in, which I did.” Completed the second injection successfully. “It worked as I read…it retracted that time.” **P64 –** One participant did not		IFU image example and instructional text.	which led to a scenario where failure to push the plunger all the way down resulted in a needle stick injury. We also find that these risks are not unique to this product and exist with other prefilled syringes. Our review of the instructions for use (IFU) finds that instructions to push the plunger all the way down are clear in step 8 and the IFU is optimized to mitigate this risk. Specifically, the IFU states: • Slowly and firmly push the plunger down • Slowly and firmly push the plunger all the way down until the medicine is injected. • It is important to fully push the plunger all the way down. • Do not let go of the plunger.  Thus, we find that the residual risk acceptable.

		push plunger all the way down during the first simulated injection (she lifts out and tries to inject again), but realized error and corrected behavior during the second use. “Put back in because didn’t finish and wait 5 seconds, for future use would have known to do that, should have read all instructions first. Yes full dose, it is helpful when you know it’s done it retracts on its own, I didn’t lift off I waited for it to pop up.” **Second Injection**: (n = 1) **P14** – One participant pushed all the way down during first injection, but not on the second,			

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		however, as soon as she removed the syringe from the pad she realized the error she had made. “It felt like it snapped back in last time, I can’t have pushed it far enough.” Pushed plunger to a point where it looked like she was completed, however not enough to engage the safety mechanism. “I was able to turn it a little bit so that I could actually see what was happening so I knew that I was at the end of the medication, but perhaps I didn’t push it right at the end as it didn’t retract like the first time.”			

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3.3 LABELS AND LABELING

Our review of the proposed Prescribing Information (PI) labeling, Instructions for Use (IFU) labeling, container label and carton labeling identified areas which may be improved to decrease risk of medication error.

Prescribing Information

- The *Dosage and Administration* section of the Highlights of Prescribing Information (HPI) lacks critical information related to the recommended dose.
- The *Dosage and Administration* section of the full PI (FPI) contains error-prone abbreviations and symbols.
- The *Dosage Forms and Strengths* section of the HPI does not contain the dosage form (i.e., injection) and Section 3 *Dosage Forms and Strengths* of the FPI inappropriately describes the dosage form as [redacted] (b) (4)
- The NDC numbers are currently presented as "XXXX-XXX-XX" in Section 16 *How Supplied/Storage and Handling* of the PI labeling.

Instructions for Use (IFU)

- We note that the Sponsor has [redacted] (b) (4) The 'before use' image of the syringe, within the "Guide to parts" section of the IFU is now inaccurate.

Carton Labeling

- The medication guide statement does not state how the Medication Guide is provided in accordance with 21 CFR 208.24(d).
- The storage instructions lack prominence which may lead to the inappropriate storage of the product and decreased product quality.

Syringe Tray Blister Labeling

- The product strength is not among the most prominently displayed information on the principal display panel (PDP).

Syringe Tray Blister Labeling and Carton Labeling

- The finished dosage form (i.e., injection) is not displayed on the syringe tray blister labeling and carton labeling in accordance with our current draft Guidance for Industry: "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors"

Container Label, Syringe Tray Blister Labeling and Carton Labeling

- The established name (i.e., inotersen) lacks prominence commensurate with the proprietary name.

Container Label

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- The container label contains the error-prone abbreviation "S.C." which may result in confusion or wrong route of administration errors if misinterpreted.
- The salt equivalency statement competes in size and prominence with the strength statement which hinders readability of this important information.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur with the use of the combination product.

4 CONCLUSION & RECOMMENDATIONS

We conclude the human factors (HF) validation study results are acceptable from a medication error perspective.

However, our review of the prescribing information, instructions for use, container label, syringe tray blister labeling and carton labeling identified areas that are vulnerable to medication error and we provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. The *Dosage and Administration* section of the Highlights of Prescribing Information (HPI) lacks dosage information. We recommend revising the first bullet point from [redacted] (b) (4) to "The recommended [redacted] (b) (4) is 284 mg [redacted] (b) (4) administered by subcutaneous injection".
2. Section 2.1 of the *Dosage and Administration* section of the full PI (FPI) contains [redacted] (b) (4)
3. Section 2.4 of the *Dosage and Administration* section of the FPI contains the error-prone symbols, < and >. The symbols, < and >, appears on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken as the opposite of their intended meaning.[b] Consider replacing the symbols, < and >, with their intended meanings (i.e., less than and greater than) throughout the PI to prevent misinterpretation and confusion.
4. The *Dosage Forms and Strengths* section of the HPI does not contain the dosage form (i.e., injection) and Section 3 *Dosage Forms and Strengths* of the FPI inappropriately describes the dosage form as [redacted] (b) (4) The HPI should be revised to include the dosage form (i.e., injection) and the dosage form in the FPI should be revised from [redacted] (b) (4)' to 'injection'.

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 JAN 17]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

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5. The NDC numbers are currently presented as "XXXX-XXX-XX" in Section 16 *How Supplied/Storage and Handling* of the PI labeling. Because the NDC number is often used as a product identifier, the placeholder "XXXX-XXX-XX" should be updated to reflect the actual NDC number.

B. Instructions for Use (IFU)

1. The "Guide to parts" section of the IFU does not provide an accurate representation of the location of the container label on the syringe. Specifically, on the 'before use' image of the syringe, the 'inspection area' and 'Body (Expiration date is provided here)' labels should be switched as the label is now located closer to the needle.

4.2 RECOMMENDATIONS FOR IONIS PHARMACEUTICALS, INC.

We recommend the following:

A. Carton Labeling

1. The carton labeling states "Federal law requires the dispensing of TRADENAME with the Medication Guide (b) (4) In accordance with 21 CFR 208.24(d), the labeling should also state how the Medication Guide is provided. Revise the statement to include how the Medication Guide will be provided. For example, "Federal law requires the dispensing of TRADENAME with the Medication Guide inside the carton."
2. The storage instructions on the carton labeling lack prominence and may be overlooked which may lead to the inappropriate storage of the product and decreased product quality. Revise and bold the statement to read: "**Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container."** Furthermore, we recommend placing the statement "Must be refrigerated prior to dispensing" on the principal display panel (PDP), in addition to the statement on the back panel. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

B. Syringe Tray Blister Labeling

1. As currently presented, the strength statement (284 mg/ 1.5 mL) is not among the most prominently displayed information on the principal display panel (PDP). Other information on the PDP such as the opening instructions and manufacturer name compete in size and prominence with the strength statement. We recommend you increase the prominence of the strength statement to increase readability of this important product identifier information.

C. Syringe Tray Blister Labeling and Carton Labeling

1. The finished dosage form (i.e., injection) is not displayed on the syringe tray blister labeling and carton labeling in accordance with our current draft Guidance for Industry: "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors"

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http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf.
The established name for drug products should include the dosage form and the dosage form should appear on the same line as the active ingredient, if space permits. We recommend you revise the format of the established name and the finished dosage form such that they appear either in the same line as the active ingredient or directly below the active ingredient. For example:

Tradename (inotersen) injection	**OR**	Tradename (inotersen) Injection

D. Container Label, Syringe Tray Blister Labeling and Carton Labeling

1. The established name (i.e., inotersen) lacks prominence commensurate with the proprietary name. We recommend you revise the established name to be at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2). Take into account all pertinent factors, including typography, layout, contrast, and other printing features.

E. Container Label

1. The container label contains the error-prone abbreviation "S.C." which appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations[c] because it has been confused as "SL", the abbreviation for sublingual. Replace the abbreviation "S.C." with its intended meaning (i.e., subcutaneous) to prevent misinterpretation and confusion. Consider decreasing the prominence of the manufacturer information, if necessary, to accomplish this, or address the concern by other means.
2. The salt equivalency statement competes in size and prominence with the strength statement which hinders readability of this important information. Consider decreasing the prominence of the salt equivalency statement. For example,

284 mg/1.5 mL
(equivalent to 300 mg inotersen sodium)

[c] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 MAR 08]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Reference ID: 4238846

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Tegsedi (inotersen) that Ionis Pharmaceuticals, Inc. submitted on November 11, 2017.

Table 4. Relevant Product Information for Tegsedi	
Initial Approval Date	N/A
Active Ingredient	Inotersen
Indication	Treatment of patients with hereditary transthyretin (TTR) amyloidosis (hATTR) [redacted] (b) (4)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	284 mg/1.5 mL
Dose and Frequency	284 mg/dose. [redacted] (b) (4) doses should be administered once every week [redacted] (b) (4)
How Supplied	Available in cartons containing 1 or 4 prefilled syringes.
Storage	Pharmacy: Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container and protect from direct light. Patients/Caregivers: Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container. Tegsedi [redacted] (b) (4) be kept at room temperature (up to 30°C [86°F]) in the original container for up to 6 weeks; if not used within the 6 weeks, discard Tegsedi.
Container Closure	The container closure consists of a prefilled syringe (PFS) [redacted] (b) (4) which is assembled into a safety syringe device (SSD). [redacted] (b) (4) (b) (4) (b) (4)

Reference ID: 4238846

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On November 30, 2017, we searched the L:drive and AIMS using the terms, ISIS 420915, inotersen, AND IND 113968 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews.[d,e,f]

In OSE Review #2016-2543[d], we identified deficiencies with the proposed human factors (HF) validation study protocol. In addition, we recommended revisions to the instructions for use (IFU) to increase clarity and ensure the safe use of the product and provided a response to the Sponsor's question relating to the use of surrogates if the appropriate number of patients with Familial Amyloid Polyneuropathy (FAP) are unable to be recruited.

On March 24, 2017, Ionis Pharmaceuticals submitted a revised HF validation protocol for Agency review. In OSE Review #2016-2543-1[e], we reviewed the revised HF validation study protocol and supporting documentation. We noted that all changes recommended previously have been incorporated in the revised protocol and IFU with two exceptions. We consulted with the Division of Medical Policy Programs (DMPP) for review of the revised IFU and for feedback from a patient labeling perspective. DMPP agreed with the Sponsor's proposed revisions to the IFU and their rationale for not implementing the two recommendations. We had no additional recommendations at the time.

On August 25, 2017 Ionis Pharmaceuticals submitted a revised IFU to address observations noted during formative HF testing. Also, changes were made to the supplier of the IFU resulting in an updated layout. In OSE Review #2016-2543-2[f], we reviewed the revised IFU and identified one concern that could lead to medication error. We also consulted DMPP for review of the revised IFU and they identified one additional concern. We confirmed that our previous recommendations were implemented.

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[d] Rider B. Review of Human Factors Validation Study Protocol for ISIS 420915/GSK2998728 (IND 113968). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 25. OSE RCM No.: 2016-2543.

[e] Rider B. Memorandum: Review of Human Factors Validation Study Protocol for ISIS 420915/GSK2998728 (IND 113968). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 APR 12. 3 p. OSE RCM No.: 2016-2543-1.

[f] Rider B. Memorandum: Review of Human Factors Validation Study Protocol for ISIS 420915/GSK2998728 (IND 113968). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 AUG 29. 6 p. OSE RCM No.: 2016-2543-2.

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B.2 PREVIOUS FDA/SPONSOR INTERACTIONS

Our search did not identify any additional previous Sponsor interactions with DMEPA or CDRH.

Reference ID: 4238846

APPENDIX C. APPENDED HUMAN FACTORS VAIDATION STUDY REPORT (SUBMITTED JANUARY 5, 2018)

The HF study protocol can be accessible in EDR via:
\\cdsesub1\evsprod\nda211172\0006\m1\us\114-labeling\114a-draft-label\1-14-1-4-human-factors-study-safety-syringe-final-report-201.pdf

Reference ID: 4238846

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

Information Request #1

Methods

On December 21, 2017, we issued an Information Request (IR) requesting that the Sponsor clarify the profile of test participants in each user group, submit Study DCR-999, product samples, and an updated use-related risk analysis (URRA), describe the functional scale used to match the surrogate patients for the level of motor/sensory deficit of interest, and append the study report to include a description of all tasks and sub task failures/use errors, close calls, and use difficulties, subjective data from study participants, root cause analysis, and mitigation strategies.

Results

The Sponsor provided responses to the IR on September 12, 2017. The responses can be accessible in EDR via: \\cdsesub1\evsprod\nda211172\0006\m1\us\12-cover-letter\response-to-information-request-5jan2018.pdf

Study DCR-999 can be accessible in EDR via: \\cdsesub1\evsprod\nda211172\0006\m1\us\114-labeling\114a-draft-label\dcr-999.pdf

Information Request #2

Methods

On January 23, 2018, we issued an IR requesting that the Sponsor clarify whether participants who failed to push the plunger all the way down failed to administer the full dose, failed to activate the needle safety mechanism, or both. And, for patients who failed to administer the full dose, provide the volume of residual drug remaining in the syringe and describe whether the volume of residual drug would result in a clinically meaningful underdose. We also requested that the Sponsor provide a detailed description of the needle stick injury, subjective feedback from the participant and their root cause analysis for each needle stick injury that occurred during the HF validation study.

Results

The Sponsor provided responses to the IR on January 31, 2018. The responses can be accessible in EDR via: \\cdsesub1\evsprod\nda211172\0018\m1\us\12-cover-letter\420915-response-to-agency-information-request-sn0018.pdf

Reference ID: 4238846

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Tegsedi (inotersen) labels and labeling submitted by Ionis Pharmaceuticals, Inc. on March 7, 2018.

- Container label
- Carton labeling
    - 1-pack carton
    - 4-pack carton
    - Syringe tray blister
- Instructions for Use (Image not shown)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container Label

(b) (4)

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BRIANA B RIDER
03/23/2018

LOLITA G WHITE
03/23/2018

QUYNHNHU T NGUYEN
03/23/2018

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

DCRP Consult NDA 211172

DATE: Date of Document: 11/6/2017
Date of Consult: 12/12/2017
Desired Completion Date: 2/9/2018
Date of Completion: 2/12/2018

FROM: Preston M. Dunnmon, M.D., M.B.A., Medical Officer
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TO: Nick Kozauer, MD, CDTL
Division of Neurology Products, HFD-120

DRUG NAME: Inotersen (ISIS 420915)

DOSE/FORMULATION: 300 mg (1.5 Ml) SC injection - [redacted] (b) (4) once-weekly SC administration

MECH OF ACTION: 2′-O-(2-methoxyethyl) (2′-MOE) antisense oligonucleotide (ASO) inhibitor of both mutant and wild-type human transthyretin (TTR) production

APPLICANT: Ionis Pharmaceuticals

CONSULT QUESTION: Please comment on the interpretability of the cardiac efficacy data from Studies CS2 and CS3

DOCUMENTS REVIEWED:

- Clinical Study Report Study CS2: A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Subjects with Familial Amyloid Polyneuropathy

Reference ID: 4223578

- Clinical Study Report Study CS3: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP) (NEURO-TTR Extension Study)

EXECUTIVE SUMMARY: Ionis Pharmaceuticals has submitted NDA 211172 seeking approval to market Inotersen "for treatment of patients with hereditary TTR amyloidosis (hATTR) [redacted] (b) (4) A single clinical study is intended to provide substantial evidence of efficacy; study CS2: a phase 2/3 randomized, double-blind, placebo-controlled study of patients with Familial Amyloid Polyneuropathy (FAP). The primary endpoint was change from baseline in the modified neuropathy impairment score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire total score in subjects with hATTR-PN. Presence or absence of ATTR-cardiomyopathy (ATTR-CM) was neither an inclusion nor exclusion criteria. Various echo parameters and NT-proBNP were measured and included as secondary endpoints but not within a plan to spare alpha.

We observe the following:

- Study CS2 does not provide any cardiac efficacy data. Imaging and serum biomarkers such as global longitudinal strain and NT-proBNP do not measure how a patient feels, functions, or survives and nor are they known to predict how a patient feels, functions, or survives and hence do not measure a clinical benefit.
- [redacted] (b) (4)
- Moreover, if one is willing to accept the data selection process, there appears to have been little effect on these cardiac biomarkers but the confidence limits on the effects within each group were large enough to have failed to resolve considerable harm.
- Additionally, one subject in study CS2 died from an intracranial hemorrhage caused by Inotersen-induced thrombocytopenia and one subject required chronic dialysis caused by Inotersen-induced nephrotoxicity.

We recommend:

- The indication sought by Ionis suggests that Inotersen is useful for treatment [redacted] (b) (4) [redacted] (b) (4) of hereditary TTR amyloidosis, [redacted] (b) (4) [redacted] (b) (4) [redacted]
  Hence we recommend that, if approved, the indication in the label should [redacted] (b) (4) state the Inotersen is intended [redacted] (b) (4) for treatment of Familial Amyloid Polyneuropathy.
- [redacted] (b) (4)

Reference ID: 4223578

BACKGROUND

TRIAL CS2: Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy

Design

This was a Phase 2/3 multicenter, double-blind, randomized, stratified, placebo-controlled study of ISIS 420915 in Stage 1 and Stage 2 FAP patients with a NIS score ≥ 10 and ≤ 130. Approximately 135 patients were to be randomized 2:1 (ISIS 420915 : PBO) to receive 300 mg ISIS 420915 or placebo for 65 weeks. Subjects withdrawn from the trial were not replaced.

All subjects underwent transthoracic echocardiography at baseline and at week 65 or early withdrawal. Patients that were eligible could consent to participate in the ECHO subgroup and underwent transthoracic ECHO at Baseline, week 41 or 47, and week 65 (an additional echo at week 41 or 47 in a subgroup with LV wall thickness ≥ 13 mm at Baseline). The ECHO subgroup included the subset of the Safety Set that has at least 1 evaluable post baseline ECHO assessment and participated in the ECHO substudy. The CM-ECHO Set included the subset of the Safety Set that has at least 1 evaluable post baseline ECHO assessment and had a diagnosis of TTR cardiomyopathy at study entry (by history, not protocol defined) but are not in the ECHO subgroup, plus patients who participated in the ECHO subgroup. Change in Global Longitudinal Strain (GLS) by ECHO from baseline to Week 65 in the ECHO subgroup and in the CM-ECHO Set was one of five predefined secondary endpoints of this study, though there was no adjustment for multiplicity.

NT-proBNP was measured on Day 1, Week 13, week 35, and week 65. 12-lead ECGs were acquired in triplicate during screening, on study Day-1, Week-8, Week-35, and Week-65, and for medical cause.

Relevant Cardiac Exclusion Criteria for Enrollment in Echo Subgroup

- Must have left ventricular wall thickness of ≥ 13 mm on transthoracic echocardiogram at Baseline
- Baseline ECHO is evaluable as ascertained by the Sponsor central reader

Relevant Cardiac Exclusion Criteria for Enrollment in Echo Subgroup

- Uncontrolled hypertension (blood pressure > 160/100)
- No known history of persistent hypertension ≥ 150 mm Hg within 12 months prior to screening
- New York Heart Association (NYHA) functional classification of ≥ 3
- Acute coronary syndrome or major surgery within 3 months of screening

Analysis Sets (sponsor CSR)

Table 6 Analysis Populations (Randomized Subjects)

	Placebo (N=60) n (%)	Inotersen 300 mg (N=113) n (%)	Total (N=173) n (%)
Number of subjects:			
Randomized	60 (100)	113 (100)	173 (100)
Dosed	60 (100)	112 (99.1)	172 (99.4)[a]
In the Safety Set (SS)	60 (100)	112 (99.1)	172 (99.4)
In the Full Analysis Set (FAS)	59 (98.3)	106 (93.8)	165 (95.4)
In the Per-Protocol Set (PPS)	52 (86.7)	83 (73.5)	135 (78.0)
In the PK Subgroup	8 (13.3)	10 (8.8)	18 (10.4)
In the PK Set	0	111 (98.2)	111 (64.2)
In the PK Subgroup (PK Set)	0	10 (8.8)	10 (5.8)
In the ECHO Subgroup	22 (36.7)	44 (38.9)	66 (38.2)
In the CM-ECHO Set	33 (55.0)	75 (66.4)	108 (62.4)
In the TTR Subgroup	18 (30.0)	37 (32.7)	55 (31.8)

Reviewer's comment: it is unclear how many subjects that could have been in the ECHO subgroup and the CM-ECHO set were not included due to lack of post-baseline assessments.

Summary of Baseline Characteristics (sponsor CSR)

Table 10 Baseline Disease Characteristics (CM-ECHO Set)

	Placebo (N=33)	Inotersen 300 mg (N=75)	Total (N=108)
TTR genotype observed in >1 subject,[a] n (%)			
Type GLU89GLN	0	5 (6.7)	5 (4.6)
Type LEU58HIS	2 (6.1)	2 (2.7)	4 (3.7)
Type PHE64LEU	1 (3.0)	2 (2.7)	3 (2.8)
Type SER50ARG	1 (3.0)	5 (6.7)	6 (5.6)
Type SER77TYR	5 (15.2)	4 (5.3)	9 (8.3)
Type THR49ALA	0	2 (2.7)	2 (1.9)
Type THR60ALA	7 (21.2)	13 (17.3)	20 (18.5)
Type VAL122ILE	0	2 (2.7)	2 (1.9)
Type VAL30MET	13 (39.4)	30 (40.0)	43 (39.8)
Duration of disease from hATTR-PN diagnosis[b] (months)			
Mean (SD)	23.3 (31.63)	35.0 (44.12)	31.4 (40.92)
Median	13.0	20.0	16.5
Minimum, Maximum	1, 159	2, 228	1, 228
Duration from onset of hATTR-PN symptoms[b] (months)			
Mean (SD)	54.0 (55.83)	63.4 (52.31)	60.6 (53.33)
Median	39.0	52.0	47.0
Minimum, Maximum	9, 277	5, 372	5, 372
Subjects diagnosed with hATTR-CM, n (%)			
Yes	22 (66.7)	45 (60.0)	67 (62.0)
No	11 (33.3)	30 (40.0)	41 (38.0)
Duration of disease from hATTR-CM diagnosis (months)			
n	22	44	66
Mean (SD)	21.0 (22.52)	25.1 (28.62)	23.7 (26.63)
Median	15.0	15.0	15.0
Minimum, Maximum	1, 81	1, 132	1, 132
Duration from onset of hATTR-CM symptoms (months)			
n	18	36	54
Mean (SD)	34.1 (29.33)	44.7 (58.00)	41.1 (50.23)
Median	29.5	26.5	29.0
Minimum, Maximum	1, 114	1, 300	1, 300

Reviewer's Comment: The sponsor correctly points out that A higher proportion of subjects in the Inotersen group (66.4%) were included in the CM-ECHO Set compared with subjects in the placebo group (55.0%), though these proportions between the ECHO sub-group were similar (Table 6). Subjects in the Inotersen CM-ECHO Set had a longer duration from onset of hATTR-CM symptoms and a mild/numerically higher mean Baseline NT-proBNP concentration at study entry compared with the placebo group (Table 10).

GLS Secondary Endpoint Analysis

The absolute value normal range for global longitudinal strain (GLS) by speckle tracking echocardiography (STE) used by the sponsor was between -18% and -25% (longitudinal shortening is a negative number by convention, Smiseth et al, European Heart Journal

(2016) 37, 1196–1207)). The sponsor reports results of the on-treatment analysis of GLS as follows:

Table 51 On-Treatment Global Longitudinal Strain

	CM-ECHO Set		ECHO Subgroup	
	Placebo (N=33)	Inotersen 300 mg (N=75)	Placebo (N=22)	Inotersen 300 mg (N=44)
Absolute value (%)				
Baseline				
n	30	68	20	41
Mean (SD)	-14.63 (3.614)	-14.44 (3.995)	-14.21 (3.564)	-14.61 (4.073)
Median	-14.25	-13.90	-14.05	-14.10
Minimum, Maximum	-23.1, -8.5	-24.0, -6.7	-23.1, -8.5	-24.0, -7.6
Change from Baseline (%)[a]				
Week 65				
n	25	50	16	30
Mean (SD)	0.46 (2.702)	0.69 (3.134)	1.05 (2.745)	0.25 (3.163)
Median	-0.10	1.25	0.80	1.00
Minimum, Maximum	-4.5, 6.3	-6.1, 7.7	-4.5, 6.3	-6.1, 5.0

	CM-ECHO Set		ECHO Subgroup	
	Placebo (N=33)	Inotersen 300 mg (N=75)	Placebo (N=22)	Inotersen 300 mg (N=44)
Statistical analysis of change from Baseline				
Total n included in statistical analysis			17	36
Week 65				
n	25	50	16	30
LSM (SE)	0.94 (0.588)	1.14 (0.497)	1.61 (0.747)	0.72 (0.577)
95% CI	-0.23, 2.11	0.15, 2.13	0.10, 3.11	-0.44, 1.88
Difference in LSM		0.20		-0.89
95% CI		-1.17, 1.56		-2.67, 0.90
p-value		0.771		0.322

Source: Table 5.02 and Table 5.03
Note: Analysis based on data collected up to 52 days after last dose of study drug.
a. Positive changes from Baseline indicate a worsening in GLS.

From these data, the sponsor concluded the following:

- Mean GLS was abnormal at Baseline in both groups in the CM-ECHO Set, as compared with established ranges
- No statistically significant differences in GLS were observed between treatment groups at Week 65 in the CM-ECHO Set or the ECHO Subgroup
- No clinically significant worsening of GLS was observed in either treatment group

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Reviewer's Comment: Results for the on-treatment GLS change between the treatment groups were similar for the Randomized set. Approximately 17 – 27% of the subjects in the CM-ECHO set and ECHO subgroup were missing data at week 65.

Exploratory Analysis of Other Echo Parameters

The sponsor reported the following:

- No statistically significant differences between treatment groups in the CM-ECHO Set were observed in selected parameters of left ventricular size and function, including interventricular septum thickness, posterior wall thickness, left ventricular ejection fraction, left ventricular mass, left ventricular mass index, left atrial strain, or E/Em lateral ratio
- No clinically significant worsening was observed in either the Inotersen group or the placebo group in the CM-ECHO Set for any of the ECHO parameters included in the exploratory analysis.

NT-pro-BNP

The sponsor reported the following:

- There were small differences in NT-proBNP levels at baseline
- NT-proBNP increased in both treatment groups at Week 35 and at Week 65. Statistically significant differences in the ratio of geometric means for NT-proBNP were observed between the Inotersen and placebo groups in the FAS at Week 13 and Week 35, but not at Week 65
- Differences of a similar magnitude were observed between treatment groups in the CM-ECHO Set; however, these differences were not statistically significant at any time point.

TRIAL CS3: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Design

This is an ongoing, multicenter OLE study. Eligible subjects who have satisfactorily completed CS2 receive 300 mg Inotersen once weekly for up to 260 weeks (5 years) while in CS3. Exceptions are given to subjects who had a dose reduction or schedule change in CS2. Subjects were excluded for any new condition or worsening of existing condition that, in the opinion of the investigator or Sponsor, would make the subject unsuitable for enrollment or could interfere with the subject participating in or completing the study.

Echo Findings

The sponsor reports that the mean GLS values were abnormal at CS2 Baseline as well as at CS3 Baseline in both groups in the CM-ECHO Set but that the changes in GLS observed in both groups were small and variable, per the sponsor table below:

Table 18 On-Treatment Global Longitudinal Strain (%) (CM-ECHO Set)

	Placebo-Inotersen (N=27)	Inotersen-Inotersen (N=52)
Absolute value		
CS2 Baseline		
N	24	49
Mean (SD)	-14.97 (3.891)	-15.01 (3.810)
Median (P25, P75)	-14.50 (-18.40, -11.85)	-14.70 (-18.60, -12.00)
Min, Max	-23.1, -8.5	-24.0, -7.6
CS3 Baseline		
N	25	48
Mean (SD)	-14.33 (4.027)	-14.44 (4.098)
Median (P25, P75)	-14.40 (-17.50, -10.90)	-14.65 (-17.70, -11.25)
Min, Max	-21.2, -7.9	-21.4, -5.5
Change from CS2 Baseline		
CS2 Week 65		
N	22	45
Mean (SD)	0.56 (2.813)	0.75 (3.267)
Median (P25, P75)	0.70 (-1.10, 2.40)	1.40 (-2.00, 3.30)
Min, Max	-4.5, 6.3	-6.1, 7.7
CS3 Week 52		
n	7	17
Mean (SD)	-0.30 (3.121)	-0.68 (4.392)
Median (P25, P75)	-1.00 (-3.10, 2.70)	-1.70 (-3.90, 3.60)
Min, Max	-3.7, 5.0	-7.4, 7.1
CS3 Week 78		
n	7	17
Mean (SD)	-0.84 (1.758)	0.05 (3.629)
Median (P25, P75)	-1.20 (-2.40, 0.40)	-1.00 (-3.30, 2.30)
Min, Max	-3.1, 1.9	-4.4, 7.6

	Placebo-Inotersen (N=27)	Inotersen-Inotersen (N=52)
Change from CS3 Baseline		
CS3 Week 52		
n	6	16
Mean (SD)	-0.03 (2.827)	-1.56 (2.639)
Median (P25, P75)	-0.65 (-2.00, 2.60)	-1.50 (-3.25, 0.60)
Min, Max	-3.5, 4.0	-6.2, 3.4
CS3 Week 78		
n	7	16
Mean (SD)	0.39 (3.361)	0.10 (2.532)
Median (P25, P75)	-0.80 (-1.30, 2.80)	-0.50 (-1.15, 1.75)
Min, Max	-4.1, 6.4	-3.5, 4.8

The sponsor also reports that no apparent differences were observed between the Inotersen-Inotersen group and the placebo-Inotersen group for left ventricular mass in the enrolled patients, ECHO subgroup, and CM-ECHO Set; however, no analyses were completed on these data.

NT-proBNP

The sponsor analyzed geometric means of NT-proBNP due to the high spread of values observed in individual subjects. Using the geometric mean, NT-proBNP decreased from CS3 baseline in both groups and the gap between the groups narrowed over time, although the changes were small (sponsor Table 23 below). The changes observed using

Reference ID: 4223578

the median values were small and not clinically significant. A similar pattern was observed for the CM-ECHO set.

Table 23 On-Treatment NT-proBNP Results (Full Analysis Set)

	Placebo-Inotersen (N=31)	Inotersen-Inotersen (N=55)
Absolute value		
CS2 Baseline		
n	31	52
Median (P25, P75)	35.0 (21.0, 130.0)	28.5 (12.0, 78.0)
Min, Max	2, 872	1, 830
CS3 Baseline		
n	31	55
Median (P25, P75)	44.0 (22.0, 151.0)	36.0 (15.0, 118.0)
Min, Max	5, 1138	2, 1085
Change from CS2 Baseline		
CS2 Week 13		
N	31	51
Median (P25, P75)	-2.0 (-8.0, 18.0)	3.0 (-3.0, 22.0)
Min, Max	-397, 210	-149, 349
CS2 Week 35		
N	31	52
Median (P25, P75)	4.0 (-7.0, 24.0)	3.5 (-2.0, 14.0)
Min, Max	-355, 242	-208, 298
CS2 Week 65		
N	31	52
Median (P25, P75)	6.0 (1.0, 42.0)	5.5 (-0.5, 29.5)
Min, Max	-350, 335	-49, 806
Change from CS3 Baseline		
CS3 Week 13		
n	31	55
Median (P25, P75)	2.0 (-9.0, 14.0)	0.0 (-10.0, 8.0)
Min, Max	-65, 573	-277, 836
CS3 Week 39		
n	22	43
Median (P25, P75)	-1.0 (-9.0, 16.0)	-2.0 (-10.0, 16.0)
Min, Max	-121, 440	-805, 1070
CS3 Week 65		
n	15	34
Median (P25, P75)	5.0 (-3.0, 29.0)	-1.0 (-15.0, 12.0)
Min, Max	-70, 74	-108, 908
CS3 Week 78		
n	11	29
Median (P25, P75)	12.0 (1.0, 23.0)	0.0 (-8.0, 7.0)
Min, Max	-5, 47	-148, 44

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/s/

PRESTON M DUNNMON
02/20/2018

STEPHEN M GRANT
02/28/2018

NORMAN L STOCKBRIDGE
03/01/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 26, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Fannie Choy, RPM
DNP

Subject: QT-IRT Consult to NDA 211172

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/20/2017 regarding the sponsor's proposed QT labeling language. The QT-IRT reviewed the following materials:

- ISIS 420915-CS1 study report submitted under NDA 211172 to sequence 0001 dated 11/3/2017;
- ISIS 420915-CS2 (NEURO-TTR) study report submitted under NDA 211172 to sequence 0001 dated 11/3/2017;
- Previous QT-IRT review under IND 113968 dated 07/11/2016 and 10/17/2016 in DARRTS;
- Thorough QT Waiver request submitted under IND 113968 to sequence 0054 dated 5/19/2016; and
- Annotated label submitted under NDA 211172 to sequence 0001 dated 11/3/2017.

1. QT-IRT Responses

Question from the Division: A thorough QT study was waived (consult reviews under IND 113968). The primary sources of QT data are the clinical studies ISIS 420915-CS2 and ISIS 420915-CS3. Please review the data submitted to support the following language that is proposed

for the Inotersen prescribing information (Section 12.2): [redacted] (b) (4)

QT-IRT's response: We do not agree with the proposed language from the sponsor, as the QTc data collected in ISIS 420915-CS2 (NEURO-TTR Study) is highly variable and difficult to interpret. However, as we noted in our previous review the data collected in ISIS 420915-CS1 can be used to characterize the relationship between inotersen concentration and QTc and supports excluding large mean increases in the QTc interval (i.e. 20 ms). This conclusion is further supported by the submitted preclinical information and categorical QTc analysis. We are therefore proposing the following labeling language for inotersen in section 12.2:

The potential for QTc prolongation with inotersen was evaluated in a randomized, placebo-controlled trial in healthy volunteers. No large changes in the mean QTc interval (>20 ms) were detected in the trial.

2. BACKGROUND

Product Information

Inotersen (also known as ISIS 420915) is a 2′-O-(2-methoxyethyl) [2′-MOE] antisense oligonucleotide (ASO) inhibitor of both mutant and wild-type human transthyretin (TTR) production. ASOs are short synthetic strings of nucleotides designed to prevent the expression of a targeted protein by selectively binding to the ribonucleic acid (RNA) that encodes the targeted protein and thereby preventing translation.

The strategy of treating patients with hereditary transthyretin amyloidosis (hATTR) with inotersen is to reduce the levels of mutated and wild-type TTR protein secreted by the liver, the primary source of TTR production and a primary organ for ASO distribution after systemic delivery. By decreasing the amount of liver-derived TTR protein circulating in the plasma, inotersen treatment likely results in a decrease in the formation of TTR amyloid fibril deposits and thus slowing or halting disease progression.

Preclinical cardiac safety

Compounds that inhibit hERG (IKr) current are associates with prolonged cardiac action potentials and, hence, QT interval in humans. The potential of inotersen to inhibit hERG tail current was measured by whole cell patch clamping in human embryonic kidney (HEK)-293 cells stably transfected with hERG cDNA (Study No. 420915-IS01). hERG currents were measured before and after exposure to vehicle (sterile water for injection), inotersen (100 or 300 μM), terfenadine (0.06 μM; positive control), or E-4031 (0.5 μM; reference substance, known inhibitor of hERG tail current) using 3 cells/concentration.

There was no significant hERG inhibition at 100 or 300 μM when compared to vehicle control values. Inotersen reduced the hERG current by 0.4 ± 0.7% at 100 μM and 0.6 ± 0.7% at 300 μM. In comparison, the vehicle control reduced the hERG current by 0.3 ± 1.0%. The IC50 for any effect of inotersen on hERG potassium current is > 300 μM. Terfenadine (0.06 μM) inhibited the hERG current by 76.1 ± 3.3%. Under the conditions of this study, inotersen was negative at blocking hERG current at concentrations up to 300 μM.

Reference ID: 4212868

In a combined CV and respiratory function study, 4 conscious male cynomolgus monkeys (6 to 7 years of age) received single SC doses of inotersen at 0 (PBS control),12 or 40 mg/kg (Study No. 420915-AS06). CV and respiratory assessments that were made by telemetry included blood pressure (BP) (systolic BP [SBP], diastolic BP [DBP] and mean arterial BP [MAP]), heart rate (HR), respiratory rate (RR; expiratory flow, inspiration and expiration time and tidal and minute volume), BT and lead-II electrocardiogram (ECG) parameters (QRS duration as well as RR, PR, QT (uncorrected) and QTc (rate-corrected) intervals with Bazett's (QTcB) and Fridericia's (QTcF) formulas) were continuously recorded/derived. Assessments were made 1 hour prior to dose administration and at 2, 4, and 24 hr (± 30 minutes) post-dose. Additionally, samples were taken on Day 3 (1 hr post-dose) to determine the plasma toxicokinetics.

Toxicokinetics data confirmed systemic exposure to inotersen in all monkeys. Plasma levels increased proportionally with the dose administered.

There were no inotersen-related effects on qualitative ECG assessment, quantitative ECG parameters, arterial BP, HR, respiratory rate, BT, arterial blood gas parameters and clinical observations following SC administration of inotersen compared to vehicle control in conscious male cynomolgus monkeys. No relevant respiratory rate and QT intervals effects were noted. No test article-related changes were observed, although slight changes in QT intervals were caused by fluctuations in RR intervals and were minimized following correction of QT for RR (QT interval corrected using Bazett's formula [QTcB] and QT interval corrected using Fredericia's formula [QTcF]). These changes were within the normal range of variation for the species.

Reviewer's Comment: The preclinical cardiac safety data submitted suggests a low potential for inotersen to directly inhibit the hERG potassium channel.

Clinical cardiac safety

The sponsor has collected ECG in three clinical studies: ISIS 420915-CS1 (SAD/MAD in healthy volunteers), ISIS 420915-CS2 (phase 3 study in patients) and ISIS 420915-CS3 (open-label extension of CS2).

ISIS 420915-CS1

This study was a SAD/MAD study of inotersen in healthy volunteers. The SAD portion of the study included 50, 100, 200 and 400 mg randomized with 4 subjects per cohort (3 inotersen / 1 placebo). The MAD portion of the study included 50, 100, 200, 300 and 400 mg with 10 subjects per cohort (8 inotersen / 2 placebo). The ECG/PK data collected in this study was previously submitted as a part of thorough QT waiver request (IND 113968, sequence 0054). The observed inotersen concentrations for the higher dose groups are comparable to what is expected in patients and the ECG/PK collection is adequate to capture peak and delayed effects.

We have previously reviewed the data from this study and agreed with the sponsor's conclusion concerning the relationship between inotersen concentration and ΔΔQTcF. This conclusion is also supported by the categorical analysis conducted by the sponsor (Table 1) and the preclinical information presented above. Overall, the data collected in this study supports concluding an absence of large mean increases in the QTc interval.

Reference ID: 4212868

Table 1: Categorical outlier analysis of the ECG parameters (SAD/MAD cohorts combined)

Parameter	Value	Placebo (N = 14)	Active ISIS 420915 Treatment					Total ISIS-Treated (N = 51)
			50 mg (N = 11)	100 mg (N = 11)	200 mg (N = 11)	300 mg (N = 8)	400 mg (N = 10)	
QT								
New > 500 ms	n/N* (%)	0/14 (0.0)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)	0/8 (0.0)	0/10 (0.0)	0/51 (0.0)
QTcF								
New > 500 ms	n/N* (%)	0/14 (0.0)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)	0/8 (0.0)	0/10 (0.0)	0/51 (0.0)
New > 450 ms for men; > 470 ms for women	n/N* (%)	0/13 (0.0)	1/11 (9.1)	0/11 (0.0)	0/11 (0.0)	0/8 (0.0)	0/10 (0.0)	1/51 (2.0)
Increase > 30 to 60 ms	n/N* (%)	1/14 (7.1)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)	0/8 (0.0)	0/10 (0.0)	0/51 (0.0)
Increase > 60 ms	n/N* (%)	0/14 (0.0)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)	0/8 (0.0)	0/10 (0.0)	0/51 (0.0)
PR								
> 25% increase and New > 250 ms	n/N* (%)	0/14 (0.0)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)	0/8 (0.0)	0/10 (0.0)	0/51 (0.0)
QRS								
> 25% increase and New > 100 ms	n/N* (%)	0/12 (0.0)	0/11 (0.0)	0/10 (0.0)	0/11 (0.0)	0/7 (0.0)	0/9 (0.0)	0/48 (0.0)

n = Number of subjects who met the notable criterion at least once
N* = number of subjects with no event (not met the notable criterion) at Baseline, and with both baseline and post-baseline values observed; %=n/N*×100

Source: Thorough QT waiver request, Table 12, Page 26

ISIS 420915-CS2 (NEURO-TTR Study)

This study is a double-blind, randomized, phase 2/3 study in 173 patients (113 on inotersen and 60 on placebo). Triplicate ECGs were collected at on day 1 (baseline, 3 h post-dose), day 240 (predose, 3 h) and day 449 (predose and 3 h). At the end of the study, eligible patients could continue in the open-label extension study (ISIS 420915-CS3).

The sponsor conducted a categorical analysis on the ECG data collected in this study and is proposing to include that information in the label. We do not agree with the inclusion of the ECG data from this study as the ECG data is highly variable and difficult to interpret. For example, subject (b) (6) has time-points where the QTc measurement varies >100 ms within a triplicate.

We therefore recommend that the ECG data collected in ISI 420915-CS1 is reported in the label.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
01/26/2018

CHRISTINE E GARNETT
01/26/2018

Ophthalmology Consult Review of NDA 211-172

NDA 211-172
IND 113,968

Submission Date: November 6, 2017
Consult Request Date: December 18, 2017
Review completed: January 25, 2018

Name: Tegsedi (inotersen)
Applicant: Ionis Pharmaceutics, Inc.
Class: Antisense oligonucleotide inhibitor of human transthyretin (TTR) protein synthesis

Consult Request: Reference is made to the November 6, 2017, submission for NDA 211172 for inotersen to treat patients with hereditary transthyretin amyloidosis (hATTR). Inotersen is a 2′-O-(2-methoxyethyl) [2′-MOE] antisense oligonucleotide (ASO) drug that targets human transthyretin (TTR) messenger ribonucleic acid (mRNA). Hybridization to the cognate TTR mRNA results in the RNase H1-mediated degradation of the transthyretin mRNA preventing production of the transthyretin protein. Hereditary transthyretin amyloidosis can have ocular manifestations.

A major function of transthyretin in the plasma is to transport retinol (vitamin A) to tissues through an association with retinol binding protein 4 (RBP4). In Study CS1 (Phase 1 healthy volunteer study), the mean reduction in transthyretin level was 75% in patients who received 300 mg inotersen per week. The NDA submission includes 2 studies of inotersen in hATTR subjects: CS2 (placebo-controlled study) and CS3 (open-label extension study). Subjects with retinol levels < lower limit of normal at screening were excluded from Studies CS2 and CS3. In Studies CS2 and CS3, subjects received electroretinograms to evaluate retinal function at baseline and post-treatment. The Sponsor's analysis of ocular adverse events potentially related to vitamin A deficiency identified no safety signal. The Sponsor's proposed label recommends [redacted] (b) (4) oral supplementation of vitamin A throughout treatment.

The Sponsor's analysis of ocular events potentially related to vitamin A deficiency is located on p. 119-125 of the Summary of Clinical Safety, which can be obtained via this link:
\\CDSESUB1\evsprod\NDA211172\0001\m2\27-clin-sum

We have the following requests and questions:

1. Please evaluate the clinical study adverse event data and electroretinogram (ERG) data for evidence of ocular toxicity related to vitamin A deficiency.
2. Please comment on whether the Sponsor adequately evaluated for ocular toxicity related to vitamin A deficiency in clinical studies of inotersen. If applicable, provide recommendations for further evaluation.
3. Please comment on the adequacy of the Sponsor's proposed labeling [redacted] (b) (4) The Sponsor's labeling (titled "proposed") can be obtained via this link:
\\CDSESUB1\evsprod\NDA211172\0001\m1\us\114-label\1141-draft-label

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Thank you for your assistance. Please let us know if any additional information may be helpful.

Reviewer's Comment: *Comments are limited to areas of ophthalmic concern.*

Protocol: ISIS 420915-CS2, A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy

Ocular Assessments

A period of 6 weeks was given to complete the screening and baseline assessments outlined in the schedule of procedures. The baseline assessments were ideally be conducted after patient eligibility had been determined. An exception to the 6-week screening and baseline assessment window was allowed for TTR genotyping and amyloid biopsy which may have been conducted up to 10 weeks prior to Study Day 1. In addition, ERG and ophthalmology examinations could have been conducted up to 1-week after Study Day 1 if needed for scheduling purposes (except for Ile84 patients that fell under exclusion criteria 3 and should have had eye examinations performed to determine eligibility).

During the treatment period, an ophthalmology examination was to be performed at Week 29 and Week 65, and an electroretinogram (ERG) examination was to have been performed at Week 65. The Week 65 ophthalmology and ERG examinations could have been done at Week 59 if needed for scheduling purposes. A window of ± 2 weeks was allowed for the Week 29 and Week 65 (or Week 59) eye examinations.

Patients with a TTR mutation at position 84 and with retinol levels < LLN at Screening, will be required to have 2 additional ophthalmology examinations at approximately 3 and 11 months after the first dose.

Reviewer's Comment: *Acceptable.*

Safety Monitoring Rules for Ocular Effects (Protocol 8.5.3)

All patients should have received an ophthalmology examination by an eye specialist at Baseline, after approximately 7 months of receiving Study Drug (Week 29) and at the end of the dosing period (Week 65). An ERG was to have been performed at Baseline and the end of the dosing period (Week 65). In addition, any patient that complained of persistent ocular symptoms compatible with vitamin A deficiency (e.g., night blindness or dry eyes) should have been referred for an ophthalmology examination. If the ophthalmologist confirmed the patient's symptoms were consistent with vitamin A deficiency and/or the examination revealed physical findings that were consistent with vitamin A deficiency (but did not reach the stopping rule criteria described in Section 8.6.4) then an ERG examination should have been conducted and analyzed by the central reader.

In addition, it was suggested that a review of diet and supplement use and an evaluation for factors which may have contributed to low vitamin A levels such as infection, alcohol

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consumption, and zinc and/or iron deficiency was to be conducted. If the ERG was changed from baseline and showed clear signs of vitamin A deficiency as assessed by the central reader and described below, then the patient would have been monitored more frequently. Frequency was to have be determined by the Sponsor Medical Monitor in consultation with the Investigator and ophthalmologist.

Clear signs of vitamin A deficiency as assessed by ERG include:
a) Changes from baseline > 50%, and
b) Values below normal range (if baseline values were within normal range), and
c) Changes that are approximately symmetrical between eyes (unless there is an alternative explanation for asymmetry)

Dosing with Study Drug may continue while these evaluations are being performed.

Reviewer's Comment:

1. *The definition of vitamin A deficiency is not clear in the protocol.*
2. *There should a statement of whether the minimum standards for ERG set by the International Society for Clinical Electrophysiology of Vision (ISCEV) have been followed, and the specific protocol for ERG testing should be provided.*
3. *Multiple light stimuli and light adaptation periods are used in ERG testing. Both amplitudes and implicit times of the waveforms are usually collected. The protocol should have specified which light stimuli, light adaptation, and portion of the generated waveform is being refer to in the "change from baseline >50%." The specific light stimuli, light adaptation periods and portions of the generated wave forms analyzed should be submitted.*
4. *A large number of patients had abnormal ERGs at baseline. The ERGs for these patients should be submitted along with identification of why each one was considered abnormal.*
5. *The criteria for a vitamin A deficiency in a patient with an abnormal baseline should be specified.*

Stopping Rule for Ocular Effects (Protocol section 8.6.4**)**
A patient was to be permanently discontinued from Study Drug if an ERG was changed from baseline and showed clear signs of vitamin A deficiency (as described in Section 8.5.3) and an ophthalmology examination revealed significant changes from baseline in any 1 of certain physical signs (Bitot's spots, xerophthalmic ulcers, keratomalacia, or other signs and symptoms of corneal necrosis) and a consultation with the central reader occurred.

Reviewer's Comment: *Acceptable. The ERG findings of any patient meeting this criteria should be submitted along with the results of the ophthalmic examination and the findings of the central reader.*

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CS2 On-Study Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency (CS2 Safety Set)

	Placebo		Inotersen 300 mg	
	Subjects, n	Number of	Subjects, n	Number of
Ocular TEAEs potentially related to	12	13	23 (20.5)	25
deficiency				
Corneal disorder	1 (1.7)	1	0	0
Deposit eye	1 (1.7)	1	2 (1.8)	2
Detachment of retinal pigment	1 (1.7)	1	0	0
Dry eye	2 (3.3)	2	4 (3.6)	4
Dyschromatopsia	1 (1.7)	1	0	0
Eye disorder	0	0	1 (0.9)	1
Eye irritation	0	0	1 (0.9)	2
Foreign body in eye	1 (1.7)	1	0	0
Keratitis	2 (3.3)	2	0	0
Macular oedema	0	0	1 (0.9)	1
Ophthalmological examination	0	0	2 (1.8)	2
Photophobia	1 (1.7)	1	0	0
Retinal detachment	0	0	1 (0.9)	1
Retinal vein occlusion	0	0	1 (0.9)	1
Ulcerative keratitis	0	0	1 (0.9)	1
Vision blurred	1 (1.7)	1	2 (1.8)	2
Visual acuity reduced	1 (1.7)	1	0	0
Visual field defect	0	0	1 (0.9)	1
Visual impairment	0	0	1 (0.9)	1
Vitamin D deficiency	0	0	3 (2.7)	3
Vitreous disorder	1 (1.7)	1	0	0
Vitreous floaters	0	0	3 (2.7)	3
Risk difference, %			0.5	
95% CI			-12.1,	

Source: Table 59, Module 5.3.5.1, CS2 CSR, Table 4.107 and Table 4.114

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

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CS3 On-Study Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency (CS3 Safety Set)

Category Preferred Term	Placebo-Inotersen		Inotersen-Inotersen		Total (N=11	
	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of
Ocular TEAEs potentially related to vitamin A	4 (10.0)	7	6 (8.1)	7	10 (8.8)	14
Visual acuity reduced	0	0	2 (2.7)	2	2 (1.8)	2
Corneal irritation	0	0	1 (1.4)	1	1 (0.9)	1
Deposit eye	2 (5.0)	4	1 (1.4)	1	3 (2.6)	5
Keratitis	0	0	1 (1.4)	1	1 (0.9)	1
Retinal haemorrhage	0	0	1 (1.4)	1	1 (0.9)	1
Vision blurred	0	0	1 (1.4)	1	1 (0.9)	1
Corneal perforation	1 (2.5)	1	0	0	1 (0.9)	1
Ulcerative keratitis	1 (2.5)	1	0	0	1 (0.9)	1
Vitamin D deficiency	1 (2.5)	1	0	0	1 (0.9)	1

Source: Table 60, Module 5.3.5.2, CS3 CSR, Table 4.99

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

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Longitudinal Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency (Longitudinal Safety Set)

Category Preferred Term	**Inotersen 300 mg**	
	Subjects, n	**Number of**
Ocular TEAEs potentially related to vitamin A	26 (23.2)	32
Dry eye	4	4
Deposit eye	3	3
Vitamin D deficiency	3	3
Vitreous floaters	3	3
Vision blurred	2	3
Ophthalmological examination abnormal	2	2
Visual acuity reduced	2	2
Eye irritation	1	2
Corneal irritation	1	1
Eye disorder	1	1
Keratitis	1	1
Macular oedema	1	1
Retinal detachment	1	1
Retinal haemorrhage	1	1
Retinal vein occlusion	1	1
Ulcerative keratitis	1	1
Visual field defect	1	1
Visual impairment	1	1

Source: Table 61, Module 5.3.5.2, CS3 CSR, Table 4.39

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

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Inotersen Integrated Set Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency

Category **Preferred Term**	**Inotersen 300 mg**	
	Subjects, n	**Number of**
Ocular TEAEs potentially related to vitamin A	30 (19.7)	39
Deposit eye	5	7
Dry eye	4	4
Vitamin D deficiency	4	4
Vitreous floaters	3 (2.0)	3
Vision blurred	2	3
Ophthalmological examination abnormal	2	3
Ulcerative keratitis	2	2
Visual acuity reduced	2	2
Eye irritation	1	2
Corneal irritation	1	1
Corneal perforation	1	1
Eye disorder	1	1
Keratitis	1	1
Macular oedema	1	1
Retinal detachment	1	1
Retinal haemorrhage	1	1
Retinal vein occlusion	1	1
Visual field defect	1	1
Visual impairment	1	1

Source: Table 62, Table 2.09

Reviewer's Comment: *No specific pattern of ocular adverse events was identified.*

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Electroretinogram Results

	CS2 On-Study (CS2 Safety Set)		CS3 On-Study (CS3 Safety Set)	
	Placebo (N=60)	Inotersen 300 mg (N=112)	Placebo-Inotersen (N=40)	Inotersen-Inotersen (N=74)
Electroretinogram result				
Baseline (CS2 data) or Inotersen Baseline (CS3 data)				
n	53	102	31	66
Normal	32 (60%)	83 (81%)	15 (48%)	56 (85%)
Abnormal	21 (40%)	19 (19%)	16 (52%)	10 (15%)
Consistent with vitamin A deficiency	5 (9%)	4 (4%)	1 (3%)	1 (1.5%)
Not consistent with vitamin A deficiency	16 (30%)	15 (15%)	15 (48%)	9 (14%)
CS2 Week 65 (CS2 data) or CS3 Week 78 (CS3 data)				
n	48	80	10	26
Normal	27 (56%)	57 (71%)	6 (60%)	20 (77%)
Abnormal	21 (44%)	23 (29%)	4 (40%)	6 (23%)
Consistent with vitamin A deficiency	1 (2%)	4 (5%)	0	1 (4%)
Not consistent with vitamin A deficiency	20 (42%)	19 (24%)	4 (40%)	5 (19%)
Any change from Baseline at CS2 Week 65 (CS2 data) or CS3 Week 78 (CS3 data)				
n	48	80	10	26
Yes	16 (33%)	19 (24%)	2 (20%)	3 (12%)
No	32 (67%)	61 (76%)	8 (80%)	23 (88%)

Source: Table 63, Module 5.3.5.1, CS2 CSR, Table 4.122; Module 5.3.5.2, CS3 CSR, Table 4.79

Reviewer's Comment:

1. *A large number of patients had abnormal ERGs at baseline. The ERGs for these patients should be submitted along with identification of why each one was considered abnormal.*
2. *The criteria used to identify a vitamin A deficiency on the ERG should be described. A copy of all abnormal ERGs should be submitted along with identification of why each one was considered abnormal.*

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Response to Questions:

1. Please evaluate the clinical study adverse event data and electroretinogram (ERG) data for evidence of ocular toxicity related to vitamin A deficiency.

Response: No specific pattern of ocular adverse events was identified. Review of the ERG data will require submission of the large number of abnormal ERGs.

2. Please comment on whether the Sponsor adequately evaluated for ocular toxicity related to vitamin A deficiency in clinical studies of inotersen. If applicable, provide recommendations for further evaluation.

Response: Additional information is needed to be able to respond to this question. Please see the Summary of Additional Comments.

3. Please comment on the adequacy of the Sponsor's proposed labeling (b) (4) The Sponsor's labeling (titled "proposed") can be obtained via this link: \\CDSESUB1\evsprod\NDA211172\0001\m1\us\114-label\1141-draft-label

Response: Additional information is needed to be able to comment on the labeling. Please see Summary of Additional Comments.

Summary of Additional Comments:

1. It should be clarified whether the minimum standards for ERGs set by the International Society for Clinical Electrophysiology of Vision (ISCEV) were followed, and a copy of the specific protocol used for ERG testing should be submitted.
2. The definition of vitamin A deficiency is not clear in the protocol. The definition used for the study report should be submitted.
3. The criteria used to identify a patient as having a vitamin A deficiency should be submitted.
4. The specific light stimuli, light adaptation, and portion of the generated waveform used to identify a “change from baseline >50%” should be submitted.
5. The criteria used to identify a vitamin A deficiency on an ERG should be submitted.
6. The ERGs for any patient considered to have an abnormal ERG should be submitted along with identification of why each one was considered abnormal.
7. The ERG findings of any patient considered to have an ERG showing a vitamin A deficiency should be submitted along with the results of the corresponding ophthalmic examination and the findings of the central reader.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
01/25/2018