

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21172Orig1s000**

**CLINICAL REVIEW(S)**



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## Glossary

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AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report

Combined Clinical/Biostatistical Review  
Clinical Reviewer – Breder; Statistical Reviewer – Massie  
NDA 211172 Tegsedī (inotersen)

PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

## 1. Executive Summary

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### 1.1. Product Introduction

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. 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, by decreasing the amount of TTR protein circulating in the plasma, inotersen treatment is proposed [REDACTED] (b) (4)

- Non-proprietary name / Proprietary name - inotersen / Tegsedi
- Dosing regimen(s), route of administration, dosage form:
  - 284 mg inotersen (300 mg sodium salt)/ 1.5 mL in a single-dose, prefilled syringe including a safety syringe device (SSD)
  - Inotersen is administered by subcutaneous injection.
  - [REDACTED] (b) (4)
- [REDACTED] doses should be administered once every week [REDACTED] (b) (4)
- The applicant's proposed indication: Inotersen is an antisense oligonucleotide inhibitor of human transthyretin (TTR) protein synthesis indicated for treatment of patients with hereditary TTR amyloidosis (hATTR) [REDACTED] (b) (4)
- Previous approvals: None

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness is based on one adequately designed and conducted clinical trial, ISIS 420915-CS2 (CS2). CS2 is a multicenter, double-blind, randomized, stratified, placebo-controlled study of inotersen in polyneuropathy associated with TTR-amyloidosis. Study drug was to be administered subcutaneously (SC) as a 300-mg dose (284 mg parent acid). A single 1.5 mL injection containing 300 mg inotersen was to be administered 3 times in the first week and then once weekly in Weeks 2 to 65.

As described in the guidance on for industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products this trial had the following characteristics that could support an approval based on a single adequate and well controlled study:

- Statistically very persuasive finding

The coprimary endpoints were the mNIS+7 and Norfolk Quality of Life Questionnaire - Diabetes Neuropathy. The change from baseline on drug versus placebo at Week 66 on the mNIS+7 focuses on the neurological exam and nerve electrophysiology, while the and Norfolk Quality of

Life Questionnaire - Diabetes Neuropathy is focused on neurological function and ability to perform tasks the effect of autonomic and neuropathy on the patient's functional status. Change from Baseline in mNIS+7 composite score showed a statistically significant difference in favor of inotersen (favorable = lower score) at Week 66. The difference in [inotersen - placebo] least squares mean between treatment groups was -19.73 (95% CI: -26.43, -13.03; p=0.00000004). Changes from Baseline in Norfolk QoL-DN total score showed a statistically significant difference in favor of inotersen at both Week 35 and Week 66. The difference in [inotersen - placebo] least squares mean between treatment groups was -11.68 (95% CI: -18.29, -5.06; p=0.0006) at Week 66.

- Multiple sites

Patients were accrued from sites in Europe (10 sites with 60 patients), North America (9 sites with 82 patients) and South America (5 sites with 30 patients).

- Consistency across study subsets

Multiple meaningful demographic analyses were performed to determine if there was an imbalance of treatment effect. Though the study was not powered for these analyses, almost everyone was statistically positive for each subgroup with none appearing to not demonstrate at least a favorable trend in treatment effect (see Section 6.1.3).

Although the evidence from Studies CS3 (open label extension study for CS2) and CS1 (an open label Phase1b Proof of Concept study in health volunteers) are, in my opinion, not needed, as confirmatory evidence, these data are nonetheless, supportive. For example, in the CS3 study, the 52 and 78 week change, from study baseline in the mNIS+7 is notably less than the 66-week change on the placebo in study CS2 despite the additional 65 weeks of disease progression in the inotersen group (a mean favorable change of for the former +14.3 versus +24.15 for the latter). A similar direction of response is noted for the Norfolk QoL-DN scale, where a positive mathematical change also reflects an undesirable change. In CS1, and from the combined results of CS2 and 3, assessment of plasma levels suggests that TTR levels are reduced to about 70% of baseline at steady state at the proposed 300-mg QD dose.

### 1.3. **Benefit-Risk Assessment**

### Benefit-Risk Integrated Assessment

Hereditary transthyretin amyloidosis is a serious and rare disease with significant disability and an associated mortality between 2 and 15 years (depending on certain demographic characteristics and the specific clinical presentations). The disease may affect several organs including the peripheral nervous system and heart. The applicant has provided substantial evidence of effectiveness for the use of inotersen for the treatment of hereditary transthyretin polyneuropathy (hTTR-PN). The evidence is based on a single, placebo controlled 66-week study, ISIS 420915-CS2, also known as CS2. Evidence from an open label extension study, ISIS 420915-CS3 (“CS3”) and a Phase 1 study, 420915-CS1 (“CS1”) were supportive.

The CS2 study was a 66-week, multicenter, double-blind, randomized study. Only one dose, 300 mg per week, was tested clinically in this program; reductions of transthyretin (TTR) levels in healthy subjects in the CS1 study suggested that this was a reasonable selection as it reduced levels by 70-80% from baseline. 172 patients were randomized in Study CS2 (112, inotersen / 60, placebo). Dropouts (34 (19.7%) were predominantly because of adverse events (17 (9.8%) and all but one of these were in the inotersen arm, without notable patterns in other reasons to discontinue.

The primary endpoints were the changes from drug versus placebo in the modified Neuropathy Impairment Scale +7 (mNIS+7) and Norfolk Quality of Life Questionnaire - Diabetes Neuropathy (Norfolk QoL-DN) at Week 66. The mNIS+7 is an objective evaluation that consists of a neurological exam and nerve electrophysiology; the Norfolk QoL-DN is a subjective assessment of the effect of autonomic changes and peripheral neuropathy on the patient’s experience of disease symptoms and functional status. Change from Baseline in mNIS+7 composite score and Norfolk QoL-DN total score showed a statistically significantly less decline in favor of inotersen at Week 66. About 16% of patients on inotersen treatment improved as assessed by both scales versus eight percent in the placebo group.

Although the evidence from Studies CS3 and CS1 are not needed as confirmatory evidence to support approval, these data are nonetheless, supportive. For example, in the CS3 study, the 52- and 78-week change from CS3 study baseline in the mNIS+7 is notably smaller than the 66-week change on the placebo in study CS2. Serving as an ‘external control’. A similar response is noted for the Norfolk QoL-DN scale. In CS1 and from the combined results of CS2 and 3 assessments of inotersen plasma levels, suggest that TTR levels are reduced to about 70% of baseline at steady state.

This review concludes that the submission provides adequate evidence of effectiveness for inotersen for the treatment of the polyneuropathy of hATTR in adults. Safety is being reviewed separately and so the conclusion regarding the approvability of the application will be addressed at the level of the Summary Review.

**Benefit-Risk Dimensions**

<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<a href="#"><u>Analysis of Condition</u></a>	<ul style="list-style-type: none"> <li>• Hereditary transthyretin amyloidosis (hATTR amyloidosis) is a genetic disease that causes slowly progressive buildup of amyloid protein in the peripheral and central nervous systems, heart, kidneys, eyes, bone, and gastrointestinal tract.</li> <li>• Death usually occurs within 5-12 years after symptom onset, most often due to cardiac dysfunction, infection, or cachexia.</li> <li>• The incidence of hATTR amyloidosis is 1/100,000 in U.S. Caucasians.</li> </ul>	hTTR-PN is a very serious disease causing significant functional morbidities and mortality
<a href="#"><u>Current Treatment Options</u></a>	<ul style="list-style-type: none"> <li>• Onpattro® (patisiran) was recently (8/10/18) approved for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.</li> <li>• Other treatment options for hATTR amyloidosis include liver transplant and medical management of associated symptoms.</li> <li>• Diflunisal, a non-steroidal anti-inflammatory drug, is sometimes used off-label to treat the disease.</li> </ul>	There continues to be an unmet need for additional treatments for this disease, since there is only one approved therapy that may not be tolerated by all patients.
<a href="#"><u>Benefit</u></a>	<ul style="list-style-type: none"> <li>• Change from Baseline in mNIS+7 composite score, an objective evaluation that consists of a neurological exam and nerve electrophysiology, and Norfolk QoL-DN total score, a subjective assessment of the effect of autonomic changes and peripheral neuropathy on the patient’s experience of disease symptoms and functional status, showed a statistically significant difference in favor of inotersen at Week 66. About 16% of patients on inotersen treatment improved as assessed by both scales versus eight percent in the placebo group.</li> </ul>	Inotersen offers a benefit in limiting the progression of decline in peripheral neurological function and in patients’ abilities to perform daily activities.
<a href="#"><u>Risk and Risk Management</u></a>	<ul style="list-style-type: none"> <li>• See Safety Review of Dr. Mentari</li> </ul>	See Safety Review of Dr. Mentari

1.4. **Patient Experience Data**

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input checked="" type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., see sections on Study Endpoints, 6.1.1, 6.1.5]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input checked="" type="checkbox"/>	Other: (Please specify)	[e.g., see section on Therapeutic Context, 0]
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., see section on Presubmission/Submission Regulatory Activity, 3.2]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

Familial or hereditary transthyretin amyloidosis is a serious disease caused by a mutation in a carrier protein for thyroxin and retinol binding protein, Transthyretin (TTR). TTR is a tetrameric protein primarily produced in hepatocytes. Genetic mutations in the TTR gene lead the tetrameric TTR protein to break into monomeric units that misfold and aggregate as amyloid fibril deposits. 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. 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, by decreasing the amount of TTR protein circulating in the plasma, inotersen treatment is proposed [REDACTED] (b) (4)

Disease onset has been described in a wide age range (18-83 years) with a median onset of 35 years of age. While about a hundred mutations have been described for the gene for TTR, the only large cluster is found in patients having the Val30Met mutation. The disease can manifest with polyneuropathy, cardiomyopathy, ocular, and/or leptomeningial signs, such as subarachnoid hemorrhage, migraine, vomiting, ataxia, sensorineural hearing loss, and pyramidal tract signs (Figure 1 and 2). The specific clinical presentation is influenced heavily by mutation type. The applicant seeks an indication for the polyneuropathy-type, or hTTR-PN. The global prevalence of hATTR-PN is estimated to be between approximately 5,000-10,000 persons, with the highest rates occurring in certain countries such as Portugal and Sweden [1]. Typical symptoms of this form of the disease are listed in Table 2. Life expectancy from the onset of symptoms is about 10 years, with a range of 5 to 15 years.

Figure 1 Relative Frequency of Organ Involvement in hTTR Amyloidosis[2]

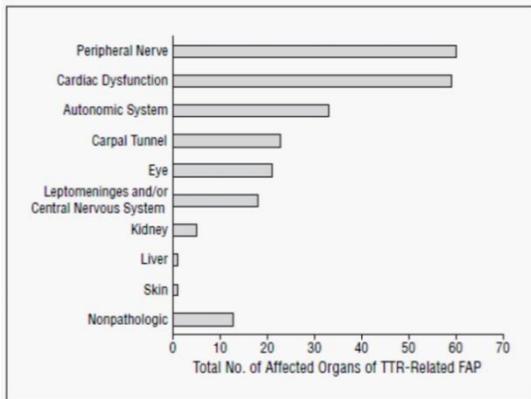
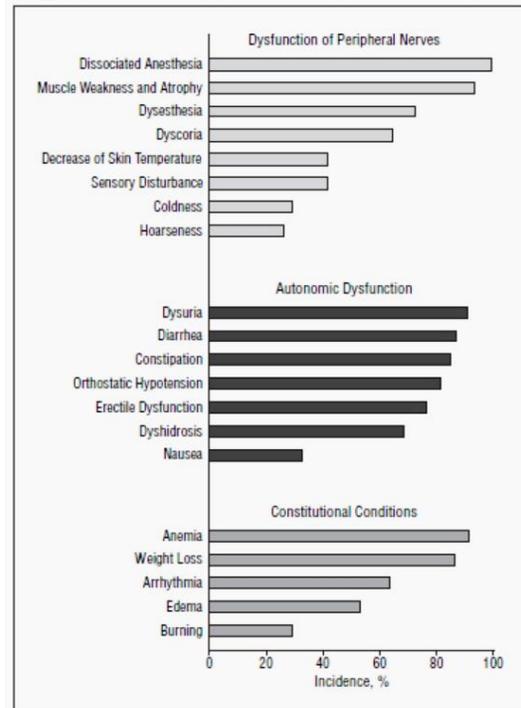


Figure 2 Manifestations of hTTR-PN[2]



## 2.2. Analysis of Current Treatment Options

Onpattro (patisiran) is a lipid complex injection recently approved (8/10/18) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. A principle tolerability issue is the occurrence of infusion-related reactions.

Orthotopic liver transplant has been the standard of care in the USA. Off-label use of diflunisal, a salicylic acid derivative, non-steroidal therapy, has been described as a stabilizer of TTR but is not an approved therapy. Tafamidis, which purports to be a TTR tetramer stabilizer, is approved in Europe but not in the US.

## 3. Regulatory Background

### 3.1. U.S. Regulatory Actions and Marketing History

Inotersen is not approved or marketed in the United States.

Combined Clinical/Biostatistical Review  
Clinical Reviewer – Breder; Statistical Reviewer – Massie  
NDA 211172 Tegsedi (inotersen)

### 3.2. Summary of Presubmission/Submission Regulatory Activity

<b>Date</b>	<b>Regulatory Activity</b>
08-Mar-2012	Type B Pre-Investigational New Drug Meeting for hATTR
24-Jul-2012	Orphan Drug Designation granted for the treatment of familial amyloid polyneuropathy (FAP)
12-Oct-2012	IND113968 included Protocol CS2, as well as Special Protocol Assessment and Fast Track Designation Request
09-Nov-2012	IND 113968 can proceed
03-Dec-2012	Fast-Track Designation granted
06-Feb-2013	Type A Meeting to discuss Special Protocol Assessment No Agreement Letter
18-Oct-2016	QTc Waiver granted for inotersen
05-Apr-2017	Written response issued to nonclinical and clinical Type C Meeting Request

### 3.3. Foreign Regulatory Actions and Marketing History

Tegsedi received a marketing authorization valid throughout the EU on 06-Jul-2018<sup>1</sup>.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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The following comments from the respective review disciplines were available in finalized reviews at the time this review was finalized.

### 4.1. Office of Scientific Investigations (OSI)

The OSI review was authored by Roy Blay, Ph.D., Reviewer, Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation with concurrence by Dr. Phillip Kronstein (team leader) and Susan Thompson (acting branch chief). 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

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<sup>1</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004782/human\\_med\\_002281.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004782/human_med_002281.jsp&mid=WC0b01ac058001d124)

Drs. Coelho and Cruz was No Action Indicated (NAI). The final classification of the inspection of Dr. Gertz was Voluntary Action Indicated (VAI) based on under-reporting of non-serious adverse events.

#### 4.2. **Product Quality**

An Immunogenicity Assay Consult was produced by Dr. Haoheng Yan, with concurrence by Bazarragchaa Damdinsuren (Team Lead) and Christopher Downey (Review Chief). The review determined that 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.

#### 4.3. **Clinical Microbiology**

Not applicable.

#### 4.4. **Nonclinical Pharmacology/Toxicology**

At the time of this review, no nonclinical issues had been identified that would preclude approval of inotersen for the treatment of adult patients with hereditary transthyretin amyloidosis with polyneuropathy. Key findings are described below.

In the monkey studies, reduction of hTTR mRNA levels was associated with substantial (~60-80%) reductions in plasma levels of TTR protein.

In the chronic toxicity studies of inotersen in mouse, rat, and monkey, accumulation of basophilic granules (consistent with drug-related material) was observed in liver, kidney, lymph nodes, injection sites, and other organs, along with associated inflammatory responses typically seen with administration of ASOs. In the 26-week rat study, adverse kidney toxicity was observed in the two highest dose groups, characterized by increases in urine protein/creatinine and albumin/creatinine ratios, glomerular cellularity, and glomerular matrix. Adverse degeneration/regeneration of proximal tubular epithelial cells was observed in the 13-week monkey study. In the 39-week monkey study, severe thrombocytopenia associated with petechiae, bruising, and internal hemorrhages was observed within the first 11-14 weeks of dosing in two animals (one in each of the two highest dose groups), necessitating early euthanasia. In the same study, five other animals across the three lowest dose groups showed perivascular mixed cell infiltration in multiple organs, associated with increases in anti-drug antibody, CRP, IL-6, MIP-1 $\beta$ , TNF $\alpha$ , and serum IgG and IgM; and (in 4/5 animals) with moderate reductions in platelet counts (49-70%, compared to baseline).

Safety margins based on AUCs at the no observed adverse effect levels (NOAELs) for severe thrombocytopenia in monkeys and kidney toxicity in rats were  $\leq$  ~2-fold, suggesting monitoring in humans may be warranted.

Key findings from a standard battery of reproductive and developmental toxicity studies in

mouse and rabbit included premature delivery and reductions in maternal and fetal body weights in the high dose group in the rabbit embryofetal development study (NOAEL = 17.5 mg/kg/week), undetectable levels of inotersen in rabbit fetal liver, low levels of inotersen in rabbit placenta (~20-fold lower than in maternal liver), and low levels of inotersen in rabbit milk (~700- to 7000-fold lower than in maternal liver).

#### 4.5. Clinical Pharmacology

Following subcutaneous administration, median time to maximum plasma concentration ( $T_{max}$ ) was 1.5 to 4 hours. The  $C_{max}$  is 12.1  $\mu\text{g/mL}$ . No therapeutic individualization is expected to be required for inotersen based on extrinsic or intrinsic factors. The Office of Clinical Pharmacology primary review from Mariam Ahmed, with sign-off by Venkatesh A Bhattaram, Theingi M Thway, Hobart Rogers, Kevin M Krudys, Sreedharan N Sabarinath and Mehul Mehta, recommend approval.

### 5. Sources of Clinical Data and Review Strategy

#### 5.1. Table of Clinical Studies

The following studies were conducted in the inotersen development program:

Table 1 Listing of Clinical Trials Relevant to this NDA

Trial Id	Trial Design	Regimen/ Schedule/ route	Study Endpoints	Treatment Duration / Follow Up	No. of patients enrolled	Population	Centers
<b><i>Controlled Studies to Support Efficacy and Safety</i></b>							
ISIS 420915-CS2	Double blind, Multicenter, Placebo Controlled	300 mg Week 1: day 1, 3, 5 Week 2-65: qWeek	Change from baseline @ Week 66 <ul style="list-style-type: none"> <li>mNIS +7</li> <li>Norfolk QoL-DN</li> </ul>	66 W	Randomized: 173; Dosed: 172	(65.7% Stage 1 hATTR-PN; 34.3% Stage 2 hATTR)	24 [10 centers (in US)]
<b><i>Studies to Support Efficacy and Safety</i></b>							
ISIS 420915-CS3	Open Label Extension	300 mg qWeek	Per CS2	Ongoing (as of 2/28/17)	114	From CS2	9 centers (in US)
<b><i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i></b>							
ISIS 420915-CS1	Open Label; Single dose and then	50, 100, 200, or 400 mg SC x 1 or as	Change and percent change from baseline	Single dose and then 6	22 Healthy volunteer	Healthy volunteers	1

<b>Trial Id</b>	<b>Trial Design</b>	<b>Regimen/ Schedule/ route</b>	<b>Study Endpoints</b>	<b>Treatment Duration / Follow Up</b>	<b>No. of patients enrolled</b>	<b>Population</b>	<b>Centers</b>
	Multiple dose	multiple doses (x 6 Weeks; MD) 3000 mg also tested as a MD	in transthyretin (TTR) level; PK; Safety	weeks	s		

## 5.2. Review Strategy

The analysis of the effectiveness of inotersen will largely focus on a verification of the reported results from Study CS2. Supportive data from the open-label trials (CS3 and CS1) will also be evaluated. Dr. Evelyn Mentari will review safety in a separate review.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. Study 1 (“ISIS 420915-CS2”, “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 (NEURO-TTR Study)

#### 6.1.1. Study Design

CS2 is a multicenter, double-blind, randomized, stratified, placebo-controlled study of inotersen in Stage 1 and Stage 2 subjects with hATTR-PN with a Neuropathy Impairment Score (NIS)  $\geq 10$  and  $\leq 130$ .

#### 6.1.2. Overview and Objective

The primary objective was the assessment of efficacy as measured by the difference between inotersen and placebo on the Modified Neuropathy Impairment score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN).

#### 6.1.3. Trial Design

#### 6.1.4. Regimen

- Study drug was to be administered subcutaneously (SC) as a 300-mg dose (284 mg parent acid). A single 1.5 mL injection containing 300 mg inotersen was to be administered 3 times in the first week and then once weekly in Weeks 2 to 65. The dose was not weight-adjusted.

- During weeks that included a clinic visit, study drug was administered at the clinic. For weeks that did not include a clinic visit, study drug was administered by either study center personnel or at home by the subject or the subject’s caregiver.
- If required for tolerability reasons, study drug administration in 2 noncontiguous injections of smaller volume (i.e., <1.5 mL each) was also allowed. Temporary dose reductions or interruptions for safety or tolerability reasons were also permitted.
- Concomitant therapy
  - Given the interaction between TTR and retinol binding protein (RBP), subjects were required to take vitamin A during the treatment and posttreatment evaluation periods. Vitamin A supplements were provided by the study center or designee.
  - Doxycycline and tauroursodeoxycholic acid (TUCA) were not allowed, unless approved by the study medical monitor. If a subject was taking doxycycline or TUCA prior to study entry, treatment had to be discontinued at least 4 days prior to Study Day 1.
  - Treatment with either tafamidis or diflunisal was not allowed at any time during the treatment period and was discouraged during the post-treatment follow-up period. If tafamidis or diflunisal were taken in the post-treatment period, the study medical monitor was to be consulted to determine if an additional mNIS+7 assessment was to be collected prior to initiating either of these treatments.
  - Because of known potential adverse effects of NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) on renal function, it was recommended that they be used with caution during the study.

### **Dose Rationale**

Per the applicant, “...*In the inotersen Phase 1 study (Study ISIS 420915-CS1), the 300 mg dose level showed a satisfactory safety profile and a substantial PD effect after 6 doses (>70% mean reduction in plasma TTR levels). The PD effect observed with the 300 mg dose level was also like that observed with the 400 mg dose level, and therefore the 300 mg per week dose (with additional loading doses in the first week) was selected for this Phase 2/3 study.*

*Preliminary PK/PD modeling (based on data from the Phase 1 ISIS 420915-CS1 study and extrapolation to steady-state) predicted mean total (wild-type and mutant) TTR steady-state reductions of ~80% with either a 300 mg/week or 400 mg/week regimen.*

### **Population**

- Eligible subjects were randomized 2:1 to receive inotersen or placebo, respectively.

There were 2 separate and independent randomizations: one for subjects who elected to be in the PK subgroup<sup>2</sup> and one for remaining subjects who elected NOT to be in the PK subgroup. Within each randomization, subjects were stratified for

- Previous treatment with Tafamidis or diflunisal vs no known previous treatment
- Stage 1 vs Stage 2 disease V30M TTR mutation vs non-V30M TTR mutation

#### Key Inclusion / Exclusion Criteria

#### Inclusion Criteria

1. Subjects with Stage 1 or Stage 2 (Table 2) hATTR-PN and all the following:
  - a. NIS score  $\geq 10$  and  $\leq 130$
  - b. Documented TTR variant by genotyping
  - c. Documented amyloid deposit by biopsy
  - d. In Germany, Portugal, and Argentina only<sup>3</sup>, Stage 1 subjects were also required to meet at least 1 of the following criteria: 1) failed Tafamidis treatment, 2) intolerant to Tafamidis treatment, or 3) not eligible for Tafamidis treatment.

Table 2 Stages of Amyloid Polyneuropathy[3]

Stage 1 – Does not require assistance with ambulation
Stage 2 – Requires assistance with ambulation
Stage 3 – Wheelchair bound

2. Aged 18 to 82 years at the time of informed consent

#### Exclusion Criteria

1. Screening laboratory results as described below, or any other clinically significant abnormalities in screening laboratory values that rendered a subject unsuitable for inclusion:
  - a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $> 1.9$  times the upper limit of normal (ULN)
  - b. Bilirubin  $\geq 1.5 \times \text{ULN}$  (subjects with bilirubin  $\geq 1.5 \times \text{ULN}$  may have been permitted following discussion with the medical monitor, if only indirect bilirubin was elevated, ALT/AST was not  $> \text{ULN}$ , and genetic testing confirmed Gilbert's disease)
  - c. Platelets  $< 125 \times 10^9/\text{L}$
  - d. Positive ( $\geq$ trace) for protein on urine dipstick. In the event of a positive test, eligibility could be restored by a quantitative total urine protein measurement of  $< 1.0 \text{ g}/24 \text{ hours}$
  - e. Positive ( $\geq$ trace) for blood on urine dipstick. In the event of a positive test, eligibility could be restored with urine microscopy showing  $\leq 5$  red blood cells (RBCs) per high power field. If  $> 5$  RBCs per high power field and there was a clearly identifiable benign cause for the microscopic hematuria (e.g., chronic urinary tract infection secondary to

<sup>2</sup> See ensuing section on Analysis Populations

<sup>3</sup> The countries included in ROW were the US, United Kingdom, France, Italy, Brazil, New Zealand, and Spain.

neurogenic bladder), eligibility was to be determined by discussion with the medical monitor

f. Thyroid-stimulating hormone (TSH) values outside normal range (unless approved by the medical monitor)

2. Retinol level at Screening less than the lower limit of normal (LLN) for subjects with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and retinol <LLN, the exclusion criterion was signs or symptoms of vitamin A deficiency (such as evidence of vitamin A deficiency on electroretinography [ERG])
3. Uncontrolled hypertension (blood pressure >160/100 mmHg)
4. Positive test result for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C
5. Karnofsky performance status  $\leq 50$
6. Renal insufficiency as defined by estimated creatinine clearance calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula <60 mL/min/1.73 m<sup>2</sup> at Screening. If the calculated creatinine clearance was thought to be artificially low, a 24-hour urine creatinine clearance was allowed with prior Sponsor approval
7. Presence of known type 1 or type 2 diabetes mellitus
8. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease)
9. Treatment with another investigational drug, biological agent, or device within 3 months of Screening, or 5 half-lives of the study agent, whichever was longer
10. If previously treated with Tafamidis, the subject must have discontinued treatment for 2 weeks prior to Study Day 1. If previously treated with diflunisal, the subject must have discontinued treatment for 3 days prior to Study Day 1
11. Previous treatment with any oligonucleotide or small interfering ribonucleic acid within 6 months of Screening. Subjects that were previously treated with oligonucleotides could be approved by the medical monitor
12. Prior liver transplant or anticipated liver transplant within 1 year of Screening
13. New York Heart Association (NYHA) functional classification of  $\geq 3$
14. Acute coronary syndrome or major surgery within 3 months of Screening
15. Known primary amyloidosis
16. Known leptomeningeal amyloidosis
17. Anticipated survival <2 years
18. Active infection requiring systemic antiviral or antimicrobial therapy that was not completed prior to Study Day 1
19. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that was successfully treated. Subjects with a history of other malignancies that were curatively treated may have also been eligible, but discussion with and approval by the medical monitor was required.
20. Known monoclonal gammopathy of undetermined significance or multiple myeloma

Subjects could also be selected for an echocardiographic (ECHO) substudy (See ensuing section on [Analysis Populations](#) for entry criteria), an evaluation of inotersen effects on cardiovascular parameters related to hATTR cardiomyopathy. These subjects were also required to meet the following entry criteria (prespecified):

1. Left ventricular wall thickness of  $\geq 13$  mm on transthoracic ECHO at Baseline

2. No known history of persistent hypertension  $\geq 150$  mmHg within 12 months prior to Screening
3. Baseline ECHO evaluable, as ascertained by the central reader

### Prespecified Analysis Populations

- The **Randomized Set** was defined as those screened subjects who received a randomization assignment. Results were summarized according to randomized treatment.
- The **Full Analysis Set (FAS)** included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) and who had a Baseline and at least 1 post-Baseline efficacy assessment for the mNIS+7 score or Norfolk QoL-DN questionnaire total score. The FAS was the primary population for analysis of efficacy and PD outcomes. Results were summarized per randomized treatment.
- The **Safety Set (SS)** included all randomized subjects who received at least 1 injection of study drug. The SS was used for analyses of all safety measures. Results were summarized per the actual treatment that was received.
- The **Per Protocol Set (PPS)** included the subset of the FAS who received at least 80% of the prescribed doses of study drug and who had no major protocol violations that could potentially affect efficacy assessments. The PPS was a secondary population for efficacy and PD analyses and was used for sensitivity analyses. The detailed criteria and definitions for major protocol violations were specified and finalized prior to unblinding; individual subjects who satisfied the violation criteria were identified after database lock and prior to unblinding. Results were summarized per actual treatment received.
- The **PK Set** was defined as all randomized subjects who received at least 1 dose of active study drug (inotersen) and had at least 1 evaluable PK sample collected and analyzed with a reportable result. Results were summarized per actual treatment received. The PK Subgroup included all subjects who participated in the PK subgroup and had at least 1 evaluable PK result. This population was used for all PK analyses. Results were summarized per actual treatment received.
- The **ECHO Subgroup** included the subset of subjects in the Randomized Set who qualified for and consented to participate in the ECHO substudy.
  - Subjects who participated in the ECHO substudy were also required to meet the following entry criteria to be included in this subgroup:
    - Left ventricular wall thickness of  $\geq 13$  mm on transthoracic ECHO at Baseline
    - No known history of persistent hypertension  $\geq 150$  mmHg within 12 months prior to Screening
    - Baseline ECHO was evaluable as ascertained by the central reader. Results were summarized per randomized treatment.
- The **CM-ECHO Set** included the subset of subjects in the Randomized Set who met at least 1 of the following criteria:
  - diagnosis of hATTR-CM at study entry or
  - eligible to participate in the ECHO subgroup (whether consented or not).

### Study Endpoints

In the Pre-IND meeting on March 8, 2012, the primary endpoint was discussed with the, then, sponsor: The Division noted that the NIS+7 contains multiple sub-endpoints, some that are clearly surrogate endpoints (e.g. nerve conduction studies), and some, like leg strength, that might be more closely related to functions like walking, but that are still, of themselves, not direct measures of clinically meaningful improvement. They noted that there is limited experience regarding the use of this endpoint in the study population of interest, and importantly, the clinical meaning of a given change in the total score is unclear in this population. The NIS constitutes the clinician's subjective assessment of the subject's motor, sensory, and reflex components of the neurological exam, and the nerve conduction studies constitute an objective measurement of the large and small nerve fiber function. The Division was particularly interested in adding an endpoint to measure the subjects' assessment of a perceived benefit. The Norfolk Quality of Life Questionnaire one of the proposed secondary endpoints, is a self-assessment of symptoms and function, and therefore can potentially corroborate an apparent improvement on the NIS+7. The Division recommended the sponsor elevate the QOL-DN as a co-primary or propose alternative strategy that will mandate a statistically significant improvement on QOL-DN (or other self-assessed measures of benefit) for the study to be positive.

#### Primary

The co-primary efficacy endpoints were the difference between inotersen and placebo in the change from Baseline to Week 66 in the mNIS+7 score and in the Norfolk QoL-DN questionnaire total score.

I. **mNIS+7** (Total score 346.32): The mNIS+7 consisted of 2 composite scores: the **NIS composite score** (Maximum of 244 points; 4 components: cranial nerves, muscle weakness, reflexes, and sensation) and the **modified +7 composite score** (maximum of 102.32 points; The modified +7 composite score consisted of 4 components: heart rate deep breathing (HRDB; see the following section B.1 for a description), nerve conduction tests, touch-pressure, and heat-pain.).

A. **NIS Composite Score** - A quantitative disease score that measures deficits in cranial nerves, muscle strength, reflexes, sensation of the big toe, and sensation of the index finger, as judged by a trained neurologist. For the sensation tests (touch-pressure, pin-prick, vibration, and joint motion) assessments are done on the dorsal surface, at the base of the nail of the terminal phalanx of the index finger and great toe on both sides of the body. Touch-pressure is assessed using long fiber cotton wool, pin-prick is assessed using straight pins, and vibration sensation is assessed using a standard 165 Hz tuning fork. Joint motion is tested by moving the terminal phalanx of the index finger and great toe.

The NIS score can range from 0 (no deficits) to a maximum score of 244 (Table 3). There is limited data for the correlation between NIS score and stage of disease, but in general, Stage 1 hTTR patients with polyneuropathy have been observed to have an NIS score from 0-40, Stage 2 from 40-120, and Stage 3 from 120-244 although there is a high degree of overlap.

**B. Modified +7 composite score**

1. The **HRDB** is a quantitative autonomic test that measures the patients change in heart rate after deep breathing. To perform the test, four ECG electrodes, two reference electrodes and a chest expansion belt are attached to the patient as instructed in the HRDB instructions. The patient is then asked to breathe deeply at the same rate as an oscillating bar for a total of 8 breaths. After a 5-minute rest the test is repeated.
2. Touch-pressure (TP) sensation determined using the CASE IV instrument
3. Heat-pain (HP) sensation determined using the CASE IV instrument
4. 5 attributes of nerve conduction (5 NC) – modified to include upper limb ulnar nerve
  - a) Fibular (peroneal) nerve measuring CMAP amplitude [REDACTED] (b) (4)  
[REDACTED]
  - b) Tibial nerve measuring CMAP amplitude [REDACTED] (b) (4)
  - c) Ulnar nerve measuring CMAP amplitude and SNAP amplitude [REDACTED] (b) (4)  
[REDACTED]
  - d) Sural nerve measuring SNAP amplitude [REDACTED] (b) (4)

Table 3 Scoring for the NIS composite score

Component	Assessment	Right Side	Left Side	Max Score	Max Sub-Totals
Cranial Nerves <sup>a</sup>	1. 3 <sup>rd</sup> Nerve	0-4	0-4	8	40
	2. 6 <sup>th</sup> Nerve	0-4	0-4	8	
	3. Facial weakness	0-4	0-4	8	
	4. Palate weakness	0-4	0-4	8	
	5. Tongue weakness	0-4	0-4	8	
Muscle Weakness <sup>a</sup>	6. Respiratory	0-4	0-4	8	152
	7. Neck flexion	0-4	0-4	8	
	8. Shoulder abduction	0-4	0-4	8	
	9. Elbow flexion	0-4	0-4	8	
	10. Brachioradialis	0-4	0-4	8	
	11. Elbow extension	0-4	0-4	8	
	12. Wrist flexion	0-4	0-4	8	
	13. Wrist extension	0-4	0-4	8	
	14. Finger flexion	0-4	0-4	8	
	15. Finger spread	0-4	0-4	8	
	16. Thumb abduction	0-4	0-4	8	
	17. Hip flexion	0-4	0-4	8	
	18. Hip extension	0-4	0-4	8	
	19. Knee flexion	0-4	0-4	8	
	20. Knee extension	0-4	0-4	8	
	21. Ankle dorsiflexors	0-4	0-4	8	
	22. Ankle plantar flexors	0-4	0-4	8	
	23. Toe extensors	0-4	0-4	8	
	24. Toe flexors	0-4	0-4	8	
Reflexes <sup>a</sup>	25. Biceps brachii	0-2	0-2	4	20
	26. Triceps brachii	0-2	0-2	4	
	27. Brachioradialis	0-2	0-2	4	
	28. Quadriceps femoris	0-2	0-2	4	
	29. triceps surae	0-2	0-2	4	
Sensation – Index Finger <sup>b</sup>	30. Touch pressure	0-2	0-2	4	16
	31. Pin-prick	0-2	0-2	4	
	32. Vibration	0-2	0-2	4	
	33. Joint position	0-2	0-2	4	
Sensation – Great Toe <sup>b</sup>	34. Touch pressure	0-2	0-2	4	16
	35. Pin-prick	0-2	0-2	4	
	36. Vibration	0-2	0-2	4	
	37. Joint position	0-2	0-2	4	
<b>NIS Score (total)</b>					<b>244</b>

a) Scoring definition for cranial nerve and muscle weakness testing;

- 0 = Normal
- 1 = 25% Weak
- 2 = 50% Weak
- 3 = 75% Weak
- 3.25 = Move against gravity
- 3.5 = Movement, gravity eliminated
- 3.75 = muscle flicker, no movement
- 4 = paralysis

b) Scoring definition for reflex and sensation testing;

- For reflexes in patients 50-69 years old, ankle reflexes which are decreased are graded 0 and when absent are graded 1. For patients ≥ 70 years, absent ankle reflexes are graded 1
- 0 = Normal
- 1 = Decreased
- 2 = Absent

Table 4 Scoring for the m+7 Composite Score

Component	Assessment	Max Score	Sub-Totals
Heart rate deep breathing (HRDB)	Heart rate decrease with deep breathing determined with CASE IV	3.72	3.72
Nerve Conduction Tests (Σ3 NC)	Fibular (peroneal) CMAP amplitude (PMAK)	3.72	18.6
	Tibial CMAP amplitude (TMAK)	3.72	
	Ulnar CMAP amplitude (UMAE)	3.72	
	Ulnar SNAP amplitude (USAW)	3.72	
	Sural SNAP amplitude (SSAB)	3.72	
Touch-Pressure (TP)	Dorsal toes	4	40
	Mid-lateral leg	4	
	Mid-anterior thigh	4	
	Anterior lower abdomen	4	
	Mid-upper abdomen	4	
	Anterior subclavicular	4	
	Dorsal finger	4	
	Mid-volar forearm	4	
	Lateral deltoid	4	
Maxilla of face	4		
Heat-Pain (HP)	Dorsal toes	4	40
	Mid-lateral leg	4	
	Mid-anterior thigh	4	
	Anterior lower abdomen	4	
	Mid-upper abdomen	4	
	Anterior subclavicular	4	
	Dorsal finger	4	
	Mid-volar forearm	4	
	Lateral deltoid	4	
Maxilla of face	4		
<b>Modified +7 Score (Total)</b>			<b>102</b>

## II. The Norfolk QoL-DN

The questionnaire contained 35 scored questions for 140 total points that comprised the entire scale. Per the original authors of the scale, “...*The original 68-item pool was refined into a 47-item questionnaire, which was then evaluated for its discriminatory ability and found to have sensitivity >75% across all domains and specificity between 71% and 90% [4, 5]. Following assessment of test/retest reliability and psychometric factor analysis, the Norfolk QOL-DN was further refined to 35 items (Vinik and Vinik, 2007). The scoring approach used in this study yielded a possible range for total quality of life (TQOL) scores of –2 to 138.*”

Questions were arranged thematically, such that the wording of the questions and the type of response were grouped together. The Norfolk QoL-DN (version: 2003) consisted of one composite score (Total QoL) and 5 sub-domain scores (physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy).

### Timing of Assessments

At Baseline, 2 mNIS+7 assessments were performed on separate days (<7 days apart) and within 14 days prior to the first dose of study drug on Day 1. The average of these 2 Baseline assessments was used in the analysis. Administration of the Baseline Norfolk QoL-DN questionnaire was performed on the same day as the first Baseline mNIS+7 assessment, but **prior** to the mNIS+7 assessment at that visit. Rarely, the Baseline mNIS+7 assessment(s) (or a subset of this assessment) were completed early in the treatment period rather than pre-treatment and were considered protocol deviations. These assessments were included in the analysis as valid Baseline assessments if they were obtained within 1 week after the first dose.

At Week 35, the mNIS+7 assessment and Norfolk QoL-DN questionnaire were conducted >24 hours from the previous week's dose of study drug, and the Norfolk QoL-DN questionnaire was administered prior to the mNIS+7 assessment during the visit.

At the end-of-treatment (EOT) assessment performed at Week 66, 2 mNIS+7 assessments were performed on separate days (<7 days apart) and within 14 days of the last dose of study drug. The first EOT mNIS+7 assessment was conducted >24 hours after the last dose of study drug. Administration of the EOT Norfolk QoL-DN questionnaire was performed on the same day as the first EOT mNIS+7 assessment, but **prior** to the mNIS+7 assessment at that visit.

### Statistical Analysis Plan

Primary Endpoint - The primary efficacy analyses were (1) the comparison of change from Baseline to Week 66 in mNIS+7 between the inotersen 300 mg group and the placebo group in the FAS, and (2) the comparison of change from Baseline to Week 66 in Norfolk QoL-DN questionnaire total score between the inotersen 300 mg group and the placebo group in the FAS. Interpretation was made in a stepwise approach; i.e., if the null hypothesis for the mNIS+7 was rejected, then the null hypothesis for the Norfolk QoL-DN questionnaire total score was tested. However, if the null hypothesis for the mNIS+7 was not rejected, testing for the Norfolk QoL-DN questionnaire total score was considered exploratory. No adjustment was needed for multiple testing (both endpoints were tested at a 2-sided alpha of 0.05) as both had to be successful.

The primary efficacy endpoint data were analyzed using a Mixed Effects Model with Repeated Measures (MMRM). The MMRM method included fixed categorical effects for treatment (2 levels), time (2 levels), treatment-by-time interaction, and each of the 3 randomization stratification factors (each with 2 levels). The Baseline value of the endpoint and the Baseline-by-time interaction were included as fixed covariates in the model. The normality assumptions for the MMRM models were to be formally tested using a Shapiro-Wilks test at the 0.01 significance level and assessed by inspection of the following plots:

- Histogram of marginal studentized residuals derived from the MMRM model.
- Normal probability plot.

If the Shapiro-Wilks test assessing normality of the MMRM residuals from week 66 was statistically significant at the 0.01 level, formal hypothesis testing for that endpoint was to be done at the 0.025 one-sided significance level using a non-parametric re-randomization test. Thus, the null hypothesis for the endpoint was to only be tested using the results from the MMRM if the p-value from the Shapiro-Wilks test was > 0.01.

### **Sample Size Considerations**

The planned sample size for this study was revised in Protocol Amendment 7 (dated 16 November 2015) from 195 subjects to 135 subjects based on published results from the placebo-controlled Phase 3 diflunisal trial [Berk, 2013] and a retrospective, multinational natural history study in 283 subjects with hATTR-PN [Adams, 2015a], as well as uncontrolled data for another TTR mRNA targeted therapeutic oligonucleotide [Adams, 2015b]. Based on these published results, the placebo group and the treatment group were estimated to have a 16-point increase and a 6.4-point increase in the mNIS+7 score from Baseline to Month 15, respectively. The standard deviation (SD) of the change from Baseline in each treatment group was estimated to be 14. Based on these assumptions, a sample size of 135 subjects (2:1 allocation ratio) would provide at least 90% power to detect a 9.6-point difference in the mean change from Baseline in mNIS+7 score between the 2 groups, with a two-sided 5% alpha level and assuming a dropout rate of approximately 25%.

For the Norfolk QoL-DN questionnaire total score, the placebo group and the treated group were estimated to have a 13.3-point and a 2.6-point change from Baseline to Month 15, respectively. The SD of the change from Baseline in each treatment group was estimated to be 18. With 135 subjects, there was at least 80% power to detect a 10.7-point difference in the change from Baseline in the Norfolk QoL total score between the 2 groups, with a 2-sided 5% alpha and assuming a dropout rate of approximately 25%.

### **Imputation of missing averaged subcomponents**

If a patient had completed at least part of the mNIS+7/NIS+7 at a visit, then the following imputation method was to be used to impute this missing assessment level data for the purposes of determining component scores for summary and analysis.

The following missing data imputation steps were to be considered and were to be used as described below for Groups A, B, and C:

Step 1: If at least 50% of averaged subcomponent scores within a component were available, the missing averaged subcomponent scores were to be set equal to the mean of the patient's other non-missing averaged subcomponent scores in that component. The component score was then to be calculated.

Step 2 (baseline): In the unlikely event that there were more than 50% of the averaged subcomponents scores within a component that were missing at baseline, the missing averaged subcomponent scores were to be set equal to mean baseline averaged subcomponent score from the parent study Randomized Set (across treatment groups). The component score was then to be calculated.

Step 3 (post-baseline visits): For certain components and only under certain conditions which are listed below, the missing averaged subcomponent scores at that visit within that component only, were to be set equal to the mean averaged subcomponent score among the subjects randomized to placebo in the Randomized Set at that visit. The component score was then to be calculated. If a post-baseline assessment did not fall into the scheduled analysis windows, there is no obvious

visit on which the mean subcomponent scores in the placebo group can be derived. To apply step 3, the following visits were to be used to derive the mean scores in the placebo group:

The components of the mNIS+7 and NIS+7 are grouped into A, B and C based on the imputation step used, as follows.

Group A: For components with multiple subcomponents except the NCT component of +7, imputation steps 1 and 2 were to be applied.

If, after applying step 1 for post-baseline visits, 6 out of the 7 components of the mNIS+7 composite score (NIS-C, NIS-R, NIS-S, NIS-W, HP, TP or NCT) were available and only one was missing at that visit, then step 3 was to be applied for the missing component.

If, after applying step 1 for post-baseline visits, 4 out of the 5 components of the NIS+7 composite score (NIS-C, NIS-R, NIS-S, NIS-W, or NCT) were available and only one was missing at that visit, then step 3 was to be applied for that the missing component.

Mean averaged subcomponent score used in the imputation described in step 3 were to be derived from the averaged subcomponent scores before step 1 imputation among the group of patients who were randomized to placebo.

If, after applying steps 1-3 as appropriate, there were still missing subcomponent scores, the component score was to be set to missing.

Group B: For the NCT component of +7, it should be noted that the following 3 of the 5 subcomponents of this component may be “not evaluable” as an additional category to missing: 1) fibular nerve motor conduction velocity (PMCVK), 2) fibular nerve distal latency (PMLA), 3) tibial nerve distal latency (TMLA). These nerve conduction attributes are not evaluable when the tibial or fibular nerve amplitude is 0, therefore, these “not evaluable” results are considered informative missing results and a slightly different imputation method was to be applied here. The following imputation rule was to be used for Nerve Conduction Tests component score of +7: The normal deviate score for PMCVK, PMLA and TMLA were to be respectively set to 3.72 (the worse response) if the recorded response was classified “not evaluable.” After this, imputation step 1 and 2 were to be applied. If, after applying step 1 for post-baseline visits, 4 out of the 5 components of the NIS+7 composite score (NIS-C, NIS-R, NIS-S, NIS-W, or NCT) were available and only one was missing at that visit, then step 3 was to be applied for that the missing component.

Mean averaged subcomponent score used in the imputation described in step 3 were to be derived from the averaged subcomponent scores before step 1 imputation among the group of patients who were randomized to placebo in the Randomized Set at that visit.

Note that these components are *not* used in the nerve conduction component of the *modified* +7, therefore Group B only includes the NCT component of the NIS+7 and not the NCT component of the mNIS+7.

Group C: The two components, HRDB and vibration tests, have only one subcomponent. Missing data for these averaged subcomponents score were to be imputed as follows:

- For baseline, the missing averaged subcomponent scores were to be set equal to the mean baseline averaged subcomponent score from the Randomized Set (across treatment groups).
- For post-baseline visits, the missing averaged subcomponent scores at that visit were to be set equal to the mean averaged subcomponent score among the subjects randomized to placebo in the Randomized Set at that visit. If a post-baseline assessment did not fall into the scheduled

analysis windows, there is no obvious visit on which the mean subcomponent scores in the placebo group can be derived.

### ***Analysis Visit Windows***

The efficacy and PD data were to be assigned to a visit according to the visit windows 209-269 for Day 239 and Day 411-501 for Day 456. Efficacy assessments that occurred more than 52 days after the last dose of Study Drug were not to be included in the efficacy analyses/summaries during the efficacy on-treatment period, even if they occurred within one of the visit windows. PD assessments, as well as body weight, BMI, and mBMI, that occurred more than 28 days after the last dose of Study Drug were not to be included in the PD analyses/summaries during the PD on-treatment period, even if they occurred within one of the visit windows. For patients who have multiple visits within a window, the visit nearest the target day was to be used unless two visits were equally near, in which case the average was to be used. Note that if there were multiple visits within a window with some being from the post-treatment evaluation period of the study, the visits from the post-treatment evaluation period were not to be used. For mNIS +7 the assignment of assessments to a visit was to be done subcomponent by subcomponent according to the date the component was assessed. As long as the component was completed within the analysis window and within 52 days of last dose it was eligible to be used for the efficacy analyses/summaries during the efficacy on-treatment period. If, after subcomponents had been assigned to visit windows, there were two or more subcomponents of the same type within a window, the subcomponent that was assessed closer to the target day was to be used (or the average of the two, if they were equally close). For baseline and Week 66 the two assessments were to be averaged (provided both assessments were within the visit window and were within 52 days of the last dose of medication). In case of averaged subcomponents, for determining proximity to the visit window target day, the date of the second assessment was to be used.

### ***Imputation of Missing Norfolk QOL-DN Domain and Total score items***

For each patient at a specific visit (defined by the analysis visit window), if at least 50% of the questions for a domain (physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy) were not missing or if at least one question was not missing for the autonomic domain, the missing questions were to be imputed as follows: If any question is missing at baseline, the mean value for this question at baseline from the study population (across all treatment groups) was to be used to impute the missing baseline question value. For post-baseline visits during the treatment period, any missing question values were to be imputed using the last observed or imputed question value (including baseline value). For the symptom domain, in the case that a patient responded on a particular question (Questions 1- 7) as not a having the symptom but also marked presence of the symptom in their feet, legs, hands, or arm, the question was to be set to missing and the imputation rules were to be followed. Otherwise, the total for that domain was to be set to missing. The Norfolk QOL-DN total score was to be calculated by summing the imputed domain scores. If any domain score after imputation was still missing, then the Norfolk QOL-DN total score was to be set to missing.

### ***Sensitivity Analyses of Primary Endpoints***

In addition to the primary efficacy analysis, the following sensitivity analyses were to be conducted on the FAS except where noted for each of the two primary efficacy endpoints:

□ **Sensitivity Analysis 1** (Non-Parametric Analysis) – The non-parametric Van-Elteren test was also to be performed for the two primary study endpoints as the sensitivity analysis. Hodges-Lehmann estimates of the differences between ISIS 420915 300 mg group and the placebo group as well as distribution-free CIs based on the Wilcoxon Rank Sum Test were also to be provided.

□ **Sensitivity Analysis 2** (Conservative Assessment Level Imputation) – To examine whether the primary analysis results are robust to the strategy for imputing missing assessment level data, an alternative strategy that results in a conservative estimate of the treatment effect was to be implemented. Patients without an assessment at a visit were not to have their score imputed for that visit.

For patients with at least one non-missing postbaseline subcomponent score, missing data was to be imputed as follows. Missing post-baseline assessment level data were to be imputed for the placebo group using their observed or imputed baseline value. Missing post-baseline assessment level data were to be imputed for the ISIS 420915 group using the placebo mean in the Randomized population for that subcomponent at that visit (done after the placebo imputation).

□ **Sensitivity Analysis 3** (Excluding Assessments done at Early Termination Visits) – In order to examine the robustness of the primary analysis to the inclusion of premature termination data, the primary efficacy analysis was to be repeated excluding data collected at early termination visits which were included in the primary analysis.

□ Sensitivity analyses were to be performed to investigate the impact of alternative missing data assumptions. These analyses were to be done on the Safety Set and were to be labeled as:

- **Sensitivity Analysis 4** – Multiple Imputation assuming Missing at Random
- **Sensitivity Analysis 5** – Multiple Imputation assuming Copy Increments from Reference
- **Sensitivity Analysis 6** – Multiple Imputation assuming Jump to Reference
- **Sensitivity Analysis 7** – Data at Withdrawal Visit Included

□ **Sensitivity Analysis 8** (Per Protocol Set) – The primary efficacy analysis was to be repeated, using the PPS population.

## Secondary Endpoints

- Change from Baseline to Week 66 in the Norfolk QoL-DN questionnaire symptoms domain score (Stage 1 subjects only) and the Norfolk QoL-DN questionnaire physical functioning/large fiber neuropathy domain score (Stage 2 subjects only)

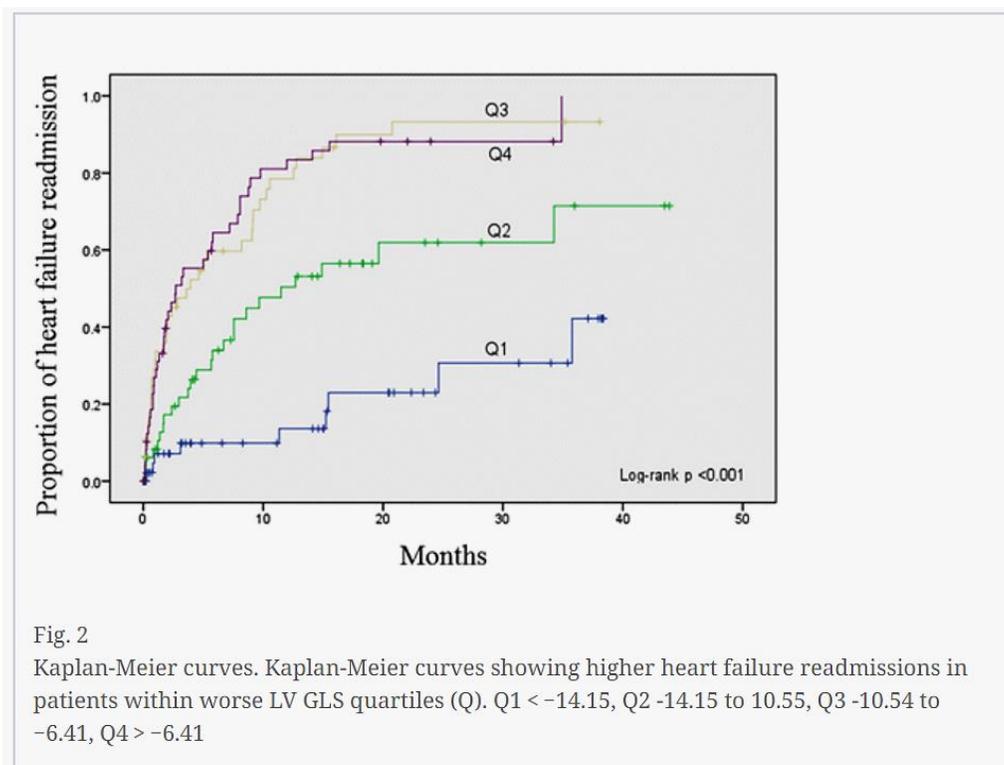
The physical functioning/large fiber domain measures deficits in gross motor movements (e.g., walking, getting out of a chair, walking down stairs, limitations to normal work activities, and pain) which are predominant features of the disease in many Stage 2 hATTR-PN patients.

- Change from Baseline to Week 65 in the mBMI
- Change from Baseline to Week 65 in the BMI
- Change from Baseline to Week 66 in the NIS
- Change from Baseline to Week 66 in the modified +7
- Change from Baseline to Week 66 in the NIS+7

- Change in Global longitudinal strain (GLS) by ECHO from Baseline to Week 65 in the ECHO subgroup and in the CM-ECHO Set

Global longitudinal strain is an assay of ventricular function performed with echocardiography. A study by Yinchoncharoen, T et al. of the Cleveland Clinic<sup>4</sup> found a mean normal GLS value of  $-19.7 \pm 0.28$  in their study of normal and clinic patients (Figure 3). More negative numbers signified worse LV function (see Figure 3 from the Yinchoncharoen reference). The results varied with systolic blood pressure but not gender or age in that reference.

Figure 3 Proportions of Heart Failure readmissions by Global Longitudinal Strain Scoring Quartiles



### Correction for multiplicity

No multiplicity adjustment method for control of the experiment-wise type I error inclusive of secondary endpoints was described in the protocol or statistical analysis plan. Therefore, from a statistical perspective the secondary endpoint results are considered exploratory.

### Interim Analyses

A PD interim analysis of reduction in plasma TTR level was performed by an independent statistician (b) (4) and reviewed by the DSMB after approximately

<sup>4</sup> [http://www.onlinejase.com/article/S0894-7317\(12\)00799-7/pdf](http://www.onlinejase.com/article/S0894-7317(12)00799-7/pdf)

45 subjects completed the Week 13 visit. This interim analysis was a futility analysis; therefore, no statistical penalty was assigned. The DSMB was to inform the Sponsor whether at least 50% of subjects treated with inotersen achieved either a 60% reduction in plasma TTR level or plasma TTR level below the limit of quantification after the first 13 weeks of treatment. The results of this interim analysis resulted in a decision to continue the study as planned. In addition to the review of TTR data for the interim analysis, the DSMB and a small group of firewalled (b) (4) staff (b) (4) also reviewed cumulative safety and efficacy data on all subjects enrolled at the time of the interim analysis.

A second unblinded interim analysis was prespecified in the original protocol that would have supported sample size recalculation based on an assessment of the variability in each of the primary endpoint measures. This interim analysis was changed from unblinded to blinded in Protocol Amendment 2 and removed from the study entirely in Protocol Amendment 5. This interim analysis was not performed.

In August 2016, the DSMB also reviewed unblinded primary efficacy results (mNIS+7 and Norfolk QoL-DN) to assess the risk:benefit of study treatment. This assessment was requested by the DSMB and results were prepared by an independent unblinded statistician (b) (4). The unblinded team at (b) (4) (statistician and at least 1 programmer) that was responsible for providing the unblinded efficacy endpoint results to the DSMB were the only individuals unblinded to treatment assignments. The DSMB package included only descriptive statistics.

### **Protocol Amendments**

Table 5 lists all the amendments by country version of the protocol, since not every amendment pertained to each country. All substantial amendments are described below. Most are concerned with increased monitoring related to thrombocytopenia or renal toxicity. No amendments substantially changed the interpretation of the efficacy outcome from the clinical perspective.

Table 5 Amendments by Country Version of the CS2 Protocol

ROW	Germany	Portugal	Argentina
Original – 21Sep2012	-	Original – 21Sep2012	-
Amend 1 – 14Dec2012	-	Amend 1 – 12Feb2013	-
Amend 2 – 05Mar2013	Original – 19Apr2013	Amend 2 – 07Mar2013	-
Amend 3 – 09Dec2013	Amend 1 – 12Dec2013	Amend 3 – 13Dec2013	-
Amend 4 – 12Jun2014	Amend 2 – 23Jun2014	Amend 4 – 03Sep2014	Amend 4 – 20Nov2014
Amend 5 – 09Jan2015	Amend 3 – 30Jan2015	Amend 5 – 13Jan2015	-
Amend 6 – 29Apr2015	Amend 4 – 15May2015	Amend 6 – 14May2015	Amend 5 – 07May2015
Amend 7 – 16Nov2015	Amend 5 – 01Dec2015	Amend 7 – 30Nov2015	Amend 6 – 02Dec2015
Amend 8 – 07Mar2016	Amend 6 – 18Mar2016	Amend 8 – 16Mar2016	Amend 7 – 17Mar2016
Amend 9 – 13May2016	Amend 7 – 02Jun2016	Amend 9 – 31May2016	Amend 8 – 03Jun2016

ROW countries were US, UK, France, Italy, Brazil, New Zealand, and Spain.  
 Note: Protocol Amendment 4 (dated 20 November 2014) was the original protocol submitted for regulatory approval in Argentina.  
 Abbreviations: Amend=amendment; ROW=rest of the world; UK=United Kingdom

Source: Table 1, Clinical Study Report ISIS 420915-CS2, p. 31/6232

- Amendment 2
  - Moved the Norfolk QoL-DN questionnaire total score from a key secondary endpoint to 1 of the 2 primary endpoints with the mNIS+7. The mNIS+7 and Norfolk QoL-DN primary endpoints were tested using a ranking strategy, with the mNIS+7 tested first and the Norfolk QoL-DN questionnaire total score tested second.
  - Changed the sample size recalculation from unblinded to blinded. The blinded analysis re-estimated the variability separately for each of the primary endpoints (mNIS+7 and Norfolk QoL-DN) to determine if an increase in the sample size was required to maintain an acceptable level of statistical power. No statistical penalty was applied.
  - Required the NIS evaluator to be insulated from the subject’s general study procedures and adverse events. In addition, for an individual subject, every effort was made to ensure the same NIS evaluator performed all the NIS assessments throughout the study.
  - Removed the option to modify the protocol based on results of the TTR interim analysis. The TTR interim analysis resulted in either a decision to continue the study as planned or to stop the study.
  
- Amendment 3
  - A new platelet monitoring rule was added for subjects with platelet counts that decreased by 30% or greater from Baseline and the absolute platelet count was 100,000/mm<sup>3</sup> or less. More frequent monitoring of platelet counts was required in subjects who met these criteria. The frequency of monitoring and conduct of additional lab tests were determined by the investigator in consultation with the medical monitor.
  - The platelet monitoring stopping rules were revised to include the presence of

- major bleeding or clinically relevant non-major bleeding per definitions provided in the protocol amendment.
  - A new platelet monitoring rule was added for subjects with platelet counts that decreased by 30% or greater from Baseline and the absolute platelet count was 100,000/mm<sup>3</sup> or less. More frequent monitoring of platelet counts was required in subjects who met these criteria. The frequency of monitoring and conduct of additional lab tests were determined by the investigator in consultation with the medical monitor.
  - The platelet monitoring stopping rules were revised to include the presence of major bleeding or clinically relevant non-major bleeding per definitions provided in the protocol amendment.
- Amendment 5
  - Added GLS by ECHO as a secondary endpoint in the ECHO subgroup and in the CMECHO Set
  - Modified Inclusion Criteria 1a (increased maximum NIS score allowed from 100 to 130) and removed criterion 1b (ability to walk unaided or with the use of no more than 1 stick/cane).
  - Safety monitoring rules for renal function were revised to recommend additional monitoring for any subject whose creatinine clearance decreased below 60 mL/min/1.73 m<sup>2</sup> (instead of increased serum creatinine  $\geq 0.3$  mg/dL from Baseline or decreased calculated creatinine clearance (by CKD-EPI)  $>25\%$  from Baseline).
  - Stopping rules for renal function test results were modified to clarify that in the event of an estimated creatinine clearance by CKD-EPI  $<30$  mL/min/1.73 m<sup>2</sup> or a decrease of  $>50\%$  from Baseline, a serum creatinine and 24-hour urine sample for creatinine clearance was to be obtained. The ability to apply clinical judgment and input from a renal consultant was also added to the rule to prevent permanent discontinuation of a subject with an obvious alternative explanation for the observed changes in renal function.
- Amendment 6
  - Renal exclusion criteria were made more stringent to exclude any subject with positive ( $\geq$ trace) protein or blood on urine dipstick (instead of persistently positive (2 out of 3 consecutive tests  $\geq$ trace positive) and all subjects with CKD-EPI  $<60$  mL/min/1.73 m<sup>2</sup> at Screening were excluded (changed from CKD-EPI  $<45$  mL/min/1.73 m<sup>2</sup>).
- Amendment 7
  - Decreased the sample size from approximately 195 to approximately 135 subjects randomized.
  - Decreased number of subjects to be enrolled in the PK subgroup from approximately 30 subjects to approximately 20 subjects.
  - Safety monitoring rules for platelet counts were modified to require more frequent monitoring in subjects who had platelet counts 75,000/mm<sup>3</sup> or less (instead of 100,000/mm<sup>3</sup> or less).
  - The study drug stopping rules for platelet counts were modified to require that subjects who had a confirmed platelet count less than 50,000/mm<sup>3</sup>, and in the

absence of major bleeding or clinically relevant non-major bleeding, dosing with study drug was to be held until the platelet count returned to at least 75,000/mm<sup>3</sup> (changed from 75,000/mm<sup>3</sup> and 100,000/mm<sup>3</sup>, respectively).

- Amendment 8
  - Increased the frequency of platelet and serum creatinine monitoring and modified the platelet and renal monitoring/stopping rules.
  - For platelets, subjects who had a confirmed platelet count less than 75,000/mm<sup>3</sup>, and in the absence of major bleeding or clinically relevant non-major bleeding, dosing with study drug was to be held until the platelet count returned to at least 100,000/mm<sup>3</sup> (changed from 50,000/mm<sup>3</sup> and 75,000/mm<sup>3</sup>, respectively). In addition, platelet counts in these subjects were to be monitored weekly (or more frequently as determined by the study medical monitor) until they returned above 75,000/mm<sup>3</sup>.
  - Platelets and serum creatinine were required to be monitored every 2-3 weeks through Week 20, and then every 3 weeks through end of treatment. During the post-treatment evaluation period, monitoring occurred every 2-3 weeks for the first 4 months.
- Amendment 9
  - Increased the frequency of platelet monitoring from every 2-3 weeks, to every week throughout the treatment period and for a minimum of 6 weeks after the last dose of study drug.

#### 6.1.5. Study Results

##### **Blinding**

The DSMB was provided with unblinded safety data to conduct reviews as described in the DSMB Charter. Unblinded results were prepared for the DSMB by an independent statistician who was not involved in the regular conduct of the study (b) (4). In addition, at the request of (b) (4), the DSMB and a small group of firewalled (b) (4) staff (b) (4) were permitted access to unblinded results at the time of the planned interim analysis of TTR (see Section 9.8.3 for additional details).

##### **Financial Disclosure**

One of the investigators in the ISIS 420915-CS2 study, (b) (6), Site # (b) (6) received substantial payments in the form of an \$800,000 grant made on or after February 2, 1999. Per the guidance on Study Financial Disclosure by Clinical Investigators, the applicant provided an acceptable explanation of steps taken to minimize the potential for study bias resulting from interest or arrangement from this payment (Response to Clinical Information Request 3/30/18 SN 0036). Sensitivity analyses were also performed to determine the effect of data from this site (see text at the Investigator bookmark in this review) that suggest this site did not have a notable effect on the outcome of the study.

Other missing information from the Financial Disclosure was also furnished at that time.

## **Patient Disposition**

In CS2, a total of 173 subjects from 10 countries were randomized (inotersen: 113 subjects; placebo: 60 subjects), and 172 subjects received study treatment (Table 6). 89 subjects from the United States were randomized (53 inotersen/26 placebo). One subject in the inotersen group was randomized in error and did not initiate treatment with study drug.

80.3% of randomized subjects completed study treatment per the protocol. The proportion of subjects who discontinued study treatment early was higher in the inotersen group (23.0%) compared with the placebo group (13.3%) due primarily to adverse events (AEs). In the inotersen arm over one third of the AEs that led to permanent discontinuation of study treatment were associated with thrombocytopenia (4 inotersen subjects) or glomerulonephritis (2 inotersen subjects). Most subjects who completed treatment in CS2 (135/139) entered CS3 as of 18 April 2017; this total includes 21 subjects who completed treatment in CS2 and enrolled in CS3 after the data cut-off for the interim analysis of CS3. Approximately 96% of subjects that completed treatment in CS2 elected to enroll in CS3.

A total of 66 subjects (38.2%) were in the CS2 ECHO substudy, and the proportion of subjects included in the ECHO Subgroup was similar between treatment groups (Table 7).

Table 6 Disposition of Patients

	Placebo (N=60)	Inotersen 300 mg (N=113)	Total (N=173)
<b>Treatment completion status, n (%)</b>			
Completed <sup>a</sup>	52 (86.7)	87 (77.0)	139 (80.3)
Discontinued	8 (13.3)	26 (23.0)	34 (19.7)
<b>Primary reason for early treatment discontinuation, n (%)</b>			
Adverse event or SAE	1 (1.7)	16 (14.2)	17 (9.8)
Stopping rule met	1 (1.7)	2 (1.8)	3 (1.7)
Investigator judgment	0	0	0
Voluntary withdrawal	3 (5.0)	2 (1.8)	5 (2.9)
Pregnancy	0	0	0
Ineligibility	0	1 (0.9)	1 (0.6)
Significant protocol deviation	0	0	0
Liver transplant	0	1 (0.9)	1 (0.6)
Disease progression	3 (5.0)	2 (1.8)	5 (2.9)
Other	0	2 (1.8) <sup>b</sup>	2 (1.2)
<b>Entered open-label extension, n (%)</b>	<b>49 (81.7)</b>	<b>84 (74.3)</b>	<b>133 (76.9)<sup>c</sup></b>
<b>Post-treatment evaluation period completion status,<sup>d,e</sup> n (%)</b>			
Completed	5 (8.3)	9 (8.0)	14 (8.1)
Ongoing	1 (1.7)	2 (1.8)	3 (1.7)
Withdrawn	5 (8.3)	18 (15.9)	23 (13.3)
<b>Primary reason for withdrawal from post-treatment evaluation period, n (%)</b>			
Adverse event or SAE	1 (1.7)	8 (7.1)	9 (5.2)
Stopping rule met	0	0	0
Investigator judgment	0	0	0
Voluntary withdrawal	3 (5.0)	4 (3.5)	7 (4.0)
Pregnancy	0	0	0
Ineligibility	0	1 (0.9)	1 (0.6)
Significant protocol deviation	0	0	0
Liver transplant	1 (1.7)	1 (0.9)	2 (1.2)
Disease progression	0	1 (0.9)	1 (0.6)
Other	0	3 (2.7)	3 (1.7)

- Number of subjects who completed up to the Week 66 visit, even if individual visits were not done or doses were not taken.
- Subject (b) (6) and Subject (b) (6) prematurely discontinued study treatment due to the Sponsor's decision.
- A total of 135 subjects actually were enrolled in the OLE study. Subject (b) (6) prematurely discontinued treatment in CS2 but was allowed to enroll in CS3 by the Sponsor. Subject (b) (6) completed treatment and the 6-month follow-up period in CS2 and was subsequently enrolled in CS3.
- Analysis based on data collected during the post-treatment evaluation period.
- Completion of post-treatment follow-up means a subject fully completed the 6-month post-treatment follow-up period.

Table 7 Number of Patients by Analysis Dataset (% of Total)

	Placebo (N=60) n (%)	Inotersen 300 mg (N=113) n (%)	Total (N=173) n (%)
<b>Number of subjects:</b>			
Randomized	60 (100)	113 (100)	173 (100)
Dosed	60 (100)	112 (99.1)	172 (99.4) <sup>a</sup>
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)

Source: Table 1.08

a. Subject (b) (6) was randomized in error and did not initiate study drug (Appendix 16.2.2, Listing 5).

## Demographics

Baseline patient and disease characteristics were generally balanced (Table 8 and Table 9). The Applicant identified several demographics that seemed imbalanced. Of all the identified characteristics, the mNIS+7 difference was the most concerning on face. (Diff PBO-Active = -6.69 Pbo = 74.12, inotersen = 79.35). The difference is driven by small differences in each of the components and so if the baseline is accounted for in the statistical analysis, this should not influence the interpretation of the outcome. Small imbalances were also observed in prior treatment (tafamidis or diflunisal) demographics.

Table 8 Demographic Characteristics

	Placebo (N=60)	Inotersen 300 mg (N=112)	Total (N=172)
<b>Age (years)</b>			
Mean (SD)	59.5 (14.05)	59.0 (12.53)	59.2 (13.04)
Median	63.0	62.0	62.5
Minimum, Maximum	28, 81	27, 78	27, 81
<b>Age group (years)</b>			
≤18	0	0	0
19 to 64	34 (56.7)	64 (57.1)	98 (57.0)
≥65	26 (43.3)	48 (42.9)	74 (43.0)
<b>Sex, n (%)</b>			
Male	41 (68.3)	77 (68.8)	118 (68.6)
Female	19 (31.7)	35 (31.3)	54 (31.4)
<b>Ethnicity, n (%)</b>			
Hispanic or Latino	7 (11.7)	17 (15.2)	24 (14.0)
Not Hispanic or Latino	53 (88.3)	95 (84.8)	148 (86.0)
<b>Race, n (%)</b>			
American Indian or Alaskan Native	0	0	0
Asian	3 (5.0)	1 (0.9)	4 (2.3)
Black	1 (1.7)	3 (2.7)	4 (2.3)
Native Hawaiian/Other Pacific Islander	0	0	0
White	53 (88.3)	105 (93.8)	158 (91.9)
White and Grayish-Brown	1 (1.7)	0	1 (0.6)
Other	2 (3.3)	3 (2.7)	5 (2.9)
<b>Weight (kg)</b>			
Mean (SD)	71.07 (18.135)	70.59 (17.032)	70.76 (17.373)
Median	69.93	70.10	69.95
Minimum, Maximum	38.2, 126.0	37.0, 140.4	37.0, 140.4
<b>Region, n (%)</b>			
Europe	23 (38.3)	37 (33.0)	60 (34.9)
North America	26 (43.3)	56 (50.0)	82 (47.7)
South America/Australasia	11 (18.3)	19 (17.0)	30 (17.4)
<b>Randomization stratum by IXRS, n (%)</b>			
Previous treatment with tafamidis or diflunisal			
Yes	33 (55.0)	61 (54.5)	94 (54.7)
No	27 (45.0)	51 (45.5)	78 (45.3)
Disease stage			
Stage 1	39 (65.0)	74 (66.1)	113 (65.7)
Stage 2	21 (35.0)	38 (33.9)	59 (34.3)
V30M TTR mutation			
Yes	32 (53.3)	58 (51.8)	90 (52.3)
No	28 (46.7)	54 (48.2)	82 (47.7)
<b>Randomization stratum by CRF, n (%)</b>			
Previous treatment with tafamidis or diflunisal			
Yes	36 (60.0)	63 (56.3)	99 (57.6)
No	24 (40.0)	49 (43.8)	73 (42.4)
Disease stage			
Stage 1	42 (70.0)	74 (66.1)	116 (67.4)
Stage 2	18 (30.0)	38 (33.9)	56 (32.6)
V30M TTR mutation			
Yes	33 (55.0)	56 (50.0)	89 (51.7)
No	27 (45.0)	56 (50.0)	83 (48.3)

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Table 9 Other Baseline Characteristics (e.g., disease characteristics, concomitant drugs)

	Placebo (N=60)	Inotersen 300 mg (N=112)	Total (N=172)
<b>TTR genotype observed in &gt;1 subject,<sup>a</sup> n (%)</b>			
Type GLU89GLN	0	5 (4.5)	5 (2.9)
Type LEU58HIS	3 (5.0)	7 (6.3)	10 (5.8)
Type PHE64LEU	3 (5.0)	5 (4.5)	8 (4.7)
Type SER50ARG	1 (1.7)	5 (4.5)	6 (3.5)
Type SER77TYR	5 (8.3)	4 (3.6)	9 (5.2)
Type THR49ALA	0	2 (1.8)	2 (1.2)
Type THR60ALA	8 (13.3)	14 (12.5)	22 (12.8)
Type VAL122ILE	1 (1.7)	2 (1.8)	3 (1.7)
Type VAL30MET	33 (55.0)	56 (50.0)	89 (51.7)
<b>Duration of disease from hATTR-PN diagnosis<sup>b</sup> (months)</b>			
Mean (SD)	39.3 (40.30)	42.4 (51.19)	41.3 (47.58)
Median	24.0	23.0	23.0
Minimum, Maximum	1, 159	2, 297	1, 297
<b>Duration from onset of hATTR-PN symptoms<sup>b</sup> (months)</b>			
Mean (SD)	64.0 (52.34)	63.9 (53.16)	63.9 (52.72)
Median	48.0	50.5	49.5
Minimum, Maximum	8, 277	5, 372	5, 372
<b>Subjects diagnosed with hATTR-CM, n (%)</b>			
Yes	22 (36.7)	45 (40.2)	67 (39.0)
No	38 (63.3)	67 (59.8)	105 (61.0)
<b>Duration of disease from hATTR-CM diagnosis (months)</b>			
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
<b>Duration from onset of hATTR-CM symptoms (months)</b>			
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
<b>mNIS+7 composite scores</b>			
Mean (SD)	74.75 (39.003)	79.16 (36.958)	77.62 (37.629)
Median	74.89	76.15	75.60
Minimum, Maximum	13.2, 156.7	11.2, 174.7	11.2, 174.7
<b>NIS+7 composite scores</b>			
Mean (SD)	58.93 (29.789)	62.94 (28.930)	61.54 (29.209)
Median	56.74	61.12	58.91
Minimum, Maximum	6.2, 113.2	17.2, 136.1	6.2, 136.1
<b>NIS composite scores</b>			
Mean (SD)	43.77 (24.623)	46.27 (25.521)	45.40 (25.167)
Median	39.25	44.50	41.81
Minimum, Maximum	3.5, 88.4	9.5, 114.8	3.5, 114.8

	Placebo (N=60)	Inotersen 300 mg (N=112)	Total (N=172)
<b>Norfolk QoL-DN total scores</b>			
N	59	111	170
Mean (SD)	48.68 (26.746)	48.22 (27.503)	48.38 (27.165)
Median	48.11	45.00	47.00
Minimum, Maximum	-1.0, 111.0	-2.0, 127.0	-2.0, 127.0
<b>PND score,<sup>c</sup> n (%)</b>			
I	23 (38.3)	32 (28.6)	55 (32.0)
II	19 (31.7)	42 (37.5)	61 (35.5)
III	15 (25.0)	30 (26.8)	45 (26.2)
IV	3 (5.0)	8 (7.1)	11 (6.4)
V	0	0	0
<b>Modified body mass index (kg/m<sup>2</sup>•g/L)</b>			
N	60	111	171
Mean (SD)	1049.89 (228.426)	1010.91 (227.778)	1024.58 (228.097)
Median	1027.55	982.56	998.62
Minimum, Maximum	668.7, 1710.0	573.3, 1751.6	573.3, 1751.6
<b>Body mass index (kg/m<sup>2</sup>)</b>			
N	60	111	171
Mean (SD)	24.21 (4.858)	23.99 (4.896)	24.07 (4.869)
Median	23.81	23.50	23.60
Minimum, Maximum	14.5, 39.8	13.3, 40.2	13.3, 40.2
<b>NT-proBNP (pmol/L)</b>			
N	60	108	168
Mean (SD)	81.98 (159.151)	121.55 (255.420)	107.42 (226.076)
Median	30.50	44.50	34.00
Minimum, Maximum	2.0, 872.0	1.0, 2252.0	1.0, 2252.0
<b>NYHA score, n (%)</b>			
I	40 (66.7)	71 (63.4)	111 (64.5)
II	20 (33.3)	41 (36.6)	61 (35.5)
III	0	0	0
IV	0	0	0
<b>Karnofsky score</b>			
Karnofsky performance status ≤50	0	0	0
Mean (SD)	76.8 (10.81)	76.2 (11.20)	76.4 (11.04)
Median	80.0	80.0	80.0
Minimum, Maximum	60, 90	60, 100	60, 100
<b>TTR concentration (g/L)</b>			
Mean (SD)	0.2186 (0.04696)	0.2134 (0.06108)	0.2153 (0.05647)
Median	0.2245	0.2080	0.2115
Minimum, Maximum	0.106, 0.304	0.086, 0.397	0.086, 0.397

Source: Table 1.10

Note: Denominator is the number of subjects for each group in the SS, unless otherwise indicated.

- Eighteen other TTR mutations were observed in 1 subject each, including ALA109SER, ALA97SER, ASP38ALA, GLU54SER, GLU61LYS, GLU89LYS, GLY47ALA, GLY67ARG, ILE107PHE, ILE107VAL, ILE84SER, LYS35THR, LYS70ASN, PHE33LEU, PRO24SER, SER77PHE, THR59LYS, and TYR114CYS.
- Only year and month were collected for hATTR-PN diagnosis and onset of hATTR-PN symptoms. The duration from hATTR-PN diagnosis and onset of hATTR-PN symptoms was calculated relative to the informed consent date.
- PND score categories are defined in Section 9.6.1.4.

Table 10 Imbalances in Baseline Demographics Identified by Applicant

Parameters	Components, Sub-components, or Laboratory Parameter	Population	Placebo	Inotersen 300 mg	Percent Difference From Inotersen
<b>mNIS+7 (mean)</b>	Composite score	FAS	74.12	79.35	-6.59
	NIS	FAS	43.40	46.59	-6.85
	Modified +7 composite score	FAS	30.73	32.76	-6.20
	NIS muscle weakness score	FAS	19.99	21.20	-5.71
	NIS sensory score	FAS	13.31	14.41	-7.63
	NIS reflex score	FAS	10.10	10.95	-7.76
	Heat-pain sensory score	FAS	7.25	7.91	-8.34
	Touch-pressure sensory score	FAS	10.80	11.40	-5.26
	Heart rate to deep breathing score	FAS	1.814	1.962	-7.54
	Nerve conduction score	FAS	10.868	11.492	-5.43
<b>Norfolk QoL-DN (mean)</b>	Total score	FAS	48.60	48.57	0.06
	Symptoms score	FAS	10.68	10.65	0.28
	Physical functioning/large fiber neuropathy score	FAS	24.42	24.09	1.37
	Activities of daily living score	FAS	6.41	6.52	-1.69
	Small fiber neuropathy score	FAS	5.24	5.09	2.95
	Autonomic neuropathy score	FAS	1.84	2.22	-17.12
<b>SF-36 Physical Component Summary Score (mean)</b>		FAS	37.19	35.65	4.32
<b>SF-36 Mental Component Summary Score (mean)</b>		FAS	50.61	51.04	-0.84
	Mental health domain score	FAS	71.19	72.24	-1.45
<b>NSC (mean)</b>	Total score	FAS	22.92	24.92	-8.03
	Muscle weakness	FAS	7.68	8.31	-7.58
	Sensory (hypo/loss of sensation)	FAS	4.31	4.42	-2.49
	Sensory (paresthesia, hypersensation)	FAS	6.21	6.31	-1.58
	Autonomic (GI/urinary incontinence)	FAS	0.91	1.67	-45.51
	Autonomic (other than	FAS	3.81	4.21	-9.50

Parameters	Components, Sub-components, or Laboratory Parameter	Population	Placebo	Inotersen 300 mg	Percent Difference From Inotersen
	GI/urinary incontinence)				
<b>BMI</b> (kg/m <sup>2</sup> ) (mean)		FAS	<b>24.25</b>	24.27	-0.08
<b>mBMI</b>		FAS	<b>1053.70</b>	<b>1025.33</b>	2.77
<b>PND score</b>	I (%)	SS	38.3	<b>28.6</b>	33.92
<b>ECHO</b> (mean)	GLS (%)	Randomized	-16.49	<b>-15.92</b>	3.58
	Interventricular septum thickness (cm)	Randomized	1.321	<b>1.445</b>	-8.58
	LV mass (g)	Randomized	195.808	<b>223.734</b>	-12.48
<b>NT-proBNP</b> (pmol/L)		SS	81.98	<b>121.55</b>	-32.55
<b>NYHA Class I</b> (%)		SS	66.7	<b>63.4</b>	5.21
<b>Karnofsky performance status score</b> (mean)		SS	76.8	<b>76.2</b>	0.79
<b>Duration from onset hATTR-PN symptoms</b> (mean, months)		SS	<b>64.0</b>	63.9	0.16
<b>Duration of disease from hATTR-PN diagnosis</b> (mean, months)		SS	39.3	<b>42.4</b>	-7.31
<b>Duration from onset hATTR-CM symptoms</b> (mean, months)		SS	34.1	<b>44.7</b>	-23.71
<b>Duration of disease from hATTR-CM diagnosis</b> (mean, months)		SS	21.0	<b>25.1</b>	-16.33
<b>CM-ECHO Set</b> (% included)		Randomized	55.0	<b>66.4</b>	-17.17
<b>Laboratory</b> (Baseline mean values)					
	Platelets	SS	<b>212.19</b>	223.39	-5.01
	Serum creatinine	SS	<b>77.3</b>	76.2	1.44
	eGFR	SS	<b>87.4</b>	88.9	-1.69
	Urine albumin/creatinine	SS	3.152	<b>7.273</b>	-56.66
	Urine protein/creatinine	SS	14.6	<b>24.8</b>	-41.13
	Hemoglobin	SS	137.8	<b>135.9</b>	1.40

Source: Table 1.08, Table 1.10, Table 2.01, Table 2.02, Table 2.46, Table 2.48, Table 2.50, Table 2.56, Table 2.57, Table 2.58, Table 2.60, Table 2.69, Table 4.33, Table 4.34, Table 4.35, Table 5.01, Table 5.04.

Note: Bold numbers indicate greater severity.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Mean exposure on drug was 384.9 day (Table 11); adequacy of exposure will be reviewed in the safety review of Dr. Mentari. Dosing was interrupted in more than half of the patients (59, 52.7%) exposed to inotersen. Most of these were related to platelet levels or measurements, renal events, missed doses, or non-renal/non-platelet related AEs.

Table 11 Exposure to Drug in Study CS2

	Placebo (N=60)	Inotersen 300 mg (N=112)
<b>Total number of doses received<sup>a</sup>, n (%)</b>		
<5	0	2 (1.8)
5 to 10	1 (1.7)	4 (3.6)
11 to 20	1 (1.7)	6 (5.4)
21 to 30	1 (1.7)	5 (4.5)
31 to 40	2 (3.3)	3 (2.7)
41 to 50	2 (3.3)	6 (5.4)
51 to 60	2 (3.3)	9 (8.0)
61 to 70	51 (85.0)	77 (68.8)
Mean (SD)	61.9 (12.45)	55.6 (18.73)
Median	67.0	66.0
Minimum, Maximum	7, 69	1, 67
<b>Total dose of inotersen (mg)</b>		
n	0	112
Mean (SD)		16639.0 (5622.55)
Median		19625.0
Minimum, Maximum		300, 20100
<b>Duration of study drug exposure (days)<sup>b</sup></b>		
Mean (SD)	418.6 (87.05)	384.9 (132.16)
Median	449.0	449.0
Minimum, Maximum	36, 463	1, 458
<b>Dosing was paused, n (%)</b>		
No	37 (61.7)	53 (47.3)
Yes	23 (38.3)	59 (52.7)
<b>Reason for dosing pause<sup>c</sup></b>		
Hold due to meeting platelet monitoring rule (<75 x 10 <sup>9</sup> /L)	0	12 (10.7)
Procedural hold due to SNL on 19Feb2016 <sup>d</sup>	6 (10.0)	11 (9.8)
Hold due to missing platelet values	10 (16.7)	13 (11.6)
Hold due to investigator/medical monitor discretion - related to platelets	2 (3.3)	8 (7.1)
Hold due to investigator/medical monitor discretion - related to renal	0	15 (13.4)
Hold due to AE (non-renal and non-platelet)	3 (5.0)	12 (10.7)
Missed dose <sup>e</sup>	14 (23.3)	24 (21.4)
Other	0	0

Source: Table 1.22

Note: Denominator is the number of subjects for each group in the SS, unless otherwise indicated.

- Total number of doses received = number of doses received at Week 1 + number of weeks with study drug received after Week 1.
- Duration of study drug exposure = date of the last dose of study drug in the CS2 study - date of first dose + 1.
- A dose pause was defined as 1 or more missed doses for any reason.
- A safety notification letter (SNL) was issued to all sites in February 2016 due to a case of severe

thrombocytopenia in Subject (b) (6). Additional safety measures to increase the frequency of platelet monitoring during the study were implemented in this letter. In addition, sites were instructed to pause study drug dosing in subjects who did not have a recent (within 14 days of the date of the letter) platelet laboratory result until a blood sample for platelet monitoring was obtained.

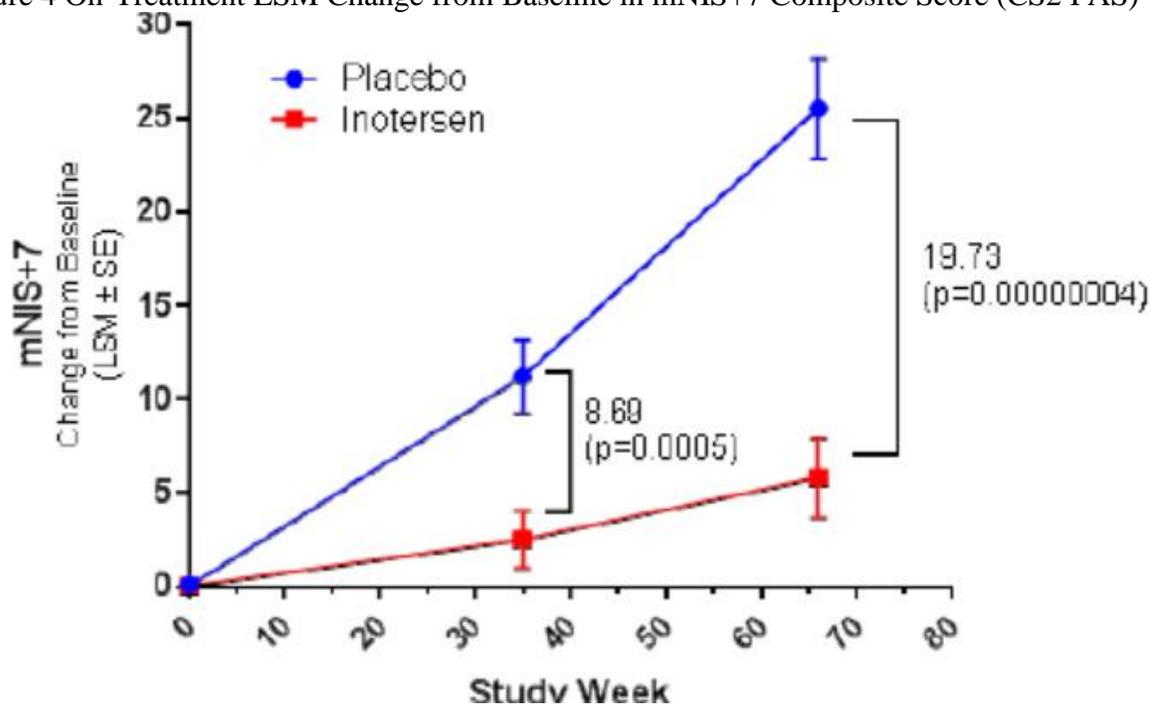
- The category of missed dose included any reason for missed dose that did not fall into the other 6 categories. This category captured non-safety and non-platelet/renal monitoring or operational issues. The most common reasons in this category were unavailability of study drug, the subject forgot to take the dose, or scheduling issues.

## Efficacy Results – Primary Endpoint

### mNIS+7

Changes from Baseline in mNIS+7 composite score showed a statistically significant difference in favor of inotersen compared with placebo at both Week 35 and Week 66. The difference in least squares mean (LSM) between treatment groups [Active – Placebo] was -8.695 (95% confidence interval [CI]: -13.49, -3.90;  $p=0.0005$ ) and -19.73 (95% CI: -26.43, -13.03;  $p=0.00000004$ ) at Week 35 and Week 66, respectively (Figure 4).

Figure 4 On-Treatment LSM Change from Baseline in mNIS+7 Composite Score (CS2 FAS)

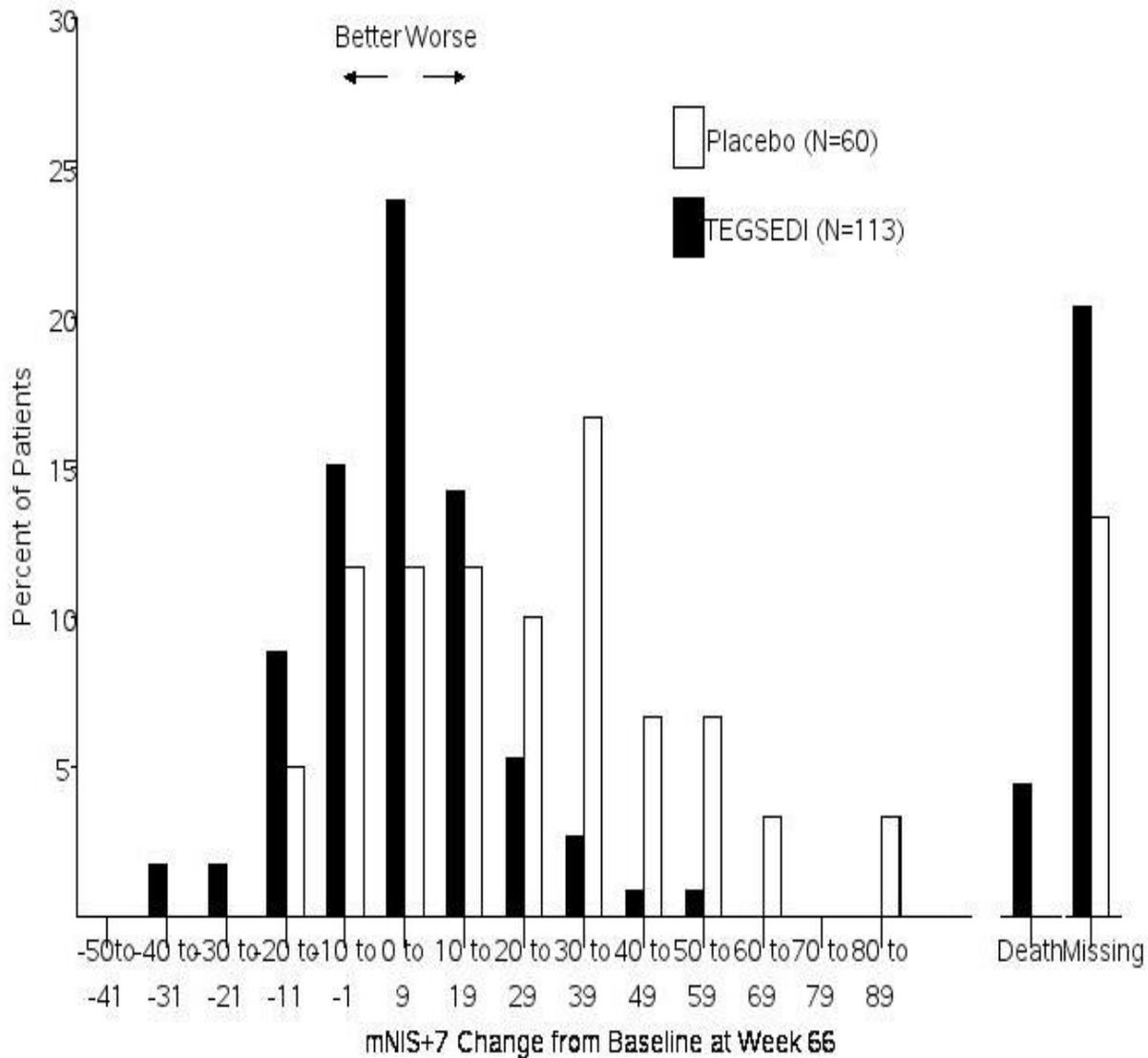


Source: SCS, p. 28/89

In a responder analysis, distributions of change from baseline at Week 66 (or last available value; LAV) were determined by counting the number of patients falling within each 10-point interval of the change from baseline to Week 66. If the Week 66 assessment is missing, then the Week 35 assessment was used. Note that the histogram should therefore be interpreted with caution and any time-specific effects should be obtained from the primary MMRM analysis. Intervals of 10 were chosen for the histogram after considering the range of the scale and the standard deviations of the changes from baseline (Figure 5). Group standard deviations were 19 for Inotersen and 21 for Placebo. Deaths are accounted for on the far right of the distribution. Ten (16.7%) placebo and 31 (27.7%) Inotersen improved on mNIS+7 at Week 66.

<sup>5</sup> lower scores show favorable effect; negative difference between treatments [Active-Placebo] also shows favorable effect

Figure 5 Group Distributions of Changes from Baseline to Week 66 (or LAV) for mNIS+7



**Evaluation of mNIS+7 by Demographic Group**

Efficacy as measured by the mNIS+7 is maintained among demographic groups (Table 12). Also, notable from this Table is that relative dropout rates are high in the inotersen versus placebo subgroups of Stage 2 patients, CM ECHO (patients with decreased heart function), V30M mutation positive, and non-white patients. This is discussed further in the Disposition section.

Table 12 Evaluation of mNIS+7 by Subgroup

Group (N Inotersen/Pbo)	Inotersen baseline N, Mean (SD)	Inotersen N, Change @ Week 66	Pbo baseline N, Mean (SD)	Pbo N, Change @ Week 66	Difference in LSM (SE) [Active-Pbo]	p-value	Ratio % INO/PBO dropouts
Total	106, 79.35 (37.52)	85, 4.16 (15.67)	59, 74.12 (39.03)	52, 23.89 (24.19)	-19.73 <sup>6</sup>	4x10 <sup>-9</sup>	
V30M mutation +	56, 77.69	39, 5.56 (3.08)	32, 77.68 (39.14)	29, 24.42 (3.62)	-18.86 (4.69)	<0.001	3.2
	50, 81.22 (37.46)	46, 5.82 (2.89)	27, 69.91 (39.21)	23, 27.09 (4.03)	-21.27 (4.95)	<0.001	0.5
Prior tafamidis, diflunisal +	59, 81.96 (35.12)	51, 7.5 (2.77)	32, 81.23 (35.16)	25, 27.52 (3.83)	-20.02 (4.63)	<0.001	0.6
	47, 76.08 (40.49)	34, 2.80(3.25)	27, 65.71 (42.29)	27, 23.64 (3.79)	-20.84 (4.96)	<0.001	N/A, PBO d/o=0
Stage 1 Stage 2	70, 68.25 (30.71)	56, 3.75 (2.60)	39, 57.34 (31.46)	33, 17.96 (3.48)	-14.20 (4.20)	<0.001	1.3
	36, 100.95 (40.48)	29, 7.02 (3.73)	20, 106.86 (31.05)	19, 36.14 (4.60)	-29.12 (5.61)	<0.001	3.9
CM ECHO +	70, 83.16 (36.42)	63, 8.71 (2.56)	32, 80.33 (38.30)	31, 25.88 (3.46)	-17.17 (4.27)	<0.001	3.2
	36, 71.95 (39.04)	26, -0.40 (3.72)	27, 66.77 (39.31)	21, 24.78 (4.22)	-25.18 (5.50)	<0.001	1.3
Race: White +	100, 80.69 (37.03)	82, 5.69 (2.18)	53, 76.22 (38.81)	47, 24.31 (2.84)	-18.62 (3.53)	<0.001	1.6
	6, 57.06 (42.36)	3, 7.13(10.915)	6, 55.65 (38.3)	5, 36.97 (8.82)	-29.84 (13.94)	0.034	3.0
Gender: Female +	31, 72.05 (37.74)	26, 5.11 (3.82)	18, 64.06 (36.04)	15, 25.4 (5.033)	-20.29 (6.286)	0.002	1.0
	75, 82.37 (37.27)	59, 6.07(2.54)	41, 78.55 (39.89)	37, 25.55 (3.21)	-19.49 (4.06)	<0.001	2.2
Age < 65yo ≥ 65yo	59, 78.16 (37.39)	50, 5.66 (2.83)	34, 69.66 (39.95)	30, 23.42 (3.61)	-17.76 (4.47)	<0.001	1.3
	47, 80.85 (38.04)	35, 5.89 (3.23)	25, 80.19 (37.68)	22, 28.16 (4.10)	-22.27 (5.22)	<0.001	2.1
Region North America	53, 74.17 (37.400)	45, 6.85 (3.022)	26, 65.12 (35.36)	23, 29.09 (4.14)	-22.24 (4.98)	<0.001	1.3

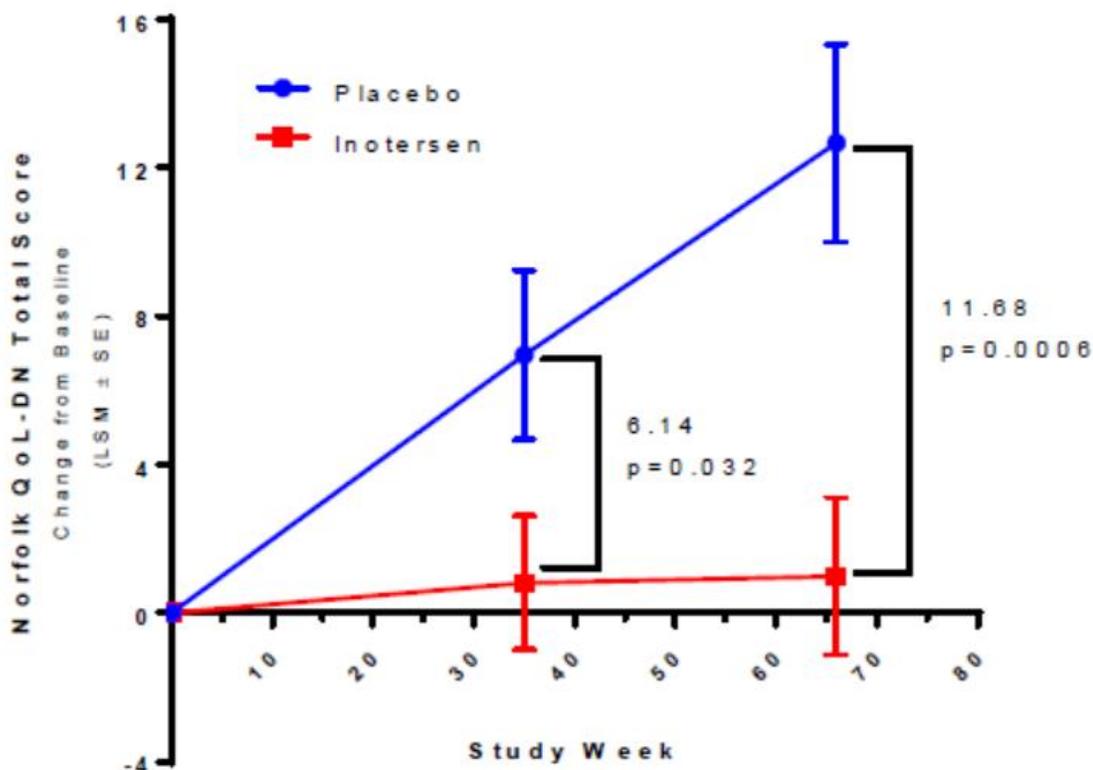
<sup>6</sup> SE not available; 95% confidence interval is (-26.43, -13.03)

### Norfolk QoL-DN Total Score

Changes from Baseline in Norfolk QoL-DN total score showed a statistically significant difference in favor of inotersen compared with placebo at both Week 35 and Week 66. The difference in LSMs between treatment groups was  $-6.14^2$  (95% CI:  $-11.77, -0.52$ ;  $p=0.032$ ) and  $-11.68$  (95% CI:  $-18.29, -5.06$ ;  $p<0.0006$ ) at Week 35 and Week 66, respectively (

Figure 6).

Figure 6 On-Treatment LSM Change from Baseline in Norfolk QoL-DN Total Score (CS2 Full Analysis Set)



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

Most demographic groups were similar in treatment effect on the Norfolk QoL-DN; however notable differences were noted in a few subgroups. There is a notable difference between the white and non-white groups, however the latter population was very small, so the meaningfulness of this difference is not clear. Treatment effect in the older subgroup,  $\geq 65$  yo, was the same as far as being in a favorable direction but much less than the younger cohort, which may reflect a more advanced stage of disease or less capacity to recover in this population. Other differences were a matter of magnitude of change but in the same direction (Table 13).

Distributions of change from baseline at Week 66 (or LAV) were determined by counting the number of patients falling within each 10-point interval of the change from baseline to Week 66. If the Week 66 assessment is missing, then the Week 35 assessment was used. Note that the histogram should therefore be interpreted with caution and any time specific effects should be obtained from the primary MMRM analysis. Intervals of 10 were chosen for the histogram after considering the range of the scale and the standard deviations of the changes from baseline. Group standard deviations were 19 for Inotersen and 21 for Placebo. Deaths are accounted for on the far right of the distribution. Fourteen (23.3%) placebo and 42 (37.5%) Inotersen patients improved on Norfolk QOL-DN at Week 66. There were 5 (8%) placebo and 18 (16%) Inotersen patients that were improved on both primary endpoint scales at Week 66.

Figure 7 Group Distributions of Changes from Baseline to Week 66 (or LAV) for Norfolk QOL-DN

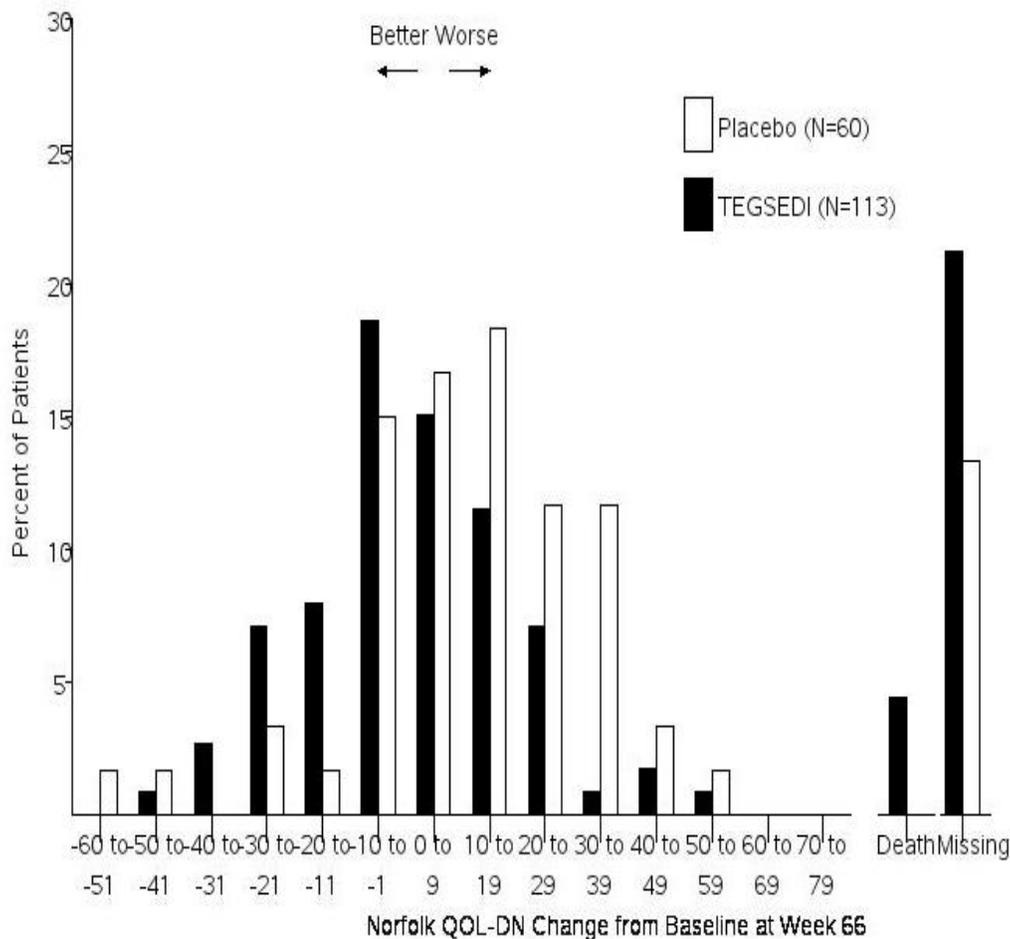


Table 13 Norfolk QoL-DN by Stratification Factors

Group (N Inotersen/Pbo)	Inotersen baseline N, Mean (SD)	Inotersen N, Change @ Week 66	Pbo Baseline N, Mean (SD)	Pbo N, Change @ Week 66	Difference in LSM (SE)[Active-Pbo]	p-value
Total	105, 48.57 (28.18)	84, -0.08 (18.97)	58, 48.6 (26.97)	52, 10.77 (21.34)	-11.68 <sup>7</sup>	0.0006
V30M mutation +	56, 43.33 (28.01)	39, 0.19 (3.08)	32, 49.68 (24.74)	29 (12.44 (3.61)	-12.25 (4.70)	0.01
	49 54.55 (27.45)	45 1.87(2.93)	26 47.28 (29.943)	23 12.99 (3.96)	-11.22 (4.92)	0.025
Prior tafamidis, diflunisal +	58 46.50 (28.83)	50 5.04 (2.74)	31 51.89 (27.60)	25 14.10 (3.79)	-9.05 (4.62)	0.052
	47 51.12 (27.46)	34 -3.64 (3.24)	27 44.83 (26.24)	27 11.06 (3.76)	-3.64 (3.24)	0.003
Stage 1	69 43.18 (26.30)	55 -2.64 (2.60)	38 42.29 (28.32)	33 7.29 (3.313)	-9.93 (4.17)	0.019
Stage 2	36 58.89 (29.16)	29 3.41 (3.57)	20 60.59 (19.76)	19 18.44 (4.45)	-15.04 (5.62)	0.008
CM ECHO Set +	70 53.12 (26.90)	59 2.88 (2.56)	32 54.21 (28.20)	31 11.93 (24.14)	-9.05 (4.27)	0.036
	35 39.46 (28.86)	25 -2.77 (3.84)	26 41.69 (24.14)	21 13.58 (4.20)	-16.35 (5.35)	0.004
Race: White Set +	99 47.85 (27.60)	81 1.18 (2.17)	52 49.12 (28.14)	47 13.42 (2.839)	-12.24 (3.52)	<0.001
	6 60.40) (37.67)	3 -3.10 (10.64)	6 44.07 (13.88)	5 5.91 (8.43)	9.01 (13.61)	0.51
Gender: Female: +	31 45.03 (28.04)	26 -0.81 (3.79)	18 47.13 (28.57)	15 9.78 (4.90)	-10.59 (6.15)	0.087
	74 50.05 (28.30)	56 (1.77) (2.52)	40 49.26 (26.57)	37 13.94 (3.18)	-12.17 (4.02)	0.003
Age < 65yo	59 49.64 (28.98)	50 -1.17 (2.78)	34 47.93) (28.89)	30 15.61 (3.54)	-16.77 (4.33)	<0.001
	46 47.19 (27.38)	34 4.10 (3.2)	24 49.55 (24.57)	22 8.59 (4.0)	-4.49 (5.12)	0.382
Region North America	52 51.57 (27.07)	44 (2.10 (3.01)	25 41.67 (25.24)	23 11.07 (4.04)	-8.97 (4.84)	0.066

<sup>7</sup> Standard Error not provided; 95% CI = (-18.29, -5.06)

### Statistical Reviewer’s Primary Efficacy Sensitivity Analyses

The full analysis set included 59 placebo and 106 Inotersen patients. There was a higher proportion of inotersen patients with no post-baseline assessments, but the difference from placebo was not significant. There were 5 deaths: all in the inotersen group. Two of these had post-baseline primary efficacy assessments and three did not and, therefore, were not included in the primary analysis. Altogether, nine inotersen patients had no post-baseline efficacy assessments (including the 3 deaths mentioned above). The sponsor’s primary analyses include 56 and 95 subjects for the analysis of mNIS+7 and 57 and 94 for the analysis of Norfolk QoL-DN (Table 14). The three of the 5 inotersen subjects who died but had no post-baseline primary efficacy assessments were dosed up until Day 141, 229, and 115, respectively. The 2 inotersen subjects who died but also had post-baseline primary efficacy assessments were dosed until Day 324 and 421, respectively. Their death days were Day 504 and 431, respectively, and they had last assessments classified as Week 35 assessments (Day 241 and 337, respectively).

Table 14 Completion of Key mNIS+7 Assessments and Associated Disposition Events

Completion Status	Completed mNIS+7 Assessments	N (Disposition Events)	
		Inotersen (N= 113)	Placebo (N= 60)
Completers	Weeks 35 & 66	87(86COMP;1AE)	52 (51COMP;1AE)
Dropouts	Week 35 Only	9(2DTH;1LIVT,6AE)	5 (2VW;2DP;1AE)
	Week 66 Only	6(4AE;1SP*;1DP)	2 (1DP;1COMP)
	Week 90 (OLE) <sup>@</sup> Only	1(1VW) <sup>#</sup>	0
	None	10(3DTH;1RANERR;3AE <sup>#</sup> ;1SP*;1VW;1DP)	1 (0DTH;1VW)

Table 15 summarizes the extent of the group completion of key mNIS assessments and reasons for not completing. To utilize more observed data and include more randomized patients in the sensitivity analysis, in a few cases, this reviewer relaxed the rules for inclusion of observed data related to visit windows and time of treatment discontinuation.

Table 15 Completion of Key mNIS+7 Assessments and Associated Disposition Events

Completion Status	Completed mNIS+7 Assessments	N (Disposition Events)	
		Inotersen (N= 113)	Placebo (N= 60)
Completers	Weeks 35 & 66	87(86COMP;1AE)	52 (51COMP;1AE)
Dropouts	Week 35 Only	9(2DTH;1LIVT,6AE)	5 (2VW;2DP;1AE)
	Week 66 Only	6(4AE;1SP*;1DP)	2 (1DP;1COMP)
	Week 90 (OLE) <sup>@</sup> Only	1(1VW) <sup>#</sup>	0
	None	10(3DTH;1RANERR;3AE <sup>#</sup> ;1SP*;1VW;1DP)	1 (0DTH;1VW)

ABBREVIATIONS: DTH=DEATH; AE=ADVERSE EVENT; SP=SPONSOR DECISION; RANERR=RANDOMIZATION ERROR/INELIGIBILITY; VW=VOLUNTARY WITHDRAWAL; DP=DISEASE PROGRESSION; COMP=Completed; LIVT=LIVER TRANSPLANT

<sup>@</sup>OLE=OPEN LABEL EXTENSION

<sup>#</sup>2 ISIS Day 456 Early Termination Month 3 (Day 82) and Month 7 (Day 226) 1AE and 1VW

\*2 Sponsor decisions to stop treatment were AE related (1 was unblinded)

Table 16 Completion of Key NOR QOL-DN Assessments and Associated Disposition Events

Completion Status	Completed Norfolk Assessments	N (Disposition Events)	
		Inotersen (N= 113)	Placebo (N= 60)
Completers	Weeks 35 & 66	87(86 COMP; 1AE)	52 (52 COMP)
Dropouts	Week 35 Only	12(2DTH;8AE;1COMP;1DP)	7 (2AE;3DP;2VW)
	Week 66 Only	0	0
	Week 90 (OLE) <sup>@</sup> Only	7 (3AE;1DP;2VW;1SP)	0
	None	7(3DTH; 2AE;1SP;1RANERR)	1 (1VW)

*ABBREVIATIONS: DTH=DEATH; AE=ADVERSE EVENT; SP=SPONSOR DECISION; RANERR=RANDOMIZATION ERROR/INELIGIBILITY; VW=VOLUNTARY WITHDRAWAL; DP=DISEASE PROGRESSION; COMP=Completed; <sup>@</sup>OLE=OPEN LABEL EXTENSION*

Table 16 summarizes the extent of the group completion of key Norfolk QOL-DN assessments and reasons for not completing.

Table 16 Completion of Key NOR QOL-DN Assessments and Associated Disposition Events

Completion Status	Completed Norfolk Assessments	N (Disposition Events)	
		Inotersen (N= 113)	Placebo (N= 60)
Completers	Weeks 35 & 66	87(86 COMP; 1AE)	52 (52 COMP)
Dropouts	Week 35 Only	12(2DTH;8AE;1COMP;1DP)	7 (2AE;3DP;2VW)
	Week 66 Only	0	0
	Week 90 (OLE) <sup>@</sup> Only	7 (3AE;1DP;2VW;1SP)	0
	None	7(3DTH; 2AE;1SP;1RANERR)	1 (1VW)

*ABBREVIATIONS: DTH=DEATH; AE=ADVERSE EVENT; SP=SPONSOR DECISION; RANERR=RANDOMIZATION ERROR/INELIGIBILITY; VW=VOLUNTARY WITHDRAWAL; DP=DISEASE PROGRESSION; COMP=Completed; <sup>@</sup>OLE=OPEN LABEL EXTENSION*

If the death rate is not very small, or small but all in one arm, as in this trial, then an analysis ignoring deaths may be misleading and biased. In this case, an alternative approach that takes deaths into account assigns the worst rank for deaths in the primary analysis when the primary endpoint is a functional scale (“joint rank analysis” which is typically the recommended primary analysis in clinical trials in amyotrophic lateral sclerosis). Deaths are ranked worse than those with observed post-baseline functional scores and are ranked relative to other deaths according to the survival times. This analysis approach may be more reasonable because it is not appropriate to equate death to a specific level on a functional scale, e.g., missing functional data caused by death is not meaningful, i.e., is obviously important and is not equivalent to the worst possible functional outcome score. Therefore, it should not simply be treated like other missing data. The subject IDs for the 5 deaths, all assigned to inotersen, are as follows. Three of the deaths were considered related to disease progression, 1 to disease progression with a possible contribution of the drug, and 1 related to drug.

Subject ID	Group	Day of Death
(b) (6)	ISIS 420915	202
(b) (6)	ISIS 420915	236
(b) (6)	ISIS 420915	121
(b) (6)	ISIS 420915	503
(b) (6)	ISIS 420915	430

There was also an inotersen subject who had a liver transplant (id# 420915-CS2 (b) (6) The treatment start date for this subject was 01-27-2014 and the transplant date was (b) (6) (transplant on day 388 – before Week 66). This event, perhaps suggesting a lack of efficacy, might also be treated as a bad outcome in a joint rank sensitivity analysis. There was also a placebo subject (420915-CS2/ (b) (6) who had a liver transplant, but this was beyond the double-blind treatment period (treatment start: 07-25-2014 transplant: (b) (6) so it wouldn't affect the primary analysis.

When there are deaths in a clinical trial, special methods of analysis are required to properly assess a drug effect on a functional rating scale, since comparing only within the subgroup of survivors may lead to bias. Table 17 summarizes the statistical reviewer's sensitivity analyses handling deaths by performing a rank analysis in which deaths are assigned the worst rank. The method involves a joint ranking- considering both the primary efficacy functional score and survival time. In the standard joint rank analysis, each patient's rank is determined by comparing them to every other patient and adding a score of -1 if they are worse or +1 if they are better under the various possible scenarios, i.e., if i) both died then the longer survivor is better, ii) if only one died then the other is better, iii) if both survived the functional scores are compared at the last assessment common to both patients and the better scoring patient gets a +1 for that comparison. A patient's joint rank is the sum over his/her comparisons (valued +1, -1, or 0 if tied) with all other patients. For example, suppose the ITT population consisted of 41 patients. The patient who died the earliest would get a -1 compared to the 40 other patients and so, summing over all other patients to get the joint rank would yield a joint rank of -40 for this patient. The next earliest death would have a +1 compared to the earliest death, but a -1 for the remaining 39 patients, for a net rank of 1-39=-38. At the other extreme, the surviving patient with the best mNIS+7 score at Week 66 would get a +1 in comparison with all 40 of the other patients, for a net rank of +40. Thus, if there were no ties in survival time or functional score the joint ranks over the entire clinical trial population would assume the values -40, -38, -36, ... -2, 0, 2, ... 40. These joint ranks are summed by treatment group and then compared across treatments. If there is no drug effect then under a 1:1 randomization, roughly half of the negative ranks and half of the positive ranks would be assumed by those assigned to drug, so the average rank for drug (as well as placebo) would be close to 0. If there is a drug effect, then more of the positive ranks would be assumed by drug group patients. How extreme the actually observed drug group's sum of ranks is can be formally tested with a Wilcoxon rank sum test, or, in order to adjust for covariates, ANCOVA of the ranks can be used (with the prespecified covariates of baseline score, pretreatment (Y/N), stage, TTR mutation, and Treatment group). The results of performing this sensitivity analysis approach are summarized in Table 18.

Table 17 Reviewer’s Sensitivity Analyses Incorporating Death through ranking (Joint Rank)

mNIS+7: N=164 (N= 59 P, 105 ISIS):	Analysis* Conditions	Estimated Week 66 Treatment Difference (Rank scale)	Standard Error	p-value
	Joint Rank: all 5 deaths assigned worse ranks	-26.9	7.2	0.0003
	1 liver transplant given worse rank, as for death	-25.6	7.5	0.0008
Norfolk QOL: N=161 (N=59 P,102 ISIS)	all 5 deaths accounted for	-23.1	9.7	0.0188
	1 liver transplant given worse rank, as for death	-21.4	9.8	0.0304

\*ANCOVA of Joint Rank with covariates baseline, pretreatment, stage, TTR mutation, and Treatment

Three (5%) placebo patients and no (0%) inotersen patients used protocol restricted concomitant medications. There was no plan for handling such deviations in the analysis plan other than requiring patients to have been on study treatment within 52 days of the assessment in order for an assessment to be eligible for the primary analysis. Since the use of protocol restricted concomitant medication was limited and all in the placebo group it would only tend to make the primary analysis result slightly conservative. Therefore, this is not a serious issue for this trial.

Note that there were relatively high rates of patients missing certain mNIS+7 component items at Week 66. The most frequently missing items occurred for items involving Heart Rate Deep Breathing (40-45% not evaluable) or Touch Pressure and Heat Pain at certain anatomical locations (face [70%], deltoid [70%], thigh [50%], subclav [89%], and abdominal cavity [80%]). The heart rate deep breathing was not evaluable 40-45% of the time, apparently due to the presence of a pacemaker, arrhythmia, or it was not done in error. These missing item percentages were also considerable at baseline and not too different between groups, except Touch Pressure for the Abdominal Cavity was nominally significant at Week 66 (83% Inotersen vs. 75% Placebo, but it trended the same way at baseline). Overall, the high proportions of certain mNIS+7 items being missing is not too concerning since there was a prespecified imputation plan and the groups were comparable on almost all specific items. Note that missing items were less of an issue for the co-primary Norfolk QOL-DN.

### **Investigation of Regional and Site effects**

There was some evidence of a regional difference in treatment effect at Week 66 but only on the Norfolk QoL-DN result. The estimated treatment differences were -8.97 for North America (N=68; p=0.066), -7.66 for Europe (N=45; p=0.176), and -26.64 for South America (N=26.64, nominal p<0.001). However, a sensitivity analysis restricted to the US and Europe achieved nominal significance, (-8.73 +/- 3.60, p=0.0168) which may provide some reassurance about efficacy in the US subgroup given the limited power in the US subgroup.

The trial was conducted at 27 sites from 10 countries (Table 18) shows primary efficacy differences at individual sites of interest, i.e., some results related to moderately large or influential sites. For the sake of comparison, the first row for each outcome in the table (where the SITE column value is ALL) corresponds to the Overall results at Week 66 for the treatment difference on the indicated Outcome. The other rows correspond to the overall result after excluding the site associated with the given row. The sites with the biggest estimated treatment differences are 1863 (Cruz; Rio de Janeiro), 1824 (Gertz; Rochester, MN), and 1817 (Coelho; Porto, Portugal). Site 1823 (Benson; Indianapolis, IN) was the biggest site in terms of sample size. Excluding any one of these sites does not alter the significance. Columns 8 and 9 show exploratory efficacy results in the SITE subgroup, while 6 and 7 show the Overall results when excluding the site identified in column 2 of the same row.

Table 18 Primary Analysis Results by Select Individual Sites at Week 66

Outcome	Site	N placebo	N Inot	N total	Overall (w/out given site)		Within Given Site		Location
					trt diff	pvalue	trt diff	pvalue	
MNIS	ALL	57	94	151	19.73	<0.0001	N/A	N/A	N/A
MNIS	1817	11	8	19	19.01	<0.0001	34.31	<.0001	Porto, Portugal
MNIS	1823	4	14	18	19.71	<0.0001	19.83	0.0648	Indianapolis, IN
MNIS	1824	5	8	13	18.01	<0.0001	29.22	0.0346	Rochester, MN
MNIS	1863	5	9	14	18.44	<0.0001	40.91	<.0001	Rio de Janeiro
NORF	ALL	57	94	151	11.68	0.0006	N/A	N/A	N/A
NORF	1817	11	8	19	9.72	0.0102	7.73	0.3862	Porto, Portugal
NORF	1823	4	14	18	11.79	0.0010	6.99	0.6709	Indianapolis, IN
NORF	1824	5	8	13	11.14	0.0023	17.31	0.0255	Rochester, MN
NORF	1863	5	9	14	8.85	0.0138	33.92	0.0013	Rio de Janeiro

Note: MNIS Overall Week 66 Trt Difference CI 13.03, 26.43; NORF Week 66 Trt Difference Overall CI 5.06, 18.29

### Efficacy Results – Secondary and other relevant endpoints

With exception of the cardiac secondary (GLS; see detailed description below) and BMI (P=0.051) and mBMI, the secondary endpoints in Table 19 were nominally positive. The secondary endpoints, with the exception of the BMI evaluation, were generally derivatives of the primary endpoints and so were not appropriate for labeling.

There were no differences in mBMI observed at Week 35 or Week 65 between treatment groups, but there were statistically significant differences at Week 13 and Week 53 in favor of placebo (Figure 8).

Figure 8 Modified Body Mass Index (kg/m<sup>2</sup>\*g/L): Least Squares Mean (95% CI) of Change from Baseline over Time (On- Treatment)

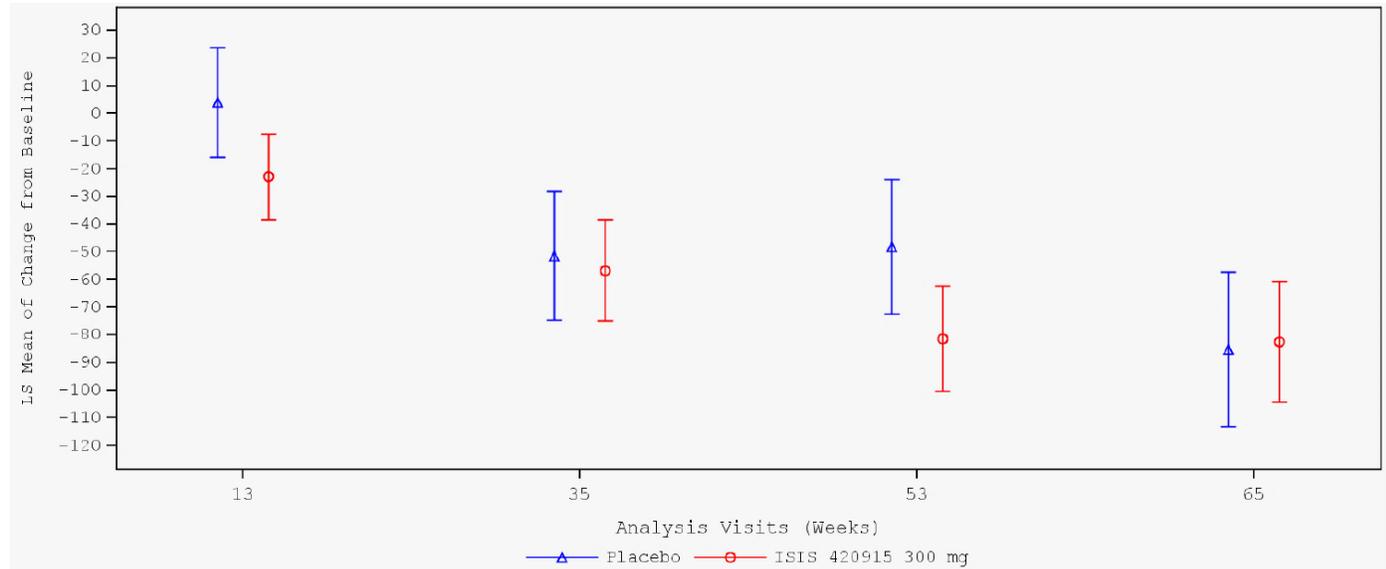


Table 19 Summary of Secondary and Exploratory Endpoints in Study CS2 (FAS)

Parameter	Placebo	Inotersen	Inotersen-placebo
	Change from Baseline	Change from Baseline	Change from Baseline
	n LSM (SE) 95% CI	n LSM (SE) 95% CI	LSM 95% CI p-value
<b>Secondary endpoints</b>			
Norfolk QoL-DN Symptoms Domain Score Stage 1	33 1.11 (0.778) -0.43, 2.66	55 -1.42 (0.608) -2.63, -0.21	-2.53 -4.49, -0.57 0.012
Norfolk QoL-DN Physical Functioning/Large Fiber Domain Score Stage 2	19 9.04 (2.481) 4.04, 14.03	29 0.78 (2.021) -3.28, 4.85	-8.25 -14.71, -1.80 0.013
Body Mass Index	49 -0.80 (0.204) -1.21, -0.40	82 -0.30 (0.159) -0.61, 0.02	0.50 0.00, 1.01 0.051
NIS Composite Score	52 18.65 (1.762) 15.16, 22.13	85 5.40 (1.403) 2.62, 8.17	-13.25 -17.65, -8.85 <0.001
Modified +7 Composite Score	52 6.95 (1.540) 3.91, 10.00	85 0.46 (1.221) -1.95, 2.87	-6.49 -10.32, -2.66 0.001
<b>Tertiary endpoints</b>			
SF-36 Physical Component Summary Score <sup>a</sup>	51 -3.65 (1.011) -5.65, -1.65	84 -0.05 (0.802) -1.64, 1.53	3.59 1.07, 6.12 0.006
SF-36 Mental Component Summary Score <sup>a</sup>	51 -1.35 (1.121) -3.57, 0.87	84 1.07 (0.888) -0.68, 2.83	2.42 -0.37, 5.22 0.088
SF-36 Mental Health Domain Score <sup>a</sup>	51 -2.48 (2.079) -6.60, 1.63	84 2.59 (1.645) -0.67, 5.84	5.07 -0.11, 10.25 0.055
Individual Components of NIS and Modified +7	See Figure 5		
Individual Domains of Norfolk QoL-DN	See Figure 6		

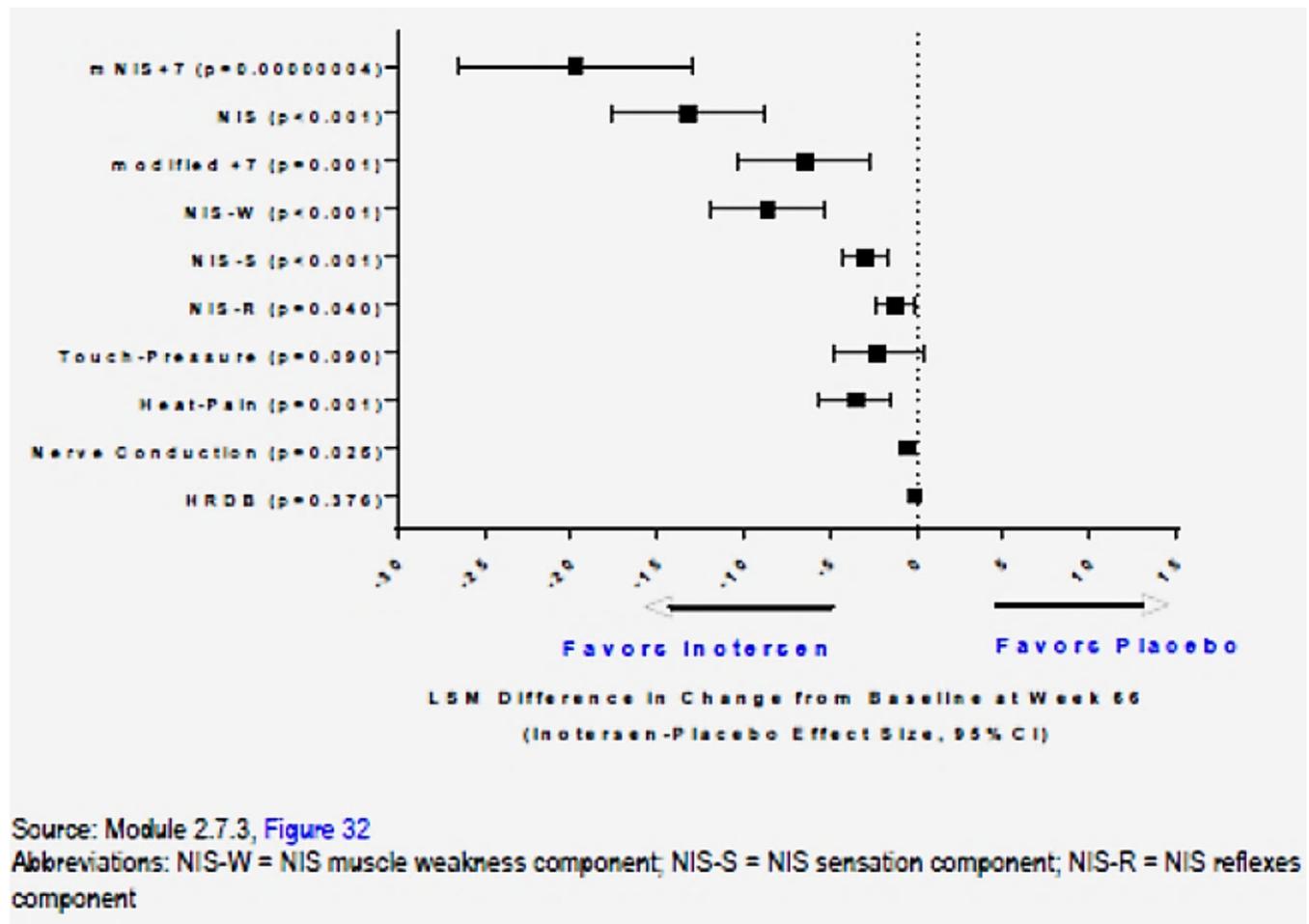
Parameter	Placebo	Inotersen	Inotersen-placebo
	Change from Baseline	Change from Baseline	Change from Baseline
	n LSM (SE) 95% CI	n LSM (SE) 95% CI	LSM 95% CI p-value
<b>Exploratory endpoints</b>			
NSC Total Score <sup>a</sup>	52 8.10 (1.121) 5.89, 10.32	85 1.77 (0.891) 0.01, 3.53	-6.33 -9.12, -3.55 <0.001
PND Score <sup>a</sup>			
Week 65, n	52	86	
Improved, n (%)	2 (3.8)	9 (10.5)	Not applicable
Not changed, n (%)	37 (71.2)	56 (65.1)	
Worsened, n (%)	13 (25.0)	21 (24.4)	

Source: Module 2.7.3, Section 3.2

Note: mBMI was also designated as secondary endpoint but is not shown here. Interpretation of mBMI results were confounded by observed changes in albumin levels that differed slightly between groups. NIS+7, +7, and individual components of +7 were also designated as secondary or tertiary endpoints but are not shown here. NIS+7, +7 and the nerve conduction component of +7 were statistically significant at Week 66. The vibration of the big toe component of +7 was not statistically significant. These endpoints were included in the study for completeness as they were used in previous hATTR-PN studies.

a. Analysis based on data collected up to 52 days after last dose of study drug.

Figure 9 Plot of LSM Differences, in Change from Baseline at Week 66 for mNIS+7 Composite Score, Modified +7, and Individual Components



Source: Module 2.7.3, Figure 32

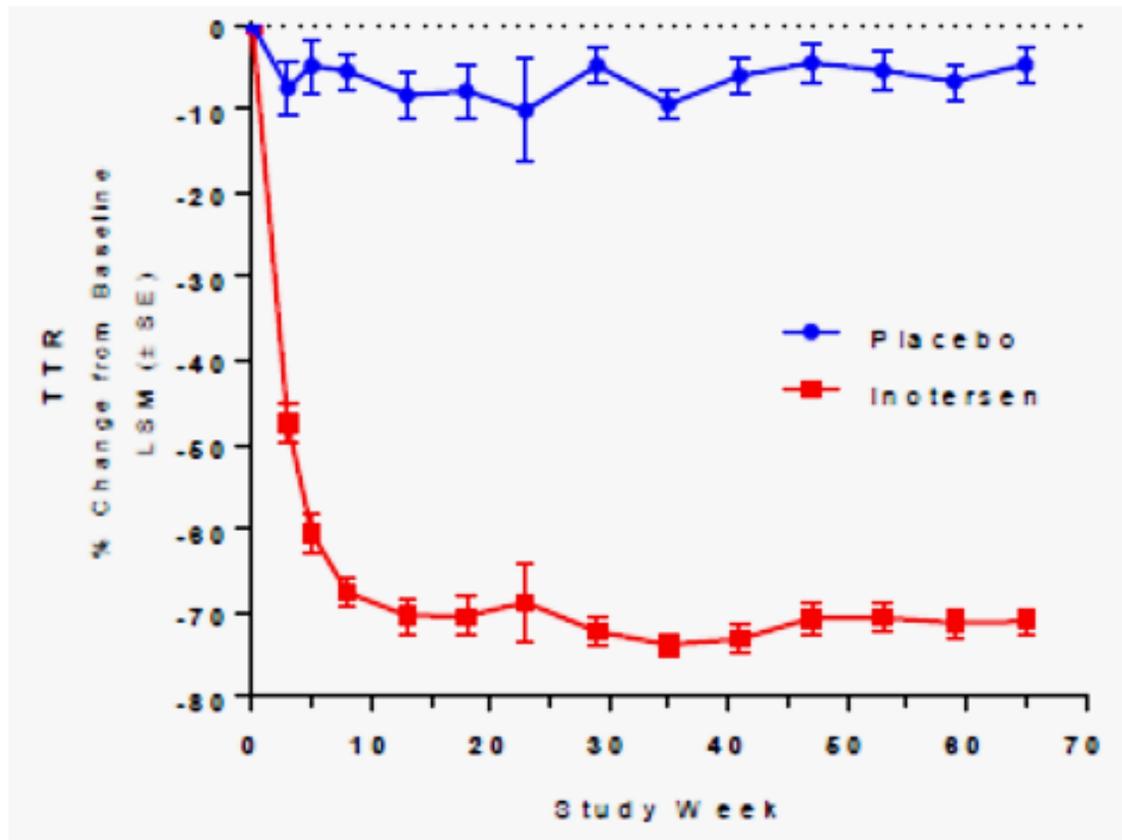
Abbreviations: NIS-W = NIS muscle weakness component; NIS-S = NIS sensation component; NIS-R = NIS reflexes component

### Exploratory and Pharmacodynamic endpoints

In the inotersen group, mean change and mean percent changes from Baseline in serum TTR levels decreased steadily through Week 13 and were sustained for the duration of the treatment period (Figure 10). From Week 13 to Week 65, mean decreases in serum TTR ranged from 68.41% to 74.03% (median range: 74.64% to 78.98%) in the inotersen group in the FAS. The differences in LSMs between the treatment groups for change from Baseline in TTR were statistically significant ( $p < 0.001$ ) at all time points. In the placebo group, mean serum TTR concentration decreased by 8.50% at Week 3 and then remained constant throughout the treatment period.

No significant relationship was observed between TTR reduction and efficacy response measured either by mNIS+7 composite score or Norfolk QoL-DN total score, but there were too few subjects with a low TTR response to allow an exploration of a relationship between TTR levels and clinical efficacy.

Figure 10 On Treatment Percent Change from Baseline in TTR by Study Week in the CS2 Study (FAS)



### GLS CS2 Secondary Analysis

Baseline GLS was on the low end of normal for both PBO and inotersen groups at baseline (normal values tend to be heterogeneous between published studies varying between -19 and -16

(less negative is worse)). The CM-ECHO and ECHO subgroup (described in the section describing Analysis Populations, p.21 ) were only marginally worse from a cardiovascular perspective using GLS. With 65 weeks of treatment, the ECHO subgroup that received inotersen had a miniscule change in the favorable direction that was not significant ( $p = 0.322$ ), while in the randomized and CM-ECHO sets of patients, the result at 65 weeks was marginally but not significantly worse than placebo. The applicant attributed these findings to baseline imbalances demographic attributes related to the disease.

*In the CM-ECHO Set, several baseline disease characteristics suggested that subjects in the inotersen treatment group had more severe cardiomyopathy at study entry compared with subjects in the placebo group (Table 10). 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%) (Table 6). Subjects in the inotersen group had a longer duration from onset of hATTR-CM symptoms and a higher mean Baseline NT-proBNP concentration at study entry compared with the placebo group. The mean duration of hATTR-PN disease from the time of diagnosis and onset of symptoms was also longer in subjects in the inotersen group (35.0 months and 63.4 months, respectively) compared with subjects in the placebo group (23.3 months and 54.0 months, respectively) in the CM-ECHO Set.*

The CS2 study was not designed to adequately evaluate any potential cardiac effects of inotersen  
(b) (4)

In an exploratory analysis of other ECHO parameters, no statistically significant differences between treatment groups in the CM-ECHO Set were observed in 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.

Assessment by the Division of Cardiovascular and Renal Products (DCRP) in response to a consultation to assess these data noted that Study CS2 did not provide any cardiac efficacy data that can support the effectiveness of inotersen on the cardiac manifestations of hATTR-CM. The DCRP consult states that imaging and serum biomarkers such as global longitudinal strain and NT-proBNP do not measure how a patient feels, functions, or survives and so do not measure a clinical benefit. (b) (4)

(b) (4) The various cardiac assessments were perhaps reasonable to monitor for adverse events. (b) (4)

(b) (4) There appears to have been little effect on these cardiac biomarkers and the confidence limits for each analysis were large, so their contribution could not be adequately resolved.

The DCRP consult concludes (b) (4)

(b) (4) . (b) (4)

(b) (4)

(b) (4)

(b) (4)

## **Dose/Dose Response**

No dose response information was available from this study.

## **Durability and Persistence of Effect**

These features are discussed in the context of the CS3 trial.

### **6.2. ISIS 420915-CS3: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)**

#### **6.2.1. Study Design**

CS3 is an ongoing, multicenter OLE study. Eligible subjects from either active or placebo arms in the CS2 study that had satisfactorily completed CS2 receive 300 mg inotersen once weekly for up to 260 weeks (5 years) in the OLE. Subjects who had a dose reduction or schedule change in the parent study are permitted to continue with the adjusted dose level or schedule in the OLE.

#### **Overview and Objective**

The primary objective of this study is to evaluate the safety and tolerability of extended dosing with inotersen in subjects with hATTR-PN.

#### **Trial Design**

This is an ongoing, multicenter OLE study. Eligible subjects who have satisfactorily completed CS2 receive 300 mg inotersen once weekly (or an adjusted dose) for up to 260 weeks (5 years)

During the treatment period, inotersen is administered as a once-weekly SC injection at the study center or at home by the subject or caregiver. Subjects report to the study center for evaluations and tests during Year 1 (Weeks 1, 7, 13, 26, 52) and 2 times in each subsequent year (at Week 26 and Week 52 of each year). Non-clinic visits for laboratory collections occur 8 times during Year 1 (Weeks 4, 10, 15, 18, 21, 23, 29, and 39) and 2 times in the subsequent years (at Week 13 and Week 39 of each year). In addition, platelets are collected weekly and serum creatinine is collected every 2 to 3 weeks by local laboratory, Sponsor-appointed home healthcare service, or the study center.

#### **Study Endpoints**

Other efficacy assessments include the following:

Combined Clinical/Biostatistical Review  
Clinical Reviewer – Breder; Statistical Reviewer – Massie  
NDA 211172 Tegsedi (inotersen)

- mNIS+7
- Norfolk QoL-DN total score
- Modified body mass index (mBMI) and body mass index (BMI)
- Polyneuropathy disability score (PND score)

The Polyneuropathy Disability Score (PND) score is a 5-stage scoring system defined below:

- Stage I – Sensory disturbances in limbs without motor impairment
  - Stage II – Difficulty walking without the need of a walking aid
  - Stage III – One stick or 1 crutch required for walking
  - Stage IV – Two sticks or 2 crutches needed
  - Stage V – Wheelchair required or subject confined to bed
- Global longitudinal strain by echocardiogram (ECHO)

In CS3, these are assessed as secondary endpoints. The efficacy endpoints in CS3 included changes from CS2 Baseline and CS3 Baseline at Week 78, Week 156, and at the end of each subsequent treatment year.

Pharmacodynamic endpoints in this study are as follows:

- Transthyretin
- Retinol binding protein 4 (RBP4 level)
- Proportion of subjects with at least 60% reduction in TTR

Exploratory endpoints include the following:

- Transthoracic ECHO
- N-terminal prohormone of brain natriuretic peptide
- SF-36 questionnaire

## Population

Completion of CS2 with the following as judged by the investigator and Sponsor:

- Satisfactory completion of dosing and End of Treatment (EOT) efficacy assessments
- No significant tolerability issues
- Satisfactory compliance to the CS2 protocol requirements
- Under special circumstances, subjects who participated in CS2 but did not complete the full treatment period may have been allowed to participate in CS3 with approval from the Sponsor
- Willingness to take vitamin A supplements

## Statistical Analysis Plan

For this study, an interim analysis (when all subjects in CS2 have completed EOT assessments) was performed for the study report at NDA submission and a final analysis at end of study (EOS) are planned. The interim analysis data are summarized only and do not include the primary statistical analysis; the MMRM analyses will be completed at the end of the study. According to

the statistical analysis plan, all endpoints were to be evaluated in an exploratory manner, including the endpoints where p-values or CI are to be presented.

Definitions for the 3 baselines used for the interim analyses are provided below:

- **Parent study baseline** – CS2 Baseline, which is defined for most endpoints, unless otherwise specified in the SAP, as the last non-missing value prior to the Day 1 of treatment, inotersen or placebo, in CS2.
- **OLE study baseline** – the last non-missing assessment prior to the first dose of inotersen in the CS3 (CS3 Study Day 1). However, the last assessment must have been collected within 3 months (90 days) before CS3 Study Day 1 of CS3 to be used to derive the baseline; i.e., if there is no assessment within 3 months, the OLE study baseline will be missing. Depending on when the assessments are scheduled to be collected, this may be derived from the CS3 Study Day 1 or the CS3 screening visit or the last non-missing assessment from CS2.
- **Inotersen baseline** will be the parent study baseline for subjects randomized to inotersen in CS2 and will be the OLE study baseline for subjects randomized to placebo in CS2.

Definitions for the Analysis Populations used for the interim analyses are provided below:

- The **Full Analysis Set (FAS)** included all enrolled subjects who received at least 1 injection of inotersen in CS3 and who had at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QoL-DN questionnaire total score collected after CS3 Study Day 1. The FAS was the primary population for analysis of efficacy and PD outcomes.
- The **Safety Set (SS)** included all enrolled subjects who received at least 1 injection of inotersen in CS3. The SS population was used for analyses of all safety measures collected in this study. Results were summarized according to the actual treatment that the subject received in CS2.
- The **Longitudinal Safety Set (LSS)** included all subjects who received at least 1 injection of inotersen in CS2. The LSS population was used for longitudinal summaries across CS2 and CS3. Note that this population included subjects who received inotersen in CS2 but did not enter CS3.
- The **PK Set** included all enrolled subjects who received at least 1 dose of inotersen in CS3 and who had at least 1 evaluable PK sample collected and analyzed with reportable result in CS3. This population was used for all PK analyses. Results were summarized under the treatment that the subjects received in CS2.
- The **ECHO subgroup** in CS3 included the ECHO subgroup subjects who enrolled in CS3. Results were summarized under the treatment to which subjects were randomized in CS2.
- The **CM-ECHO** set in CS3 included the CM-ECHO set subjects from CS2 who enrolled in CS3. Results were summarized under the treatment to which subjects were randomized in CS2.

All efficacy and PD endpoints (except ECHO parameters) were assessed for the FAS population. All safety assessments for CS3 were performed on the SS population. All longitudinal summaries were performed on the LSS population. PK endpoints were assessed in the PK Set as applicable. ECHO endpoints, including GLS, were assessed for all enrolled subjects, the ECHO subgroups, and the CM-ECHO set.

Changes from CS2 and CS3 Baselines to Week 78 and Week 156 were summarized by CS2 treatment group for the following efficacy measures: mNIS+7 score; Norfolk QoL-DN (total score, symptoms domain score for Stage 1 subjects, and physical functioning/large fiber neuropathy domain score for Stage 2 subjects); mBMI and BMI; NIS; GLS and PND score. For subjects participating in Year 4 and Year 5, mNIS+7, Norfolk QoL-DN, and PND are summarized at Year 4 Week 52 and Year 5 Week 52. For the interim analysis, only visits with data available at the time of the data analysis will be summarized.

A responder analysis based on the change in mNIS+7 score was conducted to examine whether improvement in response was consistent over a range of response thresholds using the FAS population. A responder at a visit was defined as an evaluable subject whose mNIS+7 score change from either the CS2 Baseline or the CS3 Baseline to the respective post-baseline visit in CS3 was less than or equal to several threshold values. For a subject to be evaluable at a visit he/she needed to be in the enrolled in the study long enough to have completed the assessment (e.g., a subject that was in the study for 52 weeks would not be evaluable for the Week 78 visit). Subjects were considered non-responders if they terminated treatment early, irrespective of the reason or had missed the respective post-baseline visit.

### Protocol Amendments

- Amendment 3 – Allowed use of Tafamidis after 18 months at discretion of Study Medical Monitor.
- From the CS3 CSR, p 49/4757, **Section 9.8.5. Changes in Conduct of the Study or Planned Analyses**, the time to event (e.g., platelets  $<140 \times 10^9/L$ ) was derived relative to the first dose date in CS3 for both treatment groups, rather than using the Day 1 of inotersen.

### 6.2.2. Study Results

### Financial Disclosure

See [Financial Disclosure](#) description for CS2

### Patient Disposition

At the time of data cut-off for the interim analysis of CS3 (28 February 2017), a total of 114 subjects had enrolled into CS3; 40 subjects had received placebo, and 74 subjects had received inotersen in CS2. A total of 135 subjects entered CS3 as of 18 April 2017, which includes 21 subjects who completed treatment in CS2 and enrolled in CS3 after the data cut-off for the interim analysis of CS3 (Table 20).

Table 20 Subject Disposition as of February 28<sup>th</sup>, 2017

Number of subjects	Placebo-Inotersen (N=40)	Inotersen-Inotersen (N=74)	Total (N=114)
Enrolled in CS3	40	74	114
In the Safety Set (SS)	40 (100.0)	74 (100.0)	114 (100.0)
In the Full Analysis Set (FAS)	31 (77.5)	55 (74.3)	86 (75.4)
In the PK Set	36 (90.0)	73 (98.6)	109 (95.6)
In the ECHO Subgroup	16 (40.0)	33 (44.6)	49 (43.0)
In the CM-ECHO Set	27 (67.5)	52 (70.3)	79 (69.3)

Source: Table 1.03

None of the subjects had completed study treatment, and a total of 95 subjects were still ongoing at the time of the CS3 study report. Nineteen (16.7%) subjects had discontinued treatment early.

The primary reasons for discontinuation were due to an AE or serious adverse event (SAE), investigator judgment, or voluntary withdrawal (Table 21).

In CS3, 75.4% of subjects were included in the FAS, and the proportion of subjects was similar between the 2 groups.

Table 21 Reasons for Discontinuation in CS3

	Placebo-Inotersen (N=40)	Inotersen-Inotersen (N=74)	Total (N=114)
<b>Treatment completion status, n (%)</b>			
Completed <sup>a</sup>	0	0	0
Discontinued	8 (20.0)	11 (14.9)	19 (16.7)
<b>Primary reason for early treatment discontinuation, n (%)</b>			
Adverse event or SAE	1 (2.5)	5 (6.8)	6 (5.3)
Had been stopped per stopping rules	0	0	0
Investigator judgment	3 (7.5)	1 (1.4)	4 (3.5)
Voluntary withdrawal	2 (5.0)	4 (5.4)	6 (5.3)
Pregnancy	0	0	0
Ineligibility	0	0	0
Significant protocol deviation	0	0	0
Liver transplant	0	0	0
Disease progression	1 (2.5)	0	1 (0.9)
Other	1 (2.5)	1 (1.4)	2 (1.8)
<b>Ongoing, n (%)</b>	<b>32 (80.0)</b>	<b>63 (85.1)</b>	<b>95 (83.3)</b>

Source: Table 1.01

a. Number of subjects who completed the last scheduled visit in treatment period, even if individual visits were not done or doses were not taken.

Abbreviation: SAE = serious adverse event.

## Protocol Violations/Deviations

Protocol violation types were balanced (~5%) between prior treatment arms and generally not affecting the ability of this Medical Officer to interpret the outcomes of the study.

### Table of Demographic Characteristics

Demographics were generally balanced by percent of prior (CS2) treatment group except for the following characteristics (Table 22).

Table 22 Demographic patterns with imbalance  $\geq 5\%$  between CS2 Treatment Arms at the Start of CS3

Characteristic	CS2 Arm – PBO N = 40	CS2 Arm – Inotersen N = 74
Race - Asian	3 (7.5)	0
Prior Tafamidis or Diflunisol +	23 (57.5)	49 (66.2)
V30M TTR Mutation +	21 (52.5)	29 (39.2)
SER77TYR Mutation +	4 (10)	3 (4.1)
mNIS+7 baseline @ CS3 start	99.92 (47.11)	87.55 (39.49)
Duration of disease from hATTR-PN diagnosis to CS3 start (months)	53.8 (41.8)	58.6 (53.99)
Duration from onset of hATTR-PN symptoms to CS3 study entry (months)	83.7 (60.4)	80.8 (50.27)
Duration from onset of hATTR-CM symptoms to CS3 study entry (months)	53,7 (31.4)	59.7 (65.02)

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

As of the date for the interim analysis, 114 subjects had received at least 1 dose of inotersen in CS3. The median number of doses received overall for subjects was 54.0 doses, 39.5 in the placebo-inotersen group and 57.0 in the inotersen-inotersen group. The median duration of study drug exposure from CS3 Baseline was approximately 310 days in the placebo-inotersen group and 432 days in the inotersen-inotersen group (approximately 14 months (Table 23).

Table 23 Exposure to Study Drug in Study CS3

	Placebo-Inotersen (N=40)	Inotersen-Inotersen (N=74)	Total (N=114)
<b>Total number of doses received<sup>2</sup>, n (%)</b>			
<5	2 (5.0)	8 (10.8)	10 (8.8)
5-10	5 (12.5)	4 (5.4)	9 (7.9)
11-20	4 (10.0)	4 (5.4)	8 (7.0)
21-40	9 (22.5)	12 (16.2)	21 (18.4)
41-60	4 (10.0)	12 (16.2)	16 (14.0)
61-80	8 (20.0)	15 (20.3)	23 (20.2)
81-100	5 (12.5)	10 (13.5)	15 (13.2)
101-120	3 (7.5)	6 (8.1)	9 (7.9)
121-140	0	3 (4.1)	3 (2.6)
Mean (SD)	47.1 (32.57)	56.0 (36.40)	52.9 (35.22)
Median (P25, P75)	39.5 (17.0, 68.5)	57.0 (25.0, 84.0)	54.0 (25.0, 79.0)
Min, Max	3, 117	1, 140	1, 140
<b>Total dose of inotersen (mg)</b>			
Mean (SD)	13988.0 (9705.78)	16212.7 (10789.04)	15432.1 (10433.03)
Median (P25, P75)	11850.0 (5100.0, 20100.0)	16500.0 (7500.0, 23700.0)	15900.0 (6600.0, 23400.0)
Min, Max	900, 35020	300, 42000	300, 42000
<b>Duration of study drug exposure (days)<sup>3</sup></b>			
Mean (SD)	351.5 (243.29)	414.8 (272.66)	392.6 (263.39)
Median (P25, P75)	310.0 (151.5, 548.0)	432.0 (169.0, 614.0)	386.0 (169.0, 594.0)
Min, Max	15, 825	1, 974	1, 974
<b>Dosing was paused, n (%)</b>			
No	18 (45.0)	36 (48.6%)	54 (47.4%)
Yes	22 (55.0)	38 (51.4%)	60 (52.6%)
Reason of dose pause			
Hold due to platelet monitoring rule (<75 x 10 <sup>9</sup> /L)	3 (7.5)	7 (9.5%)	10 (8.8%)
Procedural hold due to Safety Notification Letter on 19-Feb-2016	2 (5.0)	6 (8.1%)	8 (7.0%)
Hold due to missing platelet values	3 (7.5)	18 (24.3%)	21 (18.4%)
Hold due to Investigator/Medical Monitor discretion - related to platelets	6 (15.0)	11 (14.9%)	17 (14.9%)
Hold due to Investigator/Medical Monitor discretion - related to renal	1 (2.5)	1 (1.4%)	2 (1.8%)
Hold due to AE (non-renal and non-platelet)	7 (17.5)	3 (4.1%)	10 (8.8%)
Missed dose	8 (20.0)	13 (17.6%)	21 (18.4%)

Source: Table 1.06

### Efficacy Results – Primary Endpoint

Throughout CS3, the mean mNIS+7 changes from CS2 Baseline were more favorable in the group initially on inotersen (Table 24). The degree of change as a function of total time on drug time seems comparable between the groups originally on active in CS2 and those converting to active treatment from placebo in CS3. For example, the CS2 Week 66 change from CS2 baseline for the Inotersen-Inotersen group was 3.58 (14.98) versus the CS3 Week 52 change from the CS3 baseline for the Placebo-Inotersen group that was 3.91 (18.103).

Table 24 mNIS+7 Score in the CS2 and CS3 studies by CS2 Randomized Arm

Time point	N Placebo / Inotersen	Mean (SD), if a baseline score, or Mean Change from CS2 baseline (SD)	
		Pbo→Inotersen	Inotersen→Inotersen
<b>CS2 baseline</b>	31 / 55	<b>77.17 (37.58)</b>	<b>76.82 (35.45)</b>
CS2 Week 66	31 / 55	24.15 (25.19)	3.58 (14.98)
CS3 Week 26	29 / 53	30.07 (27.32)	4.28 (18.03)
CS3 Week 52	19 / 44	32.73 (28.105)	9.67 (17.17)
CS3 Week 78	11 / 28	37.43 (37.6)	12.29 (19.91)
		Mean (SD), if a baseline score, or Mean Change from CS3 baseline (SD)	
<b>CS3 baseline</b>	<b>31 / 54</b>	<b>100.79 (50.34)</b>	<b>81.13 (38.9)</b>
CS3 Week 26	29 / 53	6.04 (12.42)	-0.22 (13.74)
CS3 Week 52	19 / 44	3.91 (18.103)	4.58 (11.98)
CS3 Week 78	11 / 28	9.59 (21.66)	7.13 (16.19)

### Norfolk Quality of Life – Diabetic Neuropathy Questionnaire

Changes in the Norfolk QoL-DN total score observed in the Inotersen - inotersen group suggest that the rate of disease worsening is maintained at less than the rate observed in the placebo arm in the CS2 trial, which relates to the durability of effect (Table 25). The improvement in the Placebo-Inotersen arm in CS3 is like that seen in the Inotersen-Inotersen Arm in CS2 (e.g., -3.47 (15.10) for the former and 0.39 (16.13) for the latter).

Table 25 Norfolk QoL-DN Score in the CS2 and CS3 studies by CS2 Randomized Arm

Time point	N Placebo / Inotersen	Mean (SD), if a baseline score, or Mean Change from CS2 baseline (SD)	
		Pbo-Inotersen	Inotersen-Inotersen
<b>CS2 baseline</b>	31 / 54	<b>49.06 (29.07)</b>	<b>46.02 (27.47)</b>
CS2 Week 66	31 / 54	9.64 (23.29)	0.39 (16.13)
CS3 Week 26	29 / 53	12.38 (21.83)	2.60 (22.73)
CS3 Week 52	19 / 44	10.91 (26.77)	5.38 (17.78)
CS3 Week 78	11 / 28	16.57 (35.96)	8.48 (18.66)
		Mean (SD), if a baseline score, or Mean Change from CS3 baseline (SD)	
<b>CS3 baseline</b>	31 / 53	<b>60.41 (32.58)</b>	<b>46.64 (27.86)</b>
CS3 Week 26	29 / 53	0.98 (17.21)	0.91(12.73)
CS3 Week 52	19 / 44	-3.47 (15.10)	4.40 (14.46)
CS3 Week 78	11 / 28	0.45 (9.32)	3.83 (15.33)

### Efficacy Results – Secondary and other relevant endpoints

#### Norfolk QoL-DN Physical Functioning/Large Fiber Neuropathy Domain Score

Both groups showed less progression in CS3 at Week 78 (mean change of 3.67 points in the inotersen-inotersen group and mean change of 0.25 points in the placebo-inotersen group) compared with the 10.91 points of mean change observed in the placebo-inotersen group over 66 weeks in CS2, suggesting for the inotersen-inotersen group, a durability of effect.

Table 26 On-Treatment Norfolk QoL-DN Physical Functioning/Large Fiber Neuropathy Domain Score (Stage 2 Subjects in Full Analysis Set - Subjects with Stage 2 Disease at CS2 Baseline)

Time point	N Placebo / Inotersen	Mean, if baseline, or Mean Change from CS2 baseline	
		Pbo-Inotersen	Inotersen-Inotersen
<b>CS2 baseline</b>	11 / 17	<b>28.82 (10.37)</b>	<b>25.53 (17.10)</b>
CS2 Week 66	11 / 17	10.91 (9.25)	0.59 (9.10)
<b>CS3 baseline</b>	11 / 16	<b>39.73 (11.41)</b>	<b>26.69 (16.39)</b>
CS3 Week 26	10 / 17	7.8 (9.18)	5.35 (16.50)
CS3 Week 52	7 / 14	9.43 (11.53)	1.86 (9.39)
CS3 Week 78	4 / 9	16.25 (13.67)	2.33 (13.74)
		Mean, if baseline, or Mean Change from CS3 baseline	
<b>CS3 baseline</b>	11 / 16	<b>39.73 (11.41)</b>	<b>26.69 (16.39)</b>
CS3 Week 26	10 / 16	-3.60 (13.29)	2.75 (8.04)
CS3 Week 52	7 / 14	-3.14 (6.59)	3.00 (7.60)
CS3 Week 78	4 / 9	0.25 (0.96)	3.67 (10.92)

### Neuropathy Impairment Score

The rate of change (worsening) in the patients switching from placebo to inotersen at weeks 52 (Change post-CS3 baseline = 8.22) and 78 (Change post-CS3 baseline = 10.68) is less than the change from CS2 baseline while on placebo at Week 66 (Change = 19.29).

Table 27 Change in the Neuropathy Impairment Score in the CS2 and CS3 studies

	Placebo-Inotersen (N=31)	Inotersen-Inotersen (N=55)
<b>Absolute value</b>		
CS2 Baseline		
n	31	55
Mean (SD)	44.40 (23.054)	44.44 (24.325)
Median (P25, P75)	42.50 (23.50, 65.50)	41.63 (25.00, 56.25)
Min, Max	3.5, 84.0	10.5, 106.3
CS3 Baseline		
n	31	54
Mean (SD)	63.83 (34.663)	50.22 (28.757)
Median (P25, P75)	65.63 (28.00, 100.25)	44.56 (27.50, 68.00)
Min, Max	9.5, 112.4	1.5, 124.8
<b>Change from CS2 Baseline</b>		
CS2 Week 66		
n	31	55
Mean (SD)	19.29 (16.547)	4.85 (10.628)
Median (P25, P75)	18.63 (5.50, 32.50)	4.13 (-0.50, 9.88)
Min, Max	-10.5, 55.0	-17.8, 36.6
CS3 Week 26		
n	29	54
Mean (SD)	25.91 (21.530)	5.60 (12.980)
Median (P25, P75)	24.00 (8.50, 34.50)	4.00 (-3.00, 13.00)
Min, Max	-7.5, 80.8	-26.0, 43.5
CS3 Week 52		
n	19	44
Mean (SD)	30.09 (22.082)	9.86 (13.578)
Median (P25, P75)	26.50 (18.00, 43.25)	7.25 (0.50, 17.50)
Min, Max	-6.0, 83.8	-12.0, 46.8
CS3 Week 78		
n	11	29
Mean (SD)	35.22 (29.703)	11.72 (15.662)
Median (P25, P75)	30.50 (10.25, 56.25)	7.50 (1.50, 21.13)
Min, Max	-7.0, 84.0	-22.5, 48.1
<b>Change from CS3 Baseline</b>		
CS3 Week 26		
n	29	54
Mean (SD)	6.74 (11.698)	0.30 (10.656)
Median (P25, P75)	6.13 (0.50, 11.50)	-0.06 (-3.50, 8.13)
Min, Max	-28.0, 42.8	-41.1, 22.5
CS3 Week 52		
n	19	44
Mean (SD)	8.22 (14.378)	2.96 (9.314)
Median (P25, P75)	6.00 (0.50, 21.50)	1.75 (-2.75, 7.19)
Min, Max	-22.3, 34.8	-19.3, 27.5
	Placebo-Inotersen (N=31)	Inotersen-Inotersen (N=55)
CS3 Week 78		
n	11	29
Mean (SD)	10.68 (18.761)	4.44 (12.578)
Median (P25, P75)	6.25 (-4.00, 27.00)	3.75 (-3.00, 13.00)
Min, Max	-11.5, 46.0	-20.5, 39.8

Source: Table 2.07

### Changes in the Global longitudinal strain (GLS) by echocardiogram (ECHO) in the ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set from Baseline to Week 65

The mean GLS values were abnormal at CS2 Baseline as well as at CS3 Baseline in both groups in the CM-ECHO Set as compared with the established ranges. Changes in GLS observed in both

CS2-randomization groups were small and variable and so no apparent treatment effect is discernable.

Differences were also not apparent between the inotersen-inotersen group and the placebo-inotersen group for left ventricular mass in the enrolled patients, ECHO subgroup, and CM-ECHO Set.

Assessment by the Division of Cardiovascular and Renal Products is found in Section [GLS CS2 Secondary Analysis](#).

### Pharmacodynamic endpoint - TTR Levels

TTR levels were nearly identical between the placebo and inotersen arms at baseline in the CS2 study (Table 28). Inotersen treatment in the CS2 study resulted in a 72% reduction from baseline to Week 65. The reduction is rapid with a 73% reduction being demonstrated by Week 13 of CS2. In that same 65-Week time frame, the levels in the placebo arm remained constant (-5.03% ± 20.1%). Switching from placebo to inotersen in the CS3 study resulted in a significant TTR reduction through the 78-week assessment period (Figure 11 and Table 28). There was a slight increase in the levels on the inotersen-inotersen arm in the later part of the extension study, though the absolute levels were still less than the CS2 baseline.

Figure 11 Comparison of the TTR Levels in the CS2 and 3 Trials by Treatment

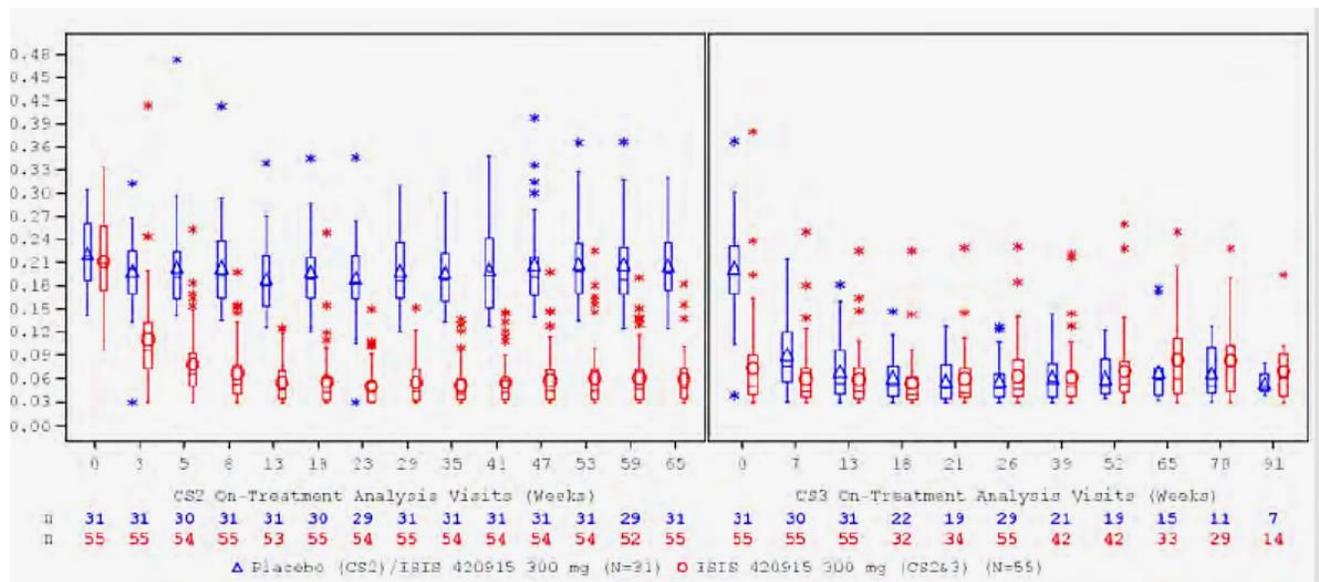


Table 28 On-Treatment Transthyretin (TTR) Level (Full Analysis Set)

	Placebo-Inotersen (N=31)	Inotersen-Inotersen (N=55)
<b>Absolute value</b>		
CS2 Baseline		
n	31	55
Mean (SD)	0.2215 (0.04456)	0.2126 (0.05309)
CS3 Baseline		
n	31	55
Mean (SD)	0.2029 (0.06360)	0.0739 (0.06060)
<b>Percent change from CS2 Baseline</b>		
CS2 Week 13		
n	31	53
Mean (SD)	-12.85 (20.325)	-73.40 (13.954)
CS2 Week 65		
n	31	55
Mean (SD)	-5.03 (20.096)	-71.63 (14.955)
<b>Percent change from CS3 Baseline</b>		
CS3 Week 13		
n	31	55
Mean (SD)	-57.65 (51.855)	-9.12 (29.285)
CS3 Week 26		
n	29	55
Mean (SD)	-66.10 (32.310)	-0.22 (45.535)
CS3 Week 52		
n	19	42
Mean (SD)	-61.28 (38.280)	9.96 (47.436)
CS3 Week 65		
n	15	33
Mean (SD)	-40.98 (109.718)	34.91 (91.225)
CS3 Week 78		
n	11	29
Mean (SD)	-40.26 (75.740)	43.41 (96.111)

### Dose/Dose Response

Only one clinical dose was tested in this study.

### Durability of Response

There is a slight reduction in the durability of effect as evidenced by the circulating TTR levels and mNIS+ & Norfolk QoL-DM scores at the end of CS3 in the inotersen-inotersen arm (Weeks 118-144 of treatment in this arm). Considering the small size of these changes natural; history of the disease, this is not expected to be clinically meaningful.

### Persistence of Effect

Persistence of effect was not formally studied in this development program.

## **Additional Analyses Conducted on the Individual Trial**

### **6.3. Abbreviated Description of Clinical Study Report 420915-CS1: A Double Blind, Placebo-Controlled, Dose-Escalation, Phase 1 Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Doses of ISIS 420915 Administered Subcutaneously to Healthy Volunteers (ISIS Study Number**

#### **6.3.1. Study Design**

A double-blinded, placebo-controlled, dose-escalation study conducted at a single center. 4 single-dose (randomized to 3 active:1 placebo) and 5 multiple-dose (randomized to 8 active:2 placebo) treatment cohorts. Subjects in the single-dose treatment cohorts received a single SC dose of study drug on Day 1: Cohort A (50 mg), Cohort B (100 mg), Cohort C (200 mg), and Cohort D (400 mg). Subjects in the multiple-dose treatment cohorts received 3 SC doses of study drug on alternate days (Days 1, 3, and 5) during Week 1 followed by once weekly SC administration during Weeks 2 to 4 (Days 8, 15, and 22) for a total of 6 doses: Cohort AA (50 mg), Cohort BB (100 mg), Cohort CC (200 mg), Cohort DD (400 mg), and Cohort EE (300 mg).

Subjects in the single-dose treatment cohorts had an overnight stay in the study center on Day 1 and had post-treatment evaluations until Day 30 (visits at Days 4, 8, and 30). Subjects in the multiple-dose treatment cohorts had an overnight stay in the study center on Day 1 and Day 22 and had a 10-week post-treatment evaluation period (visits at Weeks 5, 6, 7, 8, 10, 12, and 14).

## **Overview and Objective**

### **Population**

This study randomized healthy, normal subjects. 65 subjects were randomized and analyzed: 16 subjects in the single-dose treatment cohorts and 49 subjects in the multiple-dose treatment cohorts.

### **Treatment Regimen**

A solution of ISIS 420915 (200 mg/mL) was provided by the Sponsor; 50, 100, 200, or 400 mg SC either as a single dose or as multiple doses (6 doses) and 300 mg as multiple doses (6 doses). One product lot number was used: CP420915-001. The placebo, 0.9% sterile saline, was provided by the study center.

Single-Dose Treatment Cohorts: included a 28-day Screening Period, a 1-day treatment period, and a 29-day post-treatment evaluation period.

Multiple-Dose Treatment Cohorts: included a 28-day Screening Period, a 4-week treatment period, and a 10-week post-treatment evaluation period.

### **Study Endpoints**

Combined Clinical/Biostatistical Review  
Clinical Reviewer – Breder; Statistical Reviewer – Massie  
NDA 211172 Tegsedi (inotersen)

Pharmacokinetics: The plasma PK of ISIS 420915 was assessed following single- and multiple-dose administration. The amount of ISIS 420915 and total oligonucleotide excreted in urine at the selected 24-hour intervals was determined.

Pharmacodynamics: The pharmacodynamics (PD) of ISIS 420915 was assessed by comparing the change and percent change from baseline in transthyretin (TTR) level, the change and percent change from baseline in retinol binding protein 4 (RBP4) level, and the change and percent change from baseline in retinol level following single- and multiple-dose administration.

Safety: Safety assessments included adverse events (AEs), clinical laboratory evaluations, vital sign measurements, physical examinations, and electrocardiograms (ECGs).

### 6.3.2. Study Results

#### **Disposition**

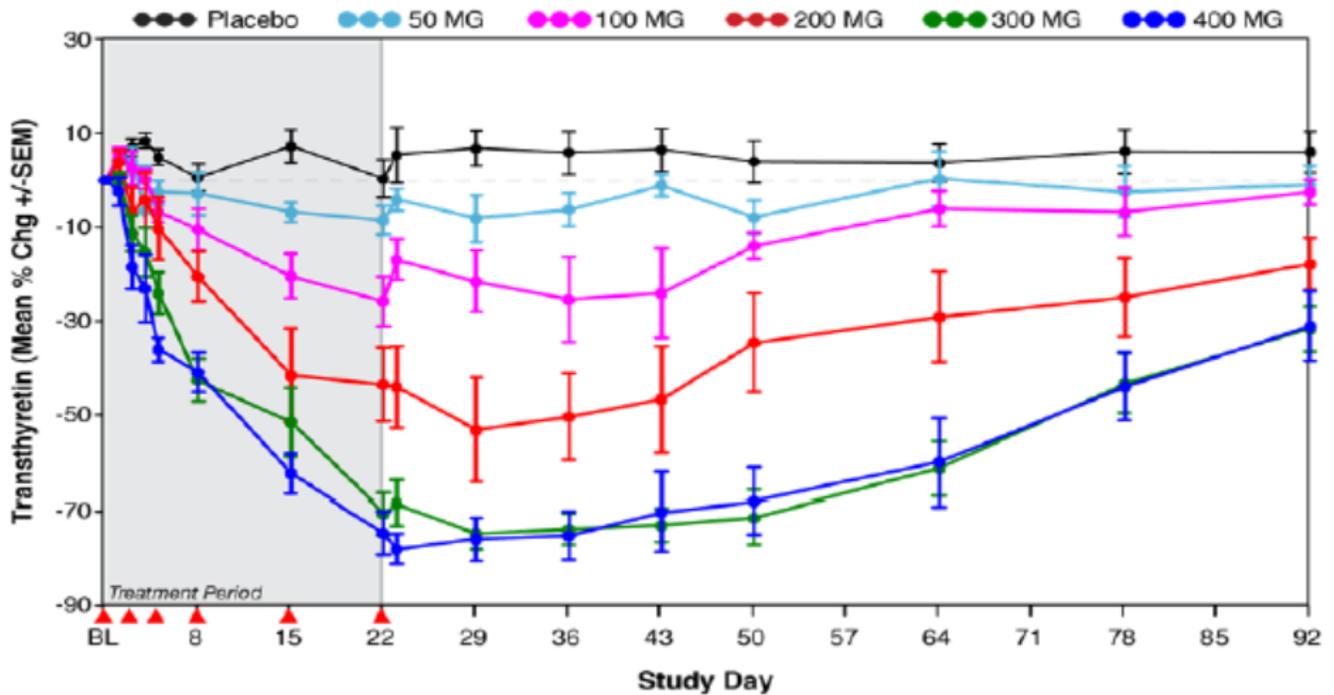
In the single-dose treatment cohorts, all subjects completed study treatment. One subject in the placebo treatment cohort did not complete follow-up.

In the multiple-dose treatment cohorts, 3 subjects receiving ISIS 420915 did not complete study treatment:

1 subject (200 mg) withdrew from study treatment due to an AE, and 2 subjects (300 and 400 mg) voluntarily withdrew from study treatment but the withdrawals were judged by the Sponsor to be associated with AEs. Two subjects receiving placebo and 3 subjects receiving ISIS 420915 did not complete the follow-up period.

#### **Efficacy Results – Primary Endpoint**

Figure 12 Mean TTR Reduction by Dose in Study CS1



Source: Ackermann, 2016

Abbreviations: BL=baseline; Chg=change; SEM=standard error of the mean

Source: Clinical Overview figure 1, p. 23/89

Preliminary PK/PD modeling, based on data from CS1 and extrapolation to steady-state, predicted mean total TTR (wild-type and mutant) steady-state reductions of ~80% with either a 300 mg/week or 400 mg/week regimen (Figure 12).

## 7. Review of Safety

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See the Clinical review of Dr. Evelyn Mentari.

## 8. Advisory Committee Meeting and Other External Consultations

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An advisory committee was not deemed necessary by the Division to evaluate the body of substantial evidence in this application.

## 9. Labeling Recommendations

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Combined Clinical/Biostatistical Review  
Clinical Reviewer – Breder; Statistical Reviewer – Massie  
NDA 211172 Tegsedı (inotersen)

### **9.1. Prescription Drug Labeling**

Specific recommendations have been suggested for the prescribing information (PI) in sections 1 and 14, with corresponding changes to Highlights and related PI section references.

## **10. Risk Evaluation and Mitigation Strategies (REMS)**

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A REMS has been proposed for the issues of thrombocytopenia and glomerulonephritis. This is discussed in the Clinical-Safety and Office of Surveillance and Epidemiology – Division of Risk Management (OSE-DRISK) reviews.

## **11. Postmarketing Requirements and Commitments**

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Postmarketing studies are not recommended from a Clinical-Efficacy perspective.

## 12. Appendices

### 12.1. Financial Disclosure

**Covered Clinical Study (Name and/or Number):**  
**ISIS 420915-CS2**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>237 (PIs and Subs)</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

### 13. References

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/s/  
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CHRISTOPHER D BREDER  
10/04/2018

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I concur with the statistical review.

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Clinical Safety Review  
 Evelyn Mentari, M.D., M.S.  
 NDA 211172 Tegsedi (inotersen)

### CLINICAL REVIEW

<b>Application Type</b>	NDA
<b>Application Number(s)</b>	211172
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	November 6, 2017
<b>Received Date(s)</b>	November 6, 2017
<b>PDUFA Goal Date</b>	October 6, 2018
<b>Division/Office</b>	Division of Neurology Products / Office of New Drugs
<b>Reviewer Name(s)</b>	Evelyn Mentari, M.D., M.S.
<b>Review Completion Date</b>	October 4, 2018
<b>Established/Proper Name</b>	Inotersen
<b>(Proposed) Trade Name</b>	Tegsedi
<b>Applicant</b>	Ionis Pharmaceuticals
<b>Dosage Form(s)</b>	284 mg inotersen (300 mg sodium salt)/1.5 mL single-dose prefilled syringe
<b>Approved Dosing Regimen</b>	Subcutaneously administer one dose per week
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults.
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Adult patients with hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN)

CDER Clinical Review Template Version date: September 6, 2017

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## Glossary

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2'-MOE	2'-O-(2-methoxyethyl)
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANCA	antineutrophil cytoplasmic autoantibody
ASO	antisense oligonucleotide
ATTR	transthyretin amyloidosis
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula
C <sub>max</sub>	maximum serum concentration
CNS	central nervous system
CRP	c-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
ECG	electrocardiogram
EDTA	ethylenediaminetetra-acetic acid
FAP	familial amyloid polyneuropathy
FDA	Food and Drug Administration
hATTR	hereditary transthyretin amyloidosis
hATTR-PN	hereditary transthyretin amyloidosis with polyneuropathy
hATTR-CM	hereditary transthyretin amyloidosis with cardiomyopathy
hs-CRP	high-sensitivity c-reactive protein
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IM	immunogenicity
IND	Investigational New Drug Application
INO	inotersen
ISIS 420915	inotersen
ISS	integrated summary of safety
IXRS	interactive voice/web response system
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

mRNA	messenger ribonucleic acid
mNIS+7	Modified Neuropathy Impairment Score +7
NDA	new drug application
NR	normal range
OSI	Office of Scientific Investigations
PBO	placebo
PD	pharmacodynamics
PK	pharmacokinetics
PMR	postmarketing requirement
PT	MedDRA Preferred Term
QRSd	QRS interval duration
REMS	Risk Evaluation and Mitigation Strategy
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SCS	summary of clinical safety
SNL	safety notification letter
SOC	MedDRA system organ class
TEAE	treatment-emergent adverse event
TTR	transthyretin
ULN	Upper limit of normal

## 1. Executive Summary

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### 1.1. Product Introduction

Inotersen is a 2'-O-(2-methoxyethyl) [2'-MOE] antisense oligonucleotide (ASO) drug that targets human TTR messenger ribonucleic acid (mRNA). Hybridization to the cognate TTR mRNA results in the RNase H1-mediated degradation of the TTR mRNA preventing production of the TTR protein. The proposed proprietary name is Tegsedi. If approved, the indication is the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

The Sponsor's proposes [REDACTED] (b) (4)  
[REDACTED] doses of 300 mg once weekly. The route of administration is subcutaneous injection.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The reader is referred to Dr. Christopher Breder's review of clinical efficacy.

### 1.3. Benefit-Risk Assessment

This document reviews the risk profile of inotersen, and a risk assessment is provided below. Please refer to Dr. Christopher Breder' review for a discussion of the benefit of inotersen.

### Risk Assessment

Inotersen is proposed to be used for the treatment of hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN). This review evaluated the safety of inotersen. If efficacy is demonstrated and the benefits of inotersen outweigh the risks, then we recommend approval with 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. Please refer to Dr. Christopher Breder' review for discussion of Analysis of Condition and Current Treatment Options and benefit.

#### Risk:

Inotersen is associated with severe, potentially fatal adverse effects.

- Platelet counts less than  $100 \times 10^9/L$  occurred in 25% of inotersen patients, compared with 2% of placebo patients. Platelet counts less than  $75 \times 10^9/L$  occurred in 14% of inotersen patients, compared to 0 placebo patients. Three inotersen patients (3%) had sudden, severe thrombocytopenia (less than  $25 \times 10^9/L$ ), 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.
- 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 and stroke within 2 days of the first inotersen 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 inotersen.

Clinical Safety Review

Evelyn Mentari, M.D., M.S.

NDA 211172 Tegsedi (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 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 patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN), compared to 3% of placebo patients; 3% of inotersen patients had an ALT at least 8 times the 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.

I recommend a post-marketing requirement to further characterize the risks of thrombocytopenia, glomerulonephritis, and neurologic toxicity [e.g., central nervous system (CNS) arterial dissection, stroke, CNS vasculitis] using the Risk Evaluation and Mitigation Strategies (REMS) program registry data. I recommend a boxed warning with recommendations for monitoring and administration to mitigate the risks of thrombocytopenia and glomerulonephritis. In the Warnings and Precautions section of the label, I recommend 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 ethylenediaminetetraacetic acid (EDTA), and (b) (4). I recommend enhanced pharmacovigilance (e.g., 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.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#"><u>Analysis of Condition</u></a>	<ul style="list-style-type: none"> <li>• Please refer to Dr. Breder’s review of clinical efficacy.</li> </ul>	
<a href="#"><u>Current Treatment Options</u></a>	<ul style="list-style-type: none"> <li>• Please refer to Dr. Breder’s review of clinical efficacy.</li> </ul>	
<a href="#"><u>Benefit</u></a>	<ul style="list-style-type: none"> <li>• Please refer to Dr. Breder’s review of clinical efficacy.</li> </ul>	
<a href="#"><u>Risk and Risk Management</u></a>	<ul style="list-style-type: none"> <li>• The safety database for inotersen includes all patients from the Phase 3 placebo-controlled study and the open-label extension study in patients with hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN). Drug exposure is adequate for NDA submission, 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.</li> <li>• In the Phase 3 placebo-controlled study, the most common adverse reactions were: Injection site reactions (49%); Nausea (31%); Headache (26%); Fatigue (25%); Thrombocytopenia (24%); Fever (20%).</li> <li>• Platelet counts less than <math>100 \times 10^9/L</math> occurred in 25% of inotersen patients, compared with 2% of placebo patients. Platelet counts less than <math>75 \times 10^9/L</math> occurred in 14% of inotersen patients, compared to 0 placebo</li> </ul>	<p>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-</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>patients. Three inotersen patients (3%) had sudden, severe thrombocytopenia (less than <math>25 \times 10^9/L</math>), 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.</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• One clinical study patient experienced carotid arterial dissection and stroke 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.</li> </ul>	<p>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.</p> <p>A patient registry as a post-marketing requirement will help to evaluate the main safety risks of inotersen in the post-marketing setting.</p> <p>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.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• 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.</li> <li>• The liver is a site of accumulation of antisense oligonucleotides. In clinical studies, 8% of inotersen patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN), compared to 3% of placebo patients; 3% of inotersen patients had an ALT at least 8 times the ULN, compared to no placebo patients. Periodic measurement of liver tests may mitigate risks to the liver with inotersen.</li> <li>• 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.</li> <li>• 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.</li> </ul>	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Other uncertainties: The optimal treatment for glomerulonephritis after inotersen use is not known.</li> <li>• A Risk Evaluation and Mitigation Strategies (REMS) program registry will help to evaluate the main safety risks of inotersen in the postmarketing setting.</li> <li>• 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.</li> </ul>	

#### 1.4. Patient Experience Data

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

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

Hereditary transthyretin amyloidosis (hATTR) is a systemic disorder characterized by the extracellular deposition of amyloid fibrils composed of transthyretin (TTR), also called prealbumin. TTR is a plasma transport protein for thyroxine and vitamin A that is produced predominantly by the liver. TTR can dissociate from its native tetramer form, misfold, and aggregate into amyloid fibrils that accumulate in various organs and tissues. Hereditary transthyretin amyloidosis is the most common form of hereditary (familial) amyloidosis and is caused by mutations that destabilize the TTR protein. There are considerable variations in phenotype across individuals and geographic locations.<sup>1</sup>

The age at onset of disease-related symptoms varies between the second and ninth decades of life, with great variations across different populations. Average life expectancy is 3 to 15 years after diagnosis. The main clinical manifestation of hATTR with polyneuropathy (hATTR-PN) is degenerative peripheral sensorimotor neuropathy and autonomic neuropathy. Cardiac involvement has been estimated to occur in 80% of cases with resultant diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure.<sup>2</sup> Amyloid renal deposits are common, and clinical nephropathy can occur with varying frequency. Ocular abnormalities may be present in approximately 10% of patients with hATTR-PN, including vitreous opacities, which can lead to gradual vision loss, and secondary glaucoma, the leading cause of irreversible blindness in these patients.

*Reviewer comment: The systemic manifestations of hATTR, which are variable across individuals and geographic locations, complicate the interpretation of several categories of adverse events.*

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<sup>1</sup> Guideline of transthyretin-related hereditary amyloidosis for clinicians. Ando Y, et al. *Orphanet J Rare Dis*. 2013 Feb 20;8:31.

<sup>2</sup> Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. Gertz, MA, et al. *J Am Coll Cardiol*. 2015 Dec 1;66(21):2451-2466.

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## 2.2. Analysis of Current Treatment Options

Currently, there are no FDA-approved treatments for this disease. The current standard of care is 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.

## 3. Regulatory Background

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### 3.1. U.S. Regulatory Actions and Marketing History

Inotersen is a new molecular entity, and it is not currently marketed in the United States.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

<b>Date</b>	<b>Regulatory Activity</b>
March 8, 2012	United States Food and Drug Administration (FDA) Type B Pre-Investigational New Drug Meeting for hATTR
April 19, 2012	Receipt of written European Union Committee for Medicinal Products for Human Use (CHMP) Scientific Advice for hATTR (Procedure Number: EMEA/H/SA/2286/1/2012/III)
July 24, 2012	FDA grants Orphan Drug Designation to inotersen for the treatment of familial amyloid polyneuropathy (FAP)
October 12, 2012	Ionis submitted IND113968 to the FDA Division of Neurology Products, which includes Protocol CS2, as well as Special Protocol Assessment and Fast Track Designation Request
November 9, 2012	FDA allows CS2 (IND-initiating study) to proceed
December 3, 2012	FDA grants Fast-Track Designation to inotersen
February 3, 2013	FDA Type A Meeting to discuss Special Protocol Assessment No Agreement Letter
March 6, 2014	European Commission adopts decision to grant Orphan Drug Designation for inotersen for the treatment of ATTR Amyloidosis
August 7, 2015	EMA grants a Pediatric Investigation Plan product-specific waiver for inotersen in all subsets of the pediatric population
October 18, 2016	FDA grants QTc Waiver for inotersen
April 5, 2017	FDA issues written response to nonclinical and clinical Type C Meeting Request
November 6, 2017	NDA application submitted to FDA
April 23, 2018	Major amendment to the NDA application submitted. User fee goal date extended to October 6, 2018.

### 3.3. **Foreign Regulatory Actions and Marketing History**

There is no foreign marketing experience. A Marketing Authorization Application was submitted to the European Medicines Agency in November 2017.

## 4. **Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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### 4.1. **Office of Scientific Investigations (OSI)**

The reader is referred to the OSI review.

### 4.2. **Product Quality**

The reader is referred to the Office of Product Quality review.

### 4.3. **Clinical Microbiology**

Not applicable.

### 4.4. **Nonclinical Pharmacology/Toxicology**

The reader is referred to the pharmacology/toxicology review.

### 4.5. **Clinical Pharmacology**

Inotersen (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 transthyretin (TTR) by binding in a complementary sequence specific manner, thereby inhibiting the production of TTR protein.

In Study CS1, a Phase 1 pharmacokinetic study in human volunteers, peak plasma levels were observed within a few hours after dosing (median  $T_{max}$  ranging from 1.5 to 4 hours). Mean inotersen plasma concentrations decreased greater than 90% from the  $C_{max}$  by 24 hours after SC injections.<sup>3</sup> The elimination half-life of inotersen is approximately 1 month, and plasma trough levels of inotersen approached approximate steady state within 3 months. The elimination of inotersen is primarily through metabolism in tissues and excretion of the formed

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<sup>3</sup> P. 20-21 Summary of Clinical Pharmacology

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metabolites in urine.<sup>4</sup>

For additional information, the reader is referred to the clinical pharmacology review.

#### **4.6. Devices and Companion Diagnostic Issues**

Not applicable.

#### **4.7. Consumer Study Reviews**

Not applicable.

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<sup>4</sup> P. 21 Clinical Overview

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

The table below summarizes clinical studies supporting safety in NDA 211172.

**Table 1. Listing of clinical studies to support safety in NDA 211172**

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment / Study Status Report Type
CS1	Safety, tolerability, PK	A Phase 1, Double-Blind, Placebo-Controlled, Dose-Escalation Study	Inotersen single doses: 50 mg, 100 mg, 200 mg, 400 mg. multiple doses: 50 mg, 100 mg, 200 mg, 300 mg and 400 mg; 3 times in Week 1 followed by once-weekly Weeks 2-4; SC	Total 65, Single-dose: 12 on inotersen and 4 on placebo, Multiple-dose: 39 on inotersen and 10 on placebo	Healthy Volunteers	1 day for Single-dose cohorts; 21 days for multiple-dose cohorts  Complete; CSR plus 2 CSR Addenda
CS2	Efficacy, safety	A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study	Inotersen 300 mg or placebo; 3 times in Week 1 followed by once weekly Weeks 2–65; SC	172 (112* on inotersen; 60 on placebo)	Patients with hATTR-PN	15 months  Complete to 6-month post-treatment follow-up visit; CSR plus CSR Addendum
CS3	Safety, efficacy	An Open-Label Extension Study	Inotersen 300mg weekly; SC	114 total  40 treated with placebo in CS2; 74 treated with inotersen in CS2.	Patients with hATTR-PN	Up to 3 years  On-going; interim CSR

Source: Tabular listing of clinical studies. Module 5.2. November 6, 2017 submission to NDA 211172. \* In Study CS2, 113 subjects were randomized to inotersen in CS2. One subject in the inotersen group (Subject (b) (6)) was a screening failure and was randomized in error and did not initiate study drug.<sup>5</sup> Thus, 112 subjects were included in the inotersen-treated safety population in Study CS2.

<sup>5</sup> P. 25 Summary of Clinical Safety

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## 5.2. Review Strategy

The clinical review of NDA 211172 is divided into a review of clinical efficacy (by Dr. Christopher Breder) and this review of clinical safety. Dr. Breder also provided safety data assessments for clinical safety sections 8.4.8 (Electrocardiograms) and 8.4.10 (Immunogenicity).

Information submitted as part of NDA 211172, as well as published information related to antisense oligonucleotides as a pharmacologic class and other relevant published literature, are discussed in this review.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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The reader is referred to Dr. Christopher Breder's review of clinical efficacy.

## 7. Integrated Review of Effectiveness

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The reader is referred to Dr. Christopher Breder's review of clinical efficacy.

## 8. Review of Safety

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### 8.1. Safety Review Approach

Three main subject pools were used 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 with continued data from Study CS3

At the time of NDA submission, the inotersen Integrated Set included 152 subjects.<sup>6</sup> In the Safety Update Report<sup>7</sup> the inotersen Integrated Set included 161 subjects (with 9 additional subjects treated with placebo and inotersen in Studies CS2 and CS3, respectively).

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<sup>6</sup> November 6, 2017

<sup>7</sup> March 6, 2018 (Data cut-off September 15, 2017)

For additional details regarding studies in the inotersen clinical development program, please refer to Section 5.1.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

The tables below describe the size and subject duration of exposure for the inotersen safety population.

**Table 2. Inotersen safety population: Size and denominators**

Inotersen Safety Database for treatment of hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)			
Clinical Trial Groups	Inotersen (n= 212)	Active Control (n= 0)	Placebo (n= 74)
Healthy volunteers	Single dose: 12 Multiple dose: 39	0	Single dose: 4 Multiple dose: 10
Controlled trials conducted for hATTR-PN indication	112	0	60
All (other than controlled) trials conducted for hATTR-PN indication	49*	0	0

\* In open label extension study CS3, 40 subjects treated with placebo in Study CS2 were dosed with inotersen at the time of NDA submission (November 6, 2017). In the safety update report, 9 additional Study CS2 placebo subjects were treated with inotersen (March 6, 2018).

**Table 3. Inotersen safety population: Duration of exposure**

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

Source: December 8, 2017 submission to NDA 21172

*Reviewer comment: When compared to International Conference on Harmonisation (ICH)*

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*guidelines,<sup>8</sup> the overall number of exposed subjects is less than the usual recommendation. However, because hATTR is a rare disease, there is no specific minimum number of patients that should be studied to establish clinical safety. The number of subjects exposed  $\geq 1$  year exceeds the ICH recommendation.*

The table below summarizes the doses received, duration of exposure, and frequency of doses pauses in Studies CS2 and CS3.

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<sup>8</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures must occur at the dose or dose range believed to be efficacious. (ICH E-1)

**Table 4. Exposure to study drug**

	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)	Total (N=114)	Inotersen 300 mg (N=112)	Inotersen 300 mg (N=152)
<b>Total number of doses received<sup>a</sup>, n (%)</b>							
Mean (SD)	61.9 (12.45)	55.6 (18.73)	47.1 (32.57)	56.0 (36.40)	52.9 (35.22)	92.6 (51.67)	80.7 (51.39)
Median	67.0	66.0	39.5	57.0	54.0	86.5	68.5
Minimum, Maximum	7, 69	1, 67	3, 117	1, 140	1, 140	1, 207	35.5, 121.5
<b>Total dose of inotersen (mg)</b>							
n	0	112	40	74	114		152
Mean (SD)		16639.0 (5622.55)	13988.0 (9705.78)	16212.7 (10789.04)	15432.1 (10433.03)	27351.0 (15258.37)	23834.4 (15176.61)
Median		19625.0	11850.0	16500.0	15900.0	24600.0	20400.0
Minimum, Maximum		300, 20100	900, 35020	300, 42000	300, 42000	300, 62100	300, 62100
<b>Duration of study drug exposure (days)<sup>b</sup></b>							
Mean (SD)	418.6 (87.05)	384.9 (132.16)	351.5 (243.29)	414.8 (272.66)	392.6 (263.39)	679.6 (376.53)	593.3 (374.86)
Median	449.0	449.0	310.0	432.0	386.0	653.0	526.0
Minimum, Maximum	36, 463	1, 458	15, 825	1, 974	1, 974	1, 1430	1, 1430
<b>Dosing was paused, n (%)</b>							
No	37 (61.7)	53 (47.3)	18 (45.0)	36 (48.6)	54 (47.4)	34 (30.4)	52 (34.2)
Yes	23 (38.3)	59 (52.7)	22 (55.0)	38 (51.4)	60 (52.6)	78 (69.6)	100 (65.8)
Reason for dosing pause <sup>c</sup>							
Hold due to platelet monitoring rule (platelet count <75 x 10 <sup>9</sup> /L)	0	12 (10.7)	3 (7.5)	7 (9.5)	10 (8.8)	15 (13.4)	18 (11.8)
Procedural hold due to SNL on 19 February 2016 <sup>d</sup>	6 (10.0)	11 (9.8)	2 (5.0)	6 (8.1)	8 (7.0)	17 (15.2)	19 (12.5)
Hold due to missing platelet values	10 (16.7)	13 (11.6)	3 (7.5)	18 (24.3)	21 (18.4)	31 (27.7)	34 (22.4)
Hold due to investigator/medical monitor discretion - related to platelets	2 (3.3)	8 (7.1)	6 (15.0)	11 (14.9)	17 (14.9)	16 (14.3)	22 (14.5)
Hold due to investigator/medical	0	15 (13.4)	1 (2.5)	1 (1.4)	2 (1.8)	16 (14.3)	17 (11.2)

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	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)	Total (N=114)	Inotersen 300 mg (N=112)	Inotersen 300 mg (N=152)
monitor discretion - related to renal							
Hold due to AE (non-renal and non-platelet)	3 (5.0)	12 (10.7)	7 (17.5)	3 (4.1)	10 (8.8)	15 (13.4)	22 (14.5)
Missed dose	14 (23.3)	24 (21.4)	8 (20.0)	13 (17.6)	21 (18.4)	32 (28.6)	40 (26.3)

Source: Table 1.03; Module 5.3.5.1, CS2 CSR, Table 1.22; Module 5.3.5.2, CS3 CSR, Table 1.06 and Table 1.07

Note: Denominator is the number of subjects for each group in the safety set, unless otherwise indicated. Data does not include subjects for whom no reason for missed dose was provided in the CRF page for "Dosing Comments." The dosing comments can be found in Module 5.3.5.2, CS3 CSR, Appendix 16.2.5, Listing 9.

- Total number of doses received = number of doses received at Week 1 + number of weeks with study drug received after Week 1.
- Duration of study drug exposure = date of the last dose of study drug in the CS2 study - date of first dose + 1.
- Subjects may have more than 1 reason for dose pauses.
- An SNL was issued to all sites in February 2016 due to a case of severe thrombocytopenia in Subject (b) (6). Additional safety measures to increase the frequency of platelet monitoring during the study were implemented due to this case. In addition, sites were instructed to discontinue study drug dosing in subjects who did not have a recent (within 14 days of the date of the letter) platelet laboratory result until a blood sample for platelet monitoring was obtained.

SNL = Safety notification letter

Source: Summary of Clinical Safety Table 5

## 8.2.2. Relevant Characteristics of the Safety Population

### Demographics

The table below displays demographics for subjects in all clinical studies of inotersen in patients with hATTR-PN (Studies CS2 and CS3). The demographic characteristics listed in the table below are balanced between the inotersen and placebo groups in Study CS2.

**Table 5. Demographic Characteristics (CS2 and CS3 Safety Sets)**

	CS2 Safety Set		CS3 Safety Set		
	Placebo (N=60)	Inotersen 300 mg (N=112)	Placebo- Inotersen (N=40)	Inotersen- Inotersen (N=74)	Total (N=114)
<b>Age (years)<sup>a</sup></b>					
Mean (SD)	59.5 (14.05)	59.0 (12.53)	61.8 (14.05)	61.2 (11.67)	61.4 (12.49)
Median	63.0	62.0	65.0	64.0	64.5
Minimum, Maximum	28, 81	27, 78	36, 82	29, 79	29, 82
<b>Age group (years)</b>					
19 to 64	34 (56.7)	64 (57.1)	19 (47.5)	38 (51.4)	57 (50.0)
≥65	26 (43.3)	48 (42.9)	21 (52.5)	36 (48.6)	57 (50.0)
<b>Sex, n (%)</b>					
Male	41 (68.3)	77 (68.8)	29 (72.5)	51 (68.9)	80 (70.2)
Female	19 (31.7)	35 (31.3)	11 (27.5)	23 (31.1)	34 (29.8)
<b>Ethnicity, n (%)</b>					
Hispanic or Latino	7 (11.7)	17 (15.2)	2 (5.0)	7 (9.5)	9 (7.9)
Not Hispanic or Latino	53 (88.3)	95 (84.8)	38 (95.0)	67 (90.5)	105 (92.1)
<b>Race, n (%)</b>					
Asian	3 (5.0)	1 (0.9)	3 (7.5)	0	3 (2.6)
Black	1 (1.7)	3 (2.7)	0	1 (1.4)	1 (0.9)
White	53 (88.3)	105 (93.8)	37 (92.5)	71 (95.9)	108 (94.7)
White and Grayish-Brown	1 (1.7)	0	0	0	0
Other	2 (3.3)	3 (2.7)	0	2 (2.7)	2 (1.8)
<b>Weight (kg)<sup>a</sup></b>					
Mean (SD)	71.07 (18.135)	70.59 (17.032)	70.16 (20.130)	71.22 (17.637)	70.85 (18.459)
Median	69.93	70.10	66.90 (55.00, 79.10)	71.40 (58.38, 76.90)	71.35 (56.90, 78.86)
Minimum, Maximum	38.2, 126.0	37.0, 140.4	40.0, 133.3	44.1, 141.6	40.0, 141.6
<b>Region, n (%)</b>					
Europe	23 (38.3)	37 (33.0)	14 (35.0)	26 (35.1)	40 (35.1)
North America	26 (43.3)	56 (50.0)	21 (52.5)	41 (55.4)	62 (54.4)
South America/Australasia	11 (18.3)	9 (17.0)	5 (12.5)	7 (9.5)	12 (10.5)

Source: Table 6 Summary of Clinical Safety

Three stages of hATTR-PN based on ambulatory status<sup>9</sup> were used to classify disease severity in Study CS2.<sup>10</sup>

- Stage 1 – does not require assistance with ambulation
- Stage 2 – requires assistance with ambulation
- Stage 3 – wheelchair bound

After randomization in Study CS2, the Sponsor discovered cases of incorrect entry of stratification data into the interactive voice/web response system (IXRS). Three additional placebo subjects had Stage 1 disease according to the correctly entered eCRF data, compared to the IXRS data.

*Reviewer comment: The 3 additional Stage 1 hATTR-PN patients randomized to placebo contributed to a slightly higher percentage of placebo subjects with Stage 1 hATTR-PN (70.0%), compared to inotersen subjects (66.1%) (see table below). The percentage of subjects diagnosed with hATTR-CM at CS2 study entry was 40.2% in inotersen subjects, compared to 36.7% in placebo subjects.*

**Table 6. Summary of randomization strata**

	CS2 Safety Set		CS3 Safety Set		
	Placebo (N=60)	Inotersen 300 mg (N=112)	Placebo- Inotersen (N=40)	Inotersen- Inotersen (N=74)	Total (N=114)
<b>Randomization stratum by IXRS, n (%)</b>					
Previous treatment with tafamidis or diflunisal					
Yes	33 (55.0)	61 (54.5)	20 (50.0)	48 (64.9)	68 (59.6)
No	27 (45.0)	51 (45.5)	20 (50.0)	26 (35.1)	46 (40.4)
Disease stage at CS2 Screen					
Stage 1	39 (65.0)	74 (66.1)	26 (65.0)	50 (67.6)	76 (66.7)
Stage 2	21 (35.0)	38 (33.9)	14 (35.0)	24 (32.4)	38 (33.3)
V30M TTR mutation					
Yes	32 (53.3)	58 (51.8)	20 (50.0)	29 (39.2)	49 (43.0)
No	28 (46.7)	54 (48.2)	20 (50.0)	45 (60.8)	65 (57.0)
<b>Randomization stratum by eCRF, n (%)</b>					
Previous treatment with tafamidis or diflunisal					
Yes	36 (60.0)	63 (56.3)	23 (57.5)	49 (66.2)	72 (63.2)
No	24 (40.0)	49 (43.8)	17 (42.5)	25 (33.8)	42 (36.8)
Disease stage					
Stage 1	42 (70.0)	74 (66.1)	29 (72.5)	51 (68.9)	80 (70.2)
Stage 2	18 (30.0)	38 (33.9)	11 (27.5)	23 (31.1)	34 (29.8)
V30M TTR mutation					
Yes	33 (55.0)	56 (50.0)	21 (52.5)	29 (39.2)	50 (43.9)
No	27 (45.0)	56 (50.0)	19 (47.5)	45 (60.8)	64 (56.1)

Source: Table 6 Summary of Clinical Safety

<sup>9</sup> Coutinho P, Martins da Silva A, Lopas Lima J. et al. Forty years of experience with type1 amyloid neuropathy. Review of 483 cases. In: Glenner GG, Pinho e Costa P, Falcao deFreitas A, editors. *Amyloid and Amyloidosis*. Amsterdam, The Netherlands 1980.

<sup>10</sup> P. 22 Study CS2 Clinical Study Report

Baseline disease characteristics in Study CS2 are summarized in the table below. The mean Modified Neuropathy Impairment Score +7 (mNIS+7) composite score difference (difference Inotersen – Placebo = 5.23; Inotersen = 79.35, Placebo = 74.12) was driven by small differences in each of the component scores. The median difference in mNIS+7 between groups was small (difference Inotersen – Placebo =1.26; Inotersen = 76.15, Placebo = 74.89).

*Reviewer comment: The Sponsor cites mean parameters as evidence of worse disease in the inotersen group compared to placebo.<sup>11</sup> However, in many cases median measurements for the same parameters indicated a smaller difference between treatment groups (i.e., mNIS+7) or indicated no difference or worse measures for the placebo group (i.e., duration of disease from hATTR-PN diagnosis, duration of disease from hATTR-CM diagnosis, duration from onset of hATTR-CM symptoms).*

In Study CS2, 40.2% of inotersen subjects had been diagnosed with hATTR-CM at baseline, compared to 36.7% of placebo subjects.

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<sup>11</sup> Table 9 Summary of Clinical Efficacy

**Table 7. Baseline disease characteristics (Study CS2)**

	Placebo (N=60)	Inotersen 300 mg (N=112)	Total (N=172)
<b>TTR genotype observed in &gt;1 subject<sup>a</sup>, n (%)</b>			
Type VAL30MET	33 (55.0)	56 (50.0)	89 (51.7)
Type THR60ALA	8 (13.3)	14 (12.5)	22 (12.8)
Type LEU58HIS	3 (5.0)	7 (6.3)	10 (5.8)
Type SER77TYR	5 (8.3)	4 (3.6)	9 (5.2)
Type PHE64LEU	3 (5.0)	5 (4.5)	8 (4.7)
Type SER50ARG	1 (1.7)	5 (4.5)	6 (3.5)
Type GLU89GLN	0	5 (4.5)	5 (2.9)
Type VAL122ILE	1 (1.7)	2 (1.8)	3 (1.7)
Type THR49ALA	0	2 (1.8)	2 (1.2)
<b>Duration of disease from hATTR-PN diagnosis (months)<sup>b</sup></b>			
Mean (SD)	39.3 (40.30)	42.4 (51.19)	41.3 (47.58)
Median	24.0	23.0	23.0
Minimum, Maximum	1, 159	2, 297	1, 297
<b>Duration from onset of hATTR-PN symptoms (months)<sup>b</sup></b>			
Mean (SD)	64.0 (52.34)	63.9 (53.16)	63.9 (52.72)
Median	48.0	50.5	49.5
Minimum, Maximum	8, 277	5, 372	5, 372
<b>Subjects diagnosed with hATTR-CM, n (%)</b>			
Yes	22 (36.7)	45 (40.2)	67 (39.0)
No	38 (63.3)	67 (59.8)	105 (61.0)
<b>Duration of disease from hATTR-CM diagnosis (months)</b>			
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
<b>Duration from onset of hATTR-CM symptoms (months)</b>			
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
<b>mNIS+7 composite scores</b>			
Mean (SD)	74.75 (39.003)	79.16 (36.958)	77.62 (37.629)
Median	74.89	76.15	75.60
Minimum, Maximum	13.2, 156.7	11.2, 174.7	11.2, 174.7
<b>Norfolk QoL-DN total scores</b>			
n	59	111	170
Mean (SD)	48.68 (26.746)	48.22 (27.503)	48.38 (27.165)
Median	48.11	45.00	47.00
Minimum, Maximum	-1.0, 111.0	-2.0, 127.0	-2.0, 127.0
<b>PND score<sup>c</sup>, n (%)</b>			
I	23 (38.3)	32 (28.6)	55 (32.0)
II	19 (31.7)	42 (37.5)	61 (35.5)
III	15 (25.0)	30 (26.8)	45 (26.2)
IV	3 (5.0)	8 (7.1)	11 (6.4)
V	0	0	0

	Placebo (N=60)	Inotersen 300 mg (N=112)	Total (N=172)
<b>Body mass index (kg/m<sup>2</sup>)</b>			
n	60	111	171
Mean (SD)	24.21 (4.858)	23.99 (4.896)	24.07 (4.869)
Median	23.81	23.50	23.60
Minimum, Maximum	14.5, 39.8	13.3, 40.2	13.3, 40.2
<b>NT-proBNP (pmol/L)</b>			
n	60	108	168
Mean (SD)	81.98 (159.151)	121.55 (255.420)	107.42 (226.076)
Median	30.50	44.50	34.00
Minimum, Maximum	2.0, 872.0	1.0, 2252.0	1.0, 2252.0
<b>NYHA score, n (%)</b>			
I	40 (66.7)	71 (63.4)	111 (64.5)
II	20 (33.3)	41 (36.6)	61 (35.5)
III	0	0	0
IV	0	0	0
<b>Karnofsky score</b>			
Karnofsky performance status ≤50	0	0	0
Mean (SD)	76.8 (10.81)	76.2 (11.20)	76.4 (11.04)
Median	80.0	80.0	80.0
Minimum, Maximum	60, 90	60, 100	60, 100
<b>TTR concentration (g/L)</b>			
Mean (SD)	0.2186 (0.04696)	0.2134 (0.06108)	0.2153 (0.05647)
Median	0.2245	0.2080	0.2115
Minimum, Maximum	0.106, 0.304	0.086, 0.397	0.086, 0.397

Source: Module 5.3.5.1, CS2 CSR, [Table 1.10](#)

Note: Denominator is the number of subjects for each group in the SS, unless otherwise indicated.

- Eighteen other TTR mutations were observed in 1 subject each, including ALA109SER, ALA97SER, ASP38ALA, GLU54SER, GLU61LYS, GLU89LYS, GLY47ALA, GLY67ARG, ILE107PHE, ILE107VAL, ILE84SER, LYS35THR, LYS70ASN, PHE33LEU, PRO24SER, SER77PHE, THR59LYS, and TYR114CYS.
- Only year and month were collected for hATTR-PN diagnosis and onset of hATTR-PN symptoms. The duration from hATTR-PN diagnosis and onset of hATTR-PN symptoms was calculated relative to the informed consent date.
- PND score categories are defined in Module 5.3.5.1, CS2 CSR, [Section 9.6.1.4](#).

Abbreviations: hATTR-CM=hereditary transthyretin amyloidosis with cardiomyopathy; hATTR-PN=hereditary transthyretin amyloidosis with polyneuropathy; mNIS= modified neuropathy impairment score; NSC= neuropathy symptoms and change; NT-proBNP= N-terminal prohormone of brain natriuretic peptide; PND=Polyneuropathy Disability; QoL-DN=Quality of Life Diabetic Neuropathy; TTR=transthyretin

Source: Summary of Clinical Efficacy Table 8

## Summary of Inclusion and Exclusion Criteria<sup>12</sup>

### Inclusion Criteria

1. Subjects with Stage 1 or Stage 2 hATTR-PN and all of the following:
  - a. NIS score  $\geq 10$  and  $\leq 130$
  - b. Documented TTR variant by genotyping
  - c. Documented amyloid deposit by biopsy
  - d. In Germany, Portugal, and Argentina only, Stage 1 subjects were also required to meet at least 1 of the following criteria: 1) failed tafamidis treatment, 2) intolerant to tafamidis treatment, or 3) not eligible for tafamidis treatment.
2. Aged 18 to 82 years at the time of informed consent

### Exclusion Criteria

1. Unwillingness to cooperate with study procedures, including follow-up
2. Screening laboratory results as described below, or any other clinically significant abnormalities in Screening laboratory values that rendered a subject unsuitable for inclusion:
  - a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $> 1.9$  times the upper limit of normal (ULN)
  - b. Bilirubin  $\geq 1.5 \times \text{ULN}$  (subjects with bilirubin  $\geq 1.5 \times \text{ULN}$  may have been permitted following discussion with the medical monitor, if only indirect bilirubin was elevated, ALT/AST was not  $> \text{ULN}$ , and genetic testing confirmed Gilbert's disease)
  - c. Platelets  $< 125 \times 10^9/\text{L}$
  - d. Positive ( $\geq$ trace) for protein on urine dipstick. In the event of a positive test, eligibility may have been confirmed by a quantitative total urine protein measurement of  $< 1.0 \text{ g}/24 \text{ hours}$
  - e. Positive ( $\geq$ trace) for blood on urine dipstick. In the event of a positive test, eligibility may have been confirmed with urine microscopy showing  $\leq 5$  red blood cells (RBCs) per high power field. If  $> 5$  RBCs per high power field and there was a clearly identifiable benign cause for the microscopic hematuria (e.g., chronic urinary tract infection secondary to neurogenic bladder), eligibility was to be determined by discussion with the medical monitor
  - f. Thyroid-stimulating hormone (TSH) values outside normal range (unless approved by the medical monitor)
3. Retinol level at Screening less than the lower limit of normal (LLN) For subjects with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and retinol  $< \text{LLN}$ , the exclusion criterion

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<sup>12</sup> For additional details, refer to the Study CS2 Inclusion Exclusion Criteria. P. 1594-1616 Sponsor responses to FDA presubmission requests. Submitted to NDA 211172 on November 6, 2017.

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was signs or symptoms of vitamin A deficiency (such as evidence of vitamin A deficiency on electroretinography [ERG])

4. QTcF>470 according to specified criteria
5. Uncontrolled hypertension (blood pressure >160/100 mmHg)
6. Positive test result for human immunodeficiency virus (HIV), hepatitis B or hepatitis C
7. Karnofsky performance status ≤50
8. Renal insufficiency as defined by estimated creatinine clearance calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula <60 mL/min/1.73 m<sup>2</sup> at Screening. If the calculated creatinine clearance was thought to be artificially low, a 24-hour urine creatinine clearance was allowed with prior Sponsor approval
9. Presence of known type 1 or type 2 diabetes mellitus
10. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease)
11. If previously treated with Vyndaqel® must have discontinued treatment for 2 weeks prior to Study Day 1. If previously treated with Diflunisal, must have discontinued treatment for 3 days prior to Study Day 1.
12. Previous treatment with any oligonucleotide or siRNA
13. Prior liver transplant or anticipated liver transplant within 1 year of screening
14. New York Heart Association (NYHA) functional classification of 2:3
15. Acute coronary syndrome or major surgery within 3 months of screening
16. Known Primary Amyloidosis
17. Known Leptomeningeal Amyloidosis
18. Anticipated survival less than 2 years
19. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
20. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
21. Have any other conditions, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
22. Known Monoclonal Gammopathy of Undetermined Significance or Multiple Myeloma

### 8.2.3. Adequacy of the Safety Database

Because hATTR-PN is a rare disease, the overall subject exposure in the inotersen clinical development program is adequate. Duration of treatment and patient demographics are acceptable.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

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In the original NDA submission<sup>13</sup> Sponsor analyses of nadir platelet count, renal parameter abnormalities, and hepatobiliary laboratory abnormalities<sup>14</sup> excluded some laboratory values that were categorized as ‘unconfirmed.’ However, according to this FDA reviewer’s assessment, most of the excluded laboratory measurements were not consistent with laboratory errors and should not be excluded.

The Sponsor defined a confirmed laboratory measurement 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.”

Four subjects<sup>15</sup> in Study CS3 had nadir platelet counts  $<50 \times 10^9/L$  that were considered unconfirmed and were not included in the Summary of Clinical Safety analyses.<sup>16</sup> While 1 subject’s nadir platelet count was consistent with a laboratory error,<sup>17</sup> 3 subjects<sup>18</sup> had nadir platelet counts, ranging from  $33\text{--}41 \times 10^9/L$ , that were not consistent with laboratory errors:

- All the subjects 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.
- One subject<sup>19</sup> received corticosteroids<sup>20</sup> in response to the nadir platelet count, which contributed to the increased confirmatory platelet count.

FDA requested revised tables with analyses that included all measured laboratory values, which were evaluated in this review (see Tables 20, 36, and 38).

### 8.3.2. Categorization of Adverse Events

The Sponsor’s process for recording AEs was appropriate. The Sponsor’s coding resulted in appropriate translation of verbatim terms to preferred terms. However, AEs were often coded to multiple different equivalent Preferred Terms, which resulted in splitting of adverse events across multiple Preferred Term categories. For example, in Study CS2, proteinuria

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<sup>13</sup> November 6, 2017

<sup>14</sup> Summary of Clinical Safety Tables 69, 80, and 85, respectively.

<sup>15</sup> Subjects (b) (6)

<sup>16</sup> ISS Table 2.31

<sup>17</sup> Study CS2 inotersen subject (b) (6) had normal platelet counts until 1 month after starting inotersen, when the subject had a single platelet count of  $5 \times 10^9/L$ . Two days later platelet count was  $106 \times 10^9/L$ . Treatment was continued, and platelet count remained  $\geq 98 \times 10^9/L$  until the final Study CS2 platelet count 6 months after starting inotersen.

<sup>18</sup> Subjects (b) (6)

<sup>19</sup> Subject (b) (6)

<sup>20</sup> Response to FDA information request. Submitted to NDA 211172 on January 8, 2018.

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adverse events (including PTs Thrombocytopenia and Platelet count decreased) occurred in 24% of subjects, compared to the Sponsor table listing of 13%, which included only the PT Thrombocytopenia.

The Sponsor categorized adverse events as mild, moderate, or severe. Adverse events were coded to MedDRA 19.1 in the integrated summary of safety.

For CS2 and CS3, treatment-emergent AEs (TEAEs) were defined as AEs that first occurred or worsened in severity after the first dose of study drug for the respective study. Adverse events that began during CS2 or in a gap between CS2 and CS3 and were ongoing at the time of entry in CS3 were therefore only considered treatment emergent in CS3 if the severity increased in CS3. For the longitudinal summaries, TEAEs were defined as AEs that first occurred or worsened after the first dose of study drug in CS2. The follow-up period included scheduled study visits that occurred up to 6 months and 13 weeks after treatment in Studies CS2 and CS3, respectively.<sup>21</sup>

### 8.3.3. Routine Clinical Tests

The schedule of procedures, including routine clinical tests, for Studies CS2 and CS3 are summarized in Appendices 13.3 and 13.4, respectively.

In the original Study CS2 protocol, platelet counts were measured approximately every 2-6 weeks. After the death of Study CS2 Subject (b) (6) from intracranial hemorrhage because of severe thrombocytopenia, platelet counts were scheduled weekly.<sup>22</sup>

## 8.4. Safety Results

### 8.4.1. Deaths

In Study CS2, 5 of 112 (4.4%) inotersen subjects died, compared to 0 of 60 placebo subjects. One death, in a subject with severe thrombocytopenia and intracranial hemorrhage, was related to inotersen. The other 4 deaths in Study CS2 were related to progression of hATTR-PN (see table below).

*Reviewer comment: In study CS2, inotersen subjects had a shorter mean duration of exposure (385 days) compared to placebo subjects (419 days) (see Table 4). Thus, the increased frequency of deaths in the inotersen group cannot be explained by disease progression over a longer duration of observation. Baseline disease characteristics in Study CS2 were generally similar between treatment groups (see Table 7), but the mean and median mNIS+7 scores were higher in the inotersen group by 5.23 and 1.26 points, respectively. See Section 8.2.2 for*

<sup>21</sup> Schedule of procedures for Studies CS2 and CS3 (Appendices 13.3 and 13.4, respectively).

<sup>22</sup> Summary of Platelet Count Rule Changes. Submitted to NDA 211172 on December 15, 2017.

a discussion of baseline disease characteristics in Study CS2.

In Studies CS2 and CS3 combined, 11 of 161 (6.8%) inotersen subjects died.<sup>23</sup> The 6 deaths in Study CS3 included with 3 deaths from disease progression, 2 deaths from infections in the setting of multiple complications of hATTR-PN, and 1 death from autoimmune hepatitis and primary biliary cirrhosis. For additional details regarding the death of Subject (b) (6) from primary biliary cirrhosis and autoimmune hepatitis, see Section 8.5.4.

**Table 8. Deaths in Studies CS2 and CS3**

Subject Number Age/Sex	hATTR Stage at Enrollment	Study	Cause of Death	Inotersen Doses Received	Reviewer Assessment
(b) (6)	2	CS2	Thrombocytopenia Intracranial hemorrhage	19	Related to inotersen. Severe drug-related thrombocytopenia leading to intracranial hemorrhage.
(b) (6)	2	CS2	Cachexia	61	Related to disease progression complicated by <i>Clostridium difficile</i> infection in the month prior to death.
(b) (6)	2	CS2	Cachexia	23	Related to disease progression. Patient also developed decreased renal function, proteinuria, and edema, which was possibly related to inotersen and may have contributed to her death.
(b) (6)	1	CS2	Intestinal perforation	35	Sigmoid volvulus leading to intestinal perforation. Events consistent with complications of hATTR-PN amyloidosis. <sup>a</sup>
(b) (6)	2	CS2	Cardiac failure congestive Cachexia	49	Related to disease progression.
(b) (6)	2	CS3	Cardiac failure congestive	68	Related to disease progression.
(b) (6)	1	CS3	Cardiac rupture (after liver transplant)	68	Related to disease progression and complication of liver transplant.
(b) (6)	2	CS3	Cardiac failure acute Bacteremia Septic shock	146	Unlikely related to inotersen. Septic shock and bacteremia in the setting of advanced hATTR with a 20-pound weight loss in 2 months prior to death.
(b) (6)	1	CS3	Neuropathy peripheral	98	Related to disease progression.
(b) (6)	2	CS3	Endocarditis	66	Unlikely related to inotersen. History of cardiac arrhythmia with pacemaker. Died from endocarditis leading to cardiogenic shock.

<sup>23</sup> Safety Update report submitted to NDA 211172 on March 6, 2018 and MedWatch report for the death of Subject (b) (6) submitted to IND 113968 on April 11, 2018.

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Subject Number Age/Sex	hAATTR Stage at Enrollment	Study	Cause of Death	Inotersen Doses Received	Reviewer Assessment
(b) (6)	1	CS3	Primary biliary cirrhosis Autoimmune hepatitis	142	Likely related to inotersen.

<sup>a</sup> Kumar SS, et al. Amyloidosis of the colon. Report of a case and review of the literature. *Dis Colon Rectum* 1983;26:541-544.

<sup>b</sup> Reported in the Safety Update Report (after the original NDA data cutoff)

<sup>c</sup> Submitted to IND 113968 on April 11, 2018.

#### 8.4.2. Serious Adverse Events

*Reviewer comment: In the review of individual serious adverse events, this reviewer evaluated information from the Sponsor's narrative summaries. In specific cases, this reviewer also evaluated information from case report forms or related medical records.*

**Table 9. Serious Treatment-Emergent Adverse Events by System Organ Class. Controlled Study CS2 and in All Inotersen-Treated Subjects**

System Organ Class	Study CS2 Inotersen Subjects N=112 n (%)	Study CS2 Placebo Subjects N=60 n (%)	All (CS2 and CS3) Inotersen Subjects N=161 n (%)
<b>Subjects with at least 1 serious TEAE</b>	<b>36 (32.1)</b>	<b>13 (21.7)</b>	<b>60 (37.3)</b>
Infections and Infestations	11 (9.8)	5 (8.3)	25 (15.5)
Cardiac Disorders	9 (8.0)	2 (3.3)	15 (9.3)
Gastrointestinal Disorders	7 (6.3)	1 (1.7)	12 (7.5)
Nervous System Disorders	6 (5.4)	1 (1.7)	13 (8.1)
Metabolism and Nutrition Disorders	6 (5.4)	0	10 (6.2)
Renal and Urinary Disorders	6 (5.4)	0	10 (6.2)
Vascular Disorders	3 (2.7)	2 (3.3)	5 (3.1)
Respiratory, Thoracic and Mediastinal Disorders	3 (2.7)	0	3 (1.9)
Blood and Lymphatic System Disorders	2 (1.8)	0	3 (1.9)
Psychiatric Disorders	2 (1.8)	0	3 (1.9)
Injury, Poisoning and Procedural Complications	1 (0.9)	3 (5.0)	5 (3.1)
General Disorders and Administration Site Conditions	1 (0.9)	0	3 (1.9)
Hepatobiliary Disorders	0	0	2 (1.2)
Neoplasms Benign, Malignant, and Unspecified	0	0	2 (1.2)
Eye Disorders	0	0	1 (0.6)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (0.6)

Source: Table 19 Summary of Clinical Safety submitted November 6, 2017 Table and Safety Update Report (Document a p. 1077-1084) submitted March 6, 2018.

TEAE = treatment-emergent adverse event

*Reviewer comment: There were no adverse events of aplastic anemia, Stevens Johnson Syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome reported in the nusinersen clinical development program.*

### Nervous System Disorders SOC

In Study CS2, 6 of 112 (5.4%) inotersen subjects had SAEs coded to the Nervous System Disorders SOC, compared to 1 of 60 (1.7%) placebo subjects. In Studies CS2 and CS3 combined, 13 of 161 (8.1%) inotersen subjects had SAEs coded to the Nervous System Disorders SOC (see table below).

**Table 10. Serious Adverse Events in Studies CS2 and CS3 coded to the Nervous System Disorders SOC**

System Organ Class Preferred Term	Study CS2 Inotersen Subjects (N=112) n (%)	Study CS2 Placebo Subjects (N=60) n (%)	All (CS2 and CS3) Inotersen Subjects (N=161) n (%)
<b>Nervous System Disorders</b>	<b>6 (5.4)</b>	<b>1 (1.7)</b>	<b>13 (8.1)</b>
Dementia	1 (0.9)	0	1 (0.6)
Embolic stroke	1 (0.9)	0	1 (0.6)
Haemorrhage intracranial	1 (0.9)	0	2 (1.2)
Myelopathy	1 (0.9)	0	1 (0.6)
Myoclonus	1 (0.9)	0	1 (0.6)
Neuritis	1 (0.9)	0	1 (0.6)
Seizure	1 (0.9)	0	1 (0.6)
Syncope	1 (0.9)	0	5 (3.1)
Neuralgia	0	1 (1.7)	0
Dizziness	0	0	1 (0.6)
Encephalopathy	0	0	1 (0.6)
Memory impairment	0	0	1 (0.6)

Source: Table 19 Summary of Clinical Safety submitted November 6, 2017 Table and Safety Update Report (Document a p. 1077-1084) submitted March 6, 2018.

The Study CS2 SAE of Haemorrhage intracranial (Study CS2 Subject (b) (6)) occurred as a result of severe immune thrombocytopenia related to inotersen. (See Section 8.5.1 for additional details.)

Study CS3 Subject (b) (6) (treated with placebo in Study CS2) had an SAE Haemorrhage intracranial during CS3 Week 24 in the setting of an elevated INR >2.5 while receiving the concomitant medication dabigatran. The subject had a history of orthostatic hypotension at baseline in Study CS2. The subject had a subarachnoid hemorrhage with no apparent neurologic sequelae.<sup>24</sup>

<sup>24</sup> P. 398-401 Document e. Safety Update Report.

The SAEs of Embolic stroke (Study CS2 Subject (b) (6)) and Myelopathy and Neuritis (Study CS2 Subject (b) (6)), are discussed in Section 8.5.3, which discusses inflammatory and immune effects of inotersen. Section 8.5.3 also includes a discussion of a neurologic disorder SAE coded as Encephalitis.<sup>25</sup>

Six inotersen-treated subjects had SAEs of Syncope and Dizziness. In addition, Study CS2 Subject (b) (6) had convulsive activity (SAE PT Seizure) that may have been related to syncope. Because autonomic dysfunction is a manifestation of hATTR, the role of inotersen in individual cases of syncope is difficult to discern. In Study CS2, adverse events of presyncope or syncope occurred in 13% of inotersen subjects, compared to 5% placebo subjects.

*Reviewer comment: This reviewer recommends including syncope in the prescribing information table of common adverse events.*

Other SAEs coded to the Nervous System Disorders SOC are briefly summarized below:

- Study CS2 Subject (b) (6), a 78-year-old female from Portugal, had SAEs coded to the PTs Dementia and Myoclonus. AE start dates were 14 months after the start of inotersen. The family said that her cognitive deterioration started 2 years prior to the AE start date. The subject had fluctuating cognitive function despite improvement in an AE of Renal failure. Epileptic seizures and a metabolic cause were excluded. A diagnosis of neurodegenerative dementia and possibly Lewy body dementia was determined based on the occurrence of visual hallucinations, fluctuating cognitive impairment, evidence of slight Parkinson's disease during the neurological observation and confirmation of long duration of the cognitive impairment.

*In this reviewer's assessment, these SAEs are unlikely related to inotersen.*

- Study CS3 Subject (b) (6), a 62-year-old male from the United States, had SAEs of Encephalopathy and Memory Impairment during an acute illness of sepsis, pneumonia, and hyponatremia.

*Because of the medical illnesses ongoing at the time of these SAEs, in this reviewer's assessment, they are unlikely related to inotersen.*

- Study CS3 Subject (b) (6), a 66-year-old female from the United States, had an SAE of Neuropathy peripheral, which was a progression of hATTR-PN disease.

*In this reviewer's assessment, this SAE was not related to inotersen.*

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<sup>25</sup> This serious adverse event in Study CS2 Subject (b) (6) was coded to the Infections and infestations SOC. However, there was no confirmation of infection. In the assessment of this reviewer, this case is possibly related to a proinflammatory effect of inotersen.

**Gastrointestinal Disorders SOC**

In Study CS2, 7 of 112 (6.3%) inotersen subjects had SAEs coded to the Gastrointestinal Disorders SOC, compared to 1 of 60 (1.7%) placebo subjects. In Studies CS2 and CS3 combined, 12 of 161 (7.5%) inotersen subjects had SAEs coded to the Gastrointestinal Disorders SOC (see table below).

**Table 11. Serious Adverse Events in Studies CS2 and CS3 coded to the Gastrointestinal Disorders SOC**

System Organ Class Preferred Term	Study CS2 Inotersen Subjects (N=112) n (%)	Study CS2 Placebo Subjects (N=60) n (%)	All (CS2 and CS3) Inotersen Subjects (N=161) n (%)
<b>Gastrointestinal Disorders</b>	<b>7 (6.3)</b>	<b>1 (1.7)</b>	<b>12 (7.5)</b>
Vomiting	1 (0.9)	1 (1.7)	2 (1.2)
Abdominal pain	1 (0.9)	0	2 (1.2)
Constipation	1 (0.9)	0	1 (0.6)
Gastrointestinal haemorrhage	1 (0.9)	0	2 (1.2)
Gastrointestinal hypomotility	1 (0.9)	0	1 (0.6)
Haemorrhoids	1 (0.9)	0	1 (0.6)
Intestinal perforation	1 (0.9)	0	1 (0.6)
Mesenteric arterial occlusion	1 (0.9)	0	1 (0.6)
Umbilical hernia	1 (0.9)	0	1 (0.6)
Diarrhoea	0	0	1 (0.6)
Nausea	0	0	1 (0.6)
Oesophageal hypomotility	0	0	1 (0.6)
Pancreatitis	0	0	1 (0.6)

Source: Table 19 Summary of Clinical Safety submitted November 6, 2017 Table and Safety Update Report (Document a p. 1077-1084) submitted March 6, 2018.

Selected SAEs coded to the Gastrointestinal Disorders SOC are briefly summarized below:

- SAEs of Intestinal perforation and Mesenteric arterial occlusion in Study CS2 inotersen subject (b) (6) occurred in the setting of sigmoid volvulus and resulted in death. These events are consistent with complications of hATTR.<sup>27</sup>
- Study CS3 Subject (b) (6) (treated with inotersen in Study CS2), a 55-year-old male, had an SAE of pancreatitis.<sup>28</sup> The cause of pancreatitis was unclear. Pancreatitis can be a manifestation of amyloidosis.<sup>29</sup>
- Study CS2 inotersen-treated Subject (b) (6) had an SAE of Vomiting as a result of an SAE of Encephalitis.

<sup>26</sup> Narrative p. 3656-3659 Study CS2 CSR

<sup>27</sup> Kumar SS, et al. Amyloidosis of the colon. Report of a case and review of the literature. *Dis Colon Rectum* 1983;26:541–544.

<sup>28</sup> Narrative p. 2963 Study CS3 CSR

<sup>29</sup> Sisk CM, et al. Acute recurring pancreatitis: A manifestation of duodenal amyloid deposition. Case report and review. *Gastrointest Endosc.* 2001 May;53(6):656-7.

### Metabolism and Nutrition Disorders SOC

In Study CS2, 6 of 112 (5.4%) inotersen subjects had SAEs coded to the Metabolism and Nutrition Disorders SOC, compared to 0 of 60 placebo subjects. In Studies CS2 and CS3 combined, 10 of 161 (6.2%) inotersen subjects had SAEs coded to the Metabolism and Nutrition Disorders SOC (see table below).

*Reviewer comment: The increased frequency of Metabolic and Nutrition Disorders SOC SAEs is complicated by multiple factors. Manifestations of amyloidosis can contribute to conditions in the table below. However, more inotersen subjects had gastrointestinal adverse events (e.g., nausea, vomiting) and constitutional symptoms, which can also contribute to dehydration, cachexia, and malnutrition.*

**Table 12. Serious Adverse Events in Studies CS2 and CS3 coded to the Metabolism and Nutrition Disorders SOC**

System Organ Class Preferred Term	Study CS2 Inotersen Subjects (N=112) n (%)	Study CS2 Placebo Subjects (N=60) n (%)	All (CS2 and CS3) Inotersen Subjects (N=161) n (%)
<b>Metabolism and Nutrition Disorders</b>	<b>6 (5.4)</b>	<b>0</b>	<b>10 (6.2)</b>
Dehydration	3 (2.7)	0	4 (2.5)
Cachexia	2 (1.8)	0	2 (1.2)
Hyponatraemia	1 (0.9)	0	3 (1.9)
Malnutrition	0	0	1 (0.6)
Fluid retention	0	0	1 (0.6)

Source: Table 19 Summary of Clinical Safety submitted November 6, 2017 Table and Safety Update Report (Document a p. 1077-1084) submitted March 6, 2018.

The SAEs below are unlikely related to inotersen according to this reviewer’s assessment:

- Study CS2 inotersen-treated Subject (b) (6) experienced a SAE Dehydration in the setting of diuretic medication adjustment.
- Study CS3 Subject (b) (6) experienced SAEs of Hyponatremia and Fluid retention in the setting of congestive heart failure.

### Cardiac Disorders

In Study CS2, 9 of 112 (8.0%) inotersen subjects had SAEs coded to the Cardiac Disorders SOC, compared to 2 of 60 (3.3%) placebo subjects. In Studies CS2 and CS3 combined, 15 of 161 (9.3%) inotersen subjects had SAEs coded to the Cardiac Disorders SOC (see table below).

*Reviewer comment: The percentage of subjects diagnosed with hATTR-CM at CS2 study entry was 40.2% in inotersen subjects, compared to 36.7% in placebo subjects. This baseline imbalance may have contributed to the increased frequency of Cardiac disorders SOC SAEs in inotersen patients compared to placebo patients.*

**Table 13. Serious Adverse Events in Studies CS2 and CS3 coded to the Cardiac Disorders SOC**

System Organ Class Preferred Term	Study CS2 Inotersen Subjects (N=112) n (%)	Study CS2 Placebo Subjects (N=60) n (%)	All (CS2 and CS3) Inotersen Subjects (N=161) n (%)
<b>Cardiac Disorders</b>	<b>9 (8.0)</b>	<b>2 (3.3)</b>	<b>15 (9.3)</b>
Cardiac failure congestive	4 (3.6)	1 (1.7)	5 (3.1)
Cardiac failure	2 (1.8)	1 (1.7)	3 (1.9)
Cardiac failure acute	2 (1.8)	0	3 (1.9)
Sinus arrest	2 (1.8)	0	2 (1.2)
Atrioventricular block	1 (0.9)	0	1 (0.6)
Bradyarrhythmia	1 (0.9)	0	1 (0.6)
Bradycardia	1 (0.9)	0	1 (0.6)
Pericardial effusion	1 (0.9)	0	1 (0.6)
Sinus bradycardia	1 (0.9)	0	1 (0.6)
Angina unstable	0	0	1 (0.6)
Arrhythmia	0	0	1 (0.6)
Atrial flutter	0	0	1 (0.6)
Atrioventricular block complete	0	0	1 (0.6)
Cardiac tamponade	0	0	1 (0.6)
Sinus node dysfunction	0	0	1 (0.6)

Source: Table 19 Summary of Clinical Safety submitted November 6, 2017 Table and Safety Update Report

### Infections and Infestations

In Study CS2, 11 of 112 (9.8%) inotersen subjects had SAEs coded to the Infections and infestations SOC, compared to 5 of 60 (8.3%) placebo subjects. In Studies CS2 and CS3 combined, 25 of 161 (15.5%) inotersen subjects had SAEs coded to the Infections and infestations SOC (see table below).

*Reviewer comment: Upon review of the SAE Encephalitis in Study CS2 Subject (b) (6) there was no confirmation of infection in the case report. In the assessment of this reviewer, this SAE is possibly an immune or inflammatory effect of inotersen. This case is discussed separately in Section 8.5.3.*

**Table 14. Serious Adverse Events in Studies CS2 and CS3 coded to the Infections and Infestations SOC**

System Organ Class Preferred Term	Study CS2 Inotersen Subjects (N=112) n (%)	Study CS2 Placebo Subjects (N=60) n (%)	All (CS2 and CS3) Inotersen Subjects (N=161) n (%)
<b>Infections and Infestations</b>	<b>11 (9.8)</b>	<b>5 (8.3)</b>	<b>25 (15.5)</b>
Pneumonia	2 (1.8)	2 (3.3)	5(3.1)
Lower respiratory tract infection	0	0	1 (0.6)
Pneumonia mycoplasmal	0	0	1 (0.6)
Bronchitis	2 (1.8)	0	2 (1.2)
Gastroenteritis	1 (0.9)	1 (1.7)	3 (1.9)
Urinary tract infection	1 (0.9)	1 (1.7)	3 (1.9)
Clostridium difficile infection	1 (0.9)	0	1 (0.6)
Clostridium difficile colitis	0	0	1 (0.6)
Encephalitis	1 (0.9)	0	1 (0.6)
Herpes zoster	1 (0.9)	0	1 (0.6)
Peritonitis	1 (0.9)	0	1 (0.6)
Pyelonephritis acute	1 (0.9)	0	2 (1.2)
Staphylococcal infection	1 (0.9)	0	1 (0.6)
Wound infection	1 (0.9)	0	1 (0.6)
Sepsis	0	0	2 (1.2)
Cellulitis	0	1 (1.7)	2 (1.2)
Endocarditis	0	0	1 (0.6)
Septic shock	0	0	1 (0.6)
Cellulitis streptococcal	0	0	1 (0.6)
Skin infection	0	0	1 (0.6)
Bacteraemia	0	0	1 (0.6)
Bacterial toxemia	0	0	1 (0.6)
Systemic infection	0	0	1 (0.6)

Source: Table 19 Summary of Clinical Safety submitted November 6, 2017 Table and Safety Update Report

### Renal and Urinary Disorders

The reader is referred to the discussion of renal impairment in Section 8.5.2.

### Hepatobiliary Disorders

The reader is referred to the discussion of hepatobiliary toxicity in Section 8.5.4.

#### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Sixteen of 112 (14.3%) inotersen subjects had at least one adverse event that led to permanent discontinuation of treatment, compared to 2 of 60 (3.3%) placebo subjects (see table below).

**Table 15. On-Study Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug in Studies CS2 and CS3. Sponsor Designation.**

System Organ Class Preferred Term	Study CS2 Inotersen Subjects N=112 n (%)	Study CS2 Placebo Subjects N=60 n (%)	All (CS2 and CS3) Inotersen Subjects N=161 n (%)
<b>Subjects with at least 1 TEAE that led to discontinuation of study drug</b>	<b>16 (14.3)</b>	<b>2 (3.3)</b>	<b>27 (16.8)</b>
<b>Nervous System Disorders</b>	<b>5 (4.5)</b>	<b>0</b>	<b>7 (4.3)</b>
Chorea	1 (0.9)	0	1 (0.6)
Dementia	1 (0.9)	0	1 (0.6)
Embolic stroke	1 (0.9)	0	1 (0.6)
Haemorrhage intracranial	1 (0.9)	0	1 (0.6)
Headache	0	0	1 (0.6)
Myelopathy	1 (0.9)	0	1 (0.6)
Myoclonus	1 (0.9)	0	1 (0.6)
Neuropathy peripheral	0	0	1 (0.6)
<b>Cardiac Disorders</b>	<b>0</b>	<b>0</b>	<b>4 (2.5)</b>
Cardiac failure	0	0	1 (0.6)
Cardiac failure acute	0	0	1 (0.6)
Cardiac failure congestive	0	0	1 (0.6)
Cardiorenal syndrome	0	0	1 (0.6)
<b>Gastrointestinal Disorders</b>	<b>2 (1.8)</b>	<b>0</b>	<b>3 (1.9)</b>
Abdominal distension	1 (0.9)	0	1 (0.6)
Intestinal perforation	1 (0.9)	0	1 (0.6)
Nausea	1 (0.9)	0	2 (1.2)
Vomiting	1 (0.9)	0	1 (0.6)
<b>Renal and Urinary Disorders</b>	<b>2 (1.8)</b>	<b>1 (1.7)</b>	<b>3 (1.9)</b>
Acute kidney injury	1 (0.9)	0	1 (0.6)
Glomerulonephritis	1 (0.9)	0	1 (0.6)
Proteinuria	0	1 (1.7)	0
Renal impairment	0	0	1 (0.6)
Tubulointerstitial nephritis	1 (0.9)	0	1 (0.6)
<b>Blood and Lymphatic System Disorders</b>	<b>2 (1.8)</b>	<b>0</b>	<b>3 (1.9)</b>
Thrombocytopenia	2 (1.8)	0	3 (1.9)
<b>General Disorders and Administration Site Conditions</b>	<b>1 (0.9)</b>	<b>1 (1.7)</b>	<b>2 (1.2)</b>
Pain	0	1 (1.7)	0
Pyrexia	1 (0.9)	0	1 (0.6)
Chills	0	0	1 (0.6)
<b>Immune System Disorders</b>	<b>1 (0.9)</b>	<b>0</b>	<b>2 (1.2)</b>
Hypersensitivity	1 (0.9)	0	2 (1.2)
<b>Investigations</b>	<b>1 (0.9)</b>	<b>1 (1.7)</b>	<b>2 (1.2)</b>
Platelet count decreased	1 (0.9)	0	2 (1.2)
Weight increased	0	1 (1.7)	0
<b>Metabolism and Nutrition Disorders</b>	<b>2 (1.8)</b>	<b>0</b>	<b>2 (1.2)</b>
Cachexia	2 (1.8)	0	2 (1.2)

System Organ Class Preferred Term	Study CS2 Inotersen Subjects N=112 n (%)	Study CS2 Placebo Subjects N=60 n (%)	All (CS2 and CS3) Inotersen Subjects N=161 n (%)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>0</b>	<b>0</b>	<b>2 (1.2)</b>
Pruritus	1 (0.9)	0	1 (0.6)
Reticular erythematous mucinosis	1 (0.9)	0	1 (0.6)
<b>Infections and Infestations</b>	<b>0</b>	<b>0</b>	<b>2 (1.2)</b>
Bacteraemia	0	0	1 (0.6)
Endocarditis	0	0	1 (0.6)
Septic shock	0	0	1 (0.6)
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>1 (0.9)</b>	<b>1 (1.7)</b>	<b>1 (0.6)</b>
Arthralgia	1 (0.9)	1 (1.7)	1 (0.6)
Myalgia	1 (0.9)	0	1 (0.6)
<b>Vascular Disorders</b>	<b>1 (0.9)</b>	<b>0</b>	<b>1 (0.6)</b>
Deep vein thrombosis	1 (0.9)	0	1 (0.6)
<b>Neoplasms Benign, Malignant, and Unspecified</b>	<b>0</b>	<b>0</b>	<b>1 (0.6)</b>
Meningioma	0	0	1 (0.6)
<b>Psychiatric Disorders</b>	<b>0</b>	<b>0</b>	<b>1 (0.6)</b>
Mental status changes	0	0	1 (0.6)

Sources: Table 53 Summary of Clinical Safety and Table 20 Safety Update Report

Reasons for permanent discontinuation of inotersen included thrombocytopenia, glomerulonephritis, and an injection site reaction (PT Pruritus). Adverse events leading to permanent discontinuation in these categories are discussed elsewhere in this review.

Events of Meningioma and Mental status changes, which led to treatment discontinuation in Study CS3 Subject (b) (6), were not related to inotersen.

### Hypersensitivity with Anti-Inotersen Antibody Formation

In clinical studies, 7 of 161 (4%) inotersen patients stopped treatment because of a hypersensitivity reaction. These reactions were associated with antibodies to inotersen and generally occurred within 2 hours of administration.

- Study CS2 early termination<sup>30</sup>
  - Subject (b) (6) (PT Hypersensitivity):<sup>31</sup> Palmar erythema, thoracic oppression, eosinophilia, and dysphagia after the Week 11 inotersen dose. She was treated with desloratadine, and symptoms resolved after 1 day.
  - Subject (b) (6): AEs nausea, vomiting, fever, arthralgia, myalgia

<sup>30</sup> P. 1516 Applicant response to FDA presubmission requests. Submitted to NDA 211172 on November 6, 2017.

<sup>31</sup> P. 3807-3808 Study CS2 clinical study report

- Subject (b) (6): Episode of involuntary choreaform movements starting 45 minutes after inotersen dosing and lasting 5 hours, as well as a second episode for which documentation of timing is missing.
- Subjects who completed Study CS2 but declined participation in Study CS3:<sup>32</sup>
  - Subject (b) (6): Flu-like symptoms
  - Subject (b) (6): Flu-like symptoms and concerns over platelets
- Study CS3 early termination<sup>33</sup>
  - Subject (b) (6) (PT Hypersensitivity): Hypersensitivity reaction after 23 months of treatment. Symptoms included shivering, flushing, headache, and chest pain with hypertension. She was treated with prednisone and required cardiac monitoring.
  - Subject (b) (6): Multiple episodes of nausea and headache beginning 1 hour after inotersen injection and lasting for 2 hours.

Four<sup>34</sup> additional subjects with antibodies to inotersen received reduced dosing of inotersen (1-46 reduced doses) because of hypersensitivity adverse events.

*Reviewer comment: The Applicant's proposed label includes history of hypersensitivity reaction to inotersen as a contraindication. I agree with this proposal, as well as describing cases of hypersensitivity with anti-inotersen antibody formation in the Warnings and Precautions section of the label.*

#### 8.4.4. Significant Adverse Events

The Applicant categorized clinical study adverse events by severity (mild, moderate, or severe) in the integrated summary of safety datasets. Most adverse events categorized as severe (and not already included in the serious adverse event assessment) are discussed elsewhere in this review.

*Reviewer comment: I have reviewed the severe adverse events not discussed elsewhere in this review. In my assessment, these events are generally consistent with manifestations of amyloidosis (e.g., cachexia, skin ulcer, peripheral ischemia, diarrhea, constipation).*

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse events that occurred in at least 5% of Study CS2 inotersen subjects and occurred at least 5% more frequently or at least 2 times as frequently as placebo subjects are summarized in the table below.

*Reviewer comment: The table below is based on a table of individual Preferred Terms provided by the Applicant,<sup>35</sup> as well as analyses to combine split terms.*

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<sup>32</sup> P. 1543 Applicant response to FDA presubmission requests. Submitted to NDA 211172 on November 6, 2017.

<sup>33</sup> P. 1538 Applicant response to FDA presubmission requests. Submitted to NDA 211172 on November 6, 2017.

<sup>34</sup> P. 9 applicant submission to NDA 211172 on April 23, 2018. Study CS3 Subjects (b) (6)

<sup>35</sup> Response to FDA information request. Submitted to NDA 211172 on April 11, 2018.

**Table 16. Adverse events that occurred in at least 5% of Study CS2 inotersen subjects and occurred at least 5% more frequently or at least 2 times as frequently as placebo subjects**

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

<sup>a</sup> Includes terms for the following reactions at the injection site: bruising, erythema, haematoma, haemorrhage, induration, inflammation, mass, oedema, pain, pruritus, rash, reaction, swelling, urticaria

<sup>b</sup> Preferred Terms = Headache and Migraine

<sup>c</sup> Preferred Terms = Preferred Terms Thrombocytopenia and Platelet count decreased

<sup>d</sup> Preferred Term = Pyrexia

<sup>e</sup> Preferred Term = Oedema peripheral

<sup>f</sup> Preferred Terms = Anaemia, Anaemia macrocytic, Haematocrit decreased, Haemoglobin decreased, Iron deficiency anaemia, Red blood cell count decreased

<sup>g</sup> Preferred Terms = 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

<sup>h</sup> Preferred Terms = Arrhythmia, Atrial fibrillation, Atrial flutter, Bradyarrhythmia, Bradycardia, Extrasystoles, Sinus arrhythmia, Sinus bradycardia, Supraventricular extrasystoles, Tachycardia, and Ventricular extrasystoles

<sup>i</sup> Preferred Terms = Arthralgia, Arthritis, and Spinal osteoarthritis

<sup>j</sup> Preferred Terms = Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Liver function test abnormal, and Transaminases increased

<sup>k</sup> Preferred Terms = Dizziness postural, Orthostatic hypotension, and Orthostatic intolerance

<sup>l</sup> Preferred Terms = Bacteraemia, Cellulitis staphylococcal, Clostridium difficile infection, Conjunctivitis bacterial, Cystitis Escherichia, Helicobacter gastritis, Helicobacter infection, and Staphylococcal infection

<sup>m</sup> Preferred Terms = Eosinophilia and Eosinophil count increased

### Adverse Events Occurring Within One Day of Inotersen Administration

The most frequent treatment-emergent constitutional symptom AEs occurring within 1 day of inotersen administration are listed in the table below. There appear to be multiple mechanisms for these adverse events. These symptoms can be related to the known ability of antisense oligonucleotides to stimulate the innate immune system, including release of inflammatory cytokines.<sup>36</sup> In 7 of 161 (4%) Study CS2 and CS3 subjects, hypersensitivity adverse events occurring within 1 day of inotersen administration were associated with antibodies to inotersen and caused discontinuation of treatment (see Section 8.4.3).

**Table 17. Most Frequent Treatment-Emergent Constitutional Symptom Adverse Events Occurring within 1 day of Inotersen Administration. All Inotersen Subjects.**

Preferred Term	Subjects (%) N=161	Time from Prior Inotersen Dose to Adverse Event Start Time (hours) Median (Range) *	Number of Subjects with Non-Missing Dose and AE Times
Nausea	39 (24%)	1.2 (0-17.8)	12
Chills	33 (21%)	1.3 (0-17.5)	26
Fatigue	31 (19%)	1.8 (0.1 – 20.5)	14
Diarrhea	28 (17%)	1.3 (0.5 – 2.1)	2
Headache	28 (17%)	4.1 (1.0 – 23.5)	9
Myalgia	25 (16%)	3.5 (0.1 – 21.6)	12

\* Median and range times based on subjects with non-missing dose and adverse event times

*Reviewer comment: In clinical studies, use of premedication to prevent post-administration symptoms was not systematically studied. It is not known whether any premedication may reduce the frequency of constitutional symptoms after administration of inotersen.*

### Injection site reactions

In Study CS2, injection site reactions occurred in 49% of inotersen subjects, compared to 10% of placebo subjects and included bruising, erythema, hematoma, haemorrhage, induration, inflammation, mass, oedema, pain, pruritus, rash, reaction, swelling, and urticaria. All of the adverse events at the injection site were categorized as mild or moderate in severity. One subject (Study CS2 Subject (b) (6)) discontinued treatment because of itching at the injection site. Injection site reactions were more common in subjects who had a positive anti-inotersen antibody test (see Section 8.4.10).

<sup>36</sup> P. 2 applicant submission to NDA 211172 on April 23, 2018.

#### 8.4.6. Laboratory Findings

##### Inflammatory Markers and Cytokines

*Reviewer comment: In Studies CS1 and CS2, measurements of inflammatory markers were performed pre-treatment or on non-treatment days. The timing of these measurements may not have captured the peak levels of inflammatory markers. Peak inotersen plasma levels were observed within a few hours after dosing (median  $T_{max}$  ranging from 1.5 to 4 hours). The timing of constitutional symptoms after inotersen administration frequently coincided with the estimated time of peak plasma levels. Mean inotersen plasma concentrations decreased greater than 90% from the  $C_{max}$  by 24 hours after subcutaneous injections.<sup>37</sup>*

Increases in cytokines and markers of inflammation mainly occurred within 2 days of the first inotersen dose. In the healthy volunteer study CS1 on Study Day 2, inotersen subjects had higher mean levels of interleukin-6 (IL-6)<sup>38</sup> and monocyte chemotactic protein-1 (MCP-1)<sup>39</sup> compared to placebo subjects. On subsequent Study Days, there were no significant differences in mean IL-6 and MCP-1 levels between the 2 subject groups.

In Study CS2, high-sensitivity C-reactive protein (hsCRP) was the only inflammatory marker measured. Inotersen subjects had higher mean levels of hsCRP compared to placebo subjects on Week 1 Days 3 and 5. On subsequent Study Days, there were no significant differences in mean hsCRP levels between the 2 subject groups (see table below).

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<sup>37</sup> Study CS1 pharmacokinetic study results. P. 20-21 Summary of Clinical Pharmacology

<sup>38</sup> Mean change from baseline at Study Day 2 in IL-6 was 22.4 (range -1.2 to 357.4) pg/mL, compared to 1.3 (range -1.7 to 5.2) pg/mL in placebo subjects. (P.17 August 17, 2018 submission to NDA 211172).

<sup>39</sup> Mean change from baseline at Study Day 2 in MCP-1 was 264.8 (range -119.7 to 3270.5) compared to -64.8 (range -228.9 to -1.5). (P.17 August 17, 2018 submission to NDA 211172).

**Table 18. High-Sensitivity C-Reactive Protein levels in Study CS2 Stratified by Treatment Group**

	Placebo (N=60)	Inotersen 300 mg (N=112)
<b>Baseline</b>		
Mean (Std)	4.1 (11.0)	3.6 (11.2)
Min - Max	0.2 - 64.6	0.2 - 105.0
<b>Change from Baseline at Week 1 Day 3</b>		
Mean (Std)	-0.1 (6.6)	57.9 (51.4)
Min - Max	-41.3 - 17.0	-6.4 - 228.0
<b>Change from Baseline at Week 1 Day 5</b>		
Mean (Std)	-1.5 (9.4)	35.7 (29.3)
Min - Max	-57.4 - 7.1	-19.5 - 115.6
<b>Change from Baseline at Week 3</b>		
Mean (Std)	-2.4 (10.9)	1.4 (22.5)
Min - Max	-64.0 - 6.8	-96.5 - 200.6
<b>Change from Baseline at Week 5</b>		
Mean (Std)	-0.2 (12.3)	-0.2 (11.3)
Min - Max	-64.4 - 45.1	-77.4 - 52.4
<b>Change from Baseline at Week 8</b>		
Mean (Std)	-0.8 (9.5)	0.8 (10.6)
Min - Max	-64.4 - 19.7	-38.1 - 79.5
<b>Change from Baseline at Week 13</b>		
Mean (Std)	-1.26 (8.7)	-0.19 (13.6)
Min - Max	-64.4 - 5.2	-103.9 - 47.3
<b>Change from Baseline at Week 35</b>		
Mean (Std)	0.5 (18.5)	-0.5 (11.1)
Min - Max	-64.4 - 116.4	-76.5 - 37.1
<b>Change from Baseline at Week 65</b>		
Mean (Std)	-1.0 (11.0)	0.0 (14.5)
Min - Max	-63.5 - 32.6	-102.0 - 69.1
<b>Change from Baseline at Follow-Up Week 6</b>		
Mean (Std)	-3.2 (7.4)	2.0 (10.5)
Min - Max	-22.5 - 0.8	-12.4 - 29.3
<b>Change from Baseline at Follow-Up Week 26</b>		
Mean (Std)	-7.1 (12.3)	-1.9 (5.4)
Min - Max	-21.2 - 0.6	-11.4 - 1.7

Std = standard deviation

Min = minimum

Max = maximum

High-sensitivity c-reactive protein reference range: 0.0-3.0 mg/L

Source: August 17, 2018 submission to NDA 211172

## Chemistry

Changes in renal and liver chemistry parameters are discussed in Sections 8.5.2 and 8.5.4, respectively.

In Study CS2, shift changes in calcium, glucose, potassium, magnesium were similar in inotersen and placebo groups.<sup>40</sup> The frequency of hypernatremia was similar in inotersen and placebo groups. However, 7 of 112 (6.3%) inotersen subjects had Grade 3-4 hyponatremia with serum sodium levels ranging from 117-129 meq/L, compared to 0 of 60 placebo subjects (normal range 134-144 meq/L).<sup>41</sup> The cases of hyponatremia were associated with renal disease or cardiac disease.

Grade 2-3 hypophosphatemia (phosphate 1 to <2.5 mg/dL) occurred in 8 of 112 (7.2%) inotersen subjects, compared to 0 of 60 placebo subjects.<sup>42</sup>

*Reviewer comment: Hypophosphatemia in inotersen subjects generally occurred with renal disease.*

## Hematology

Changes in platelet count are discussed in Section 8.5.1.

Fourteen of 116 (12.6%) had Grade 2-3 anemia with hemoglobin levels ranging from 7.3 to < 10 g/dL,<sup>43</sup> compared to 1 of 60 (1.7%) placebo subjects.

*Reviewer comment: Etiologies contributing to the increased frequency of anemia in inotersen subjects include thrombocytopenia, an increased frequency of adverse events in the Haemorrhages SMQ (see Section 8.5.6), renal disease, and the acute phase response in the setting of increased inflammation. This reviewer plans to include anemia in the prescribing information table of common adverse events.*

Increase in B lymphocyte levels were seen in Study CS2.<sup>44</sup> Inotersen subjects had increases in IgG and IgM concentrations greater than the upper limit of normal at any time post-baseline more frequently (20.6% and 44.4%, respectively) than placebo subjects (7.7% and 0%, respectively).<sup>45</sup>

### 8.4.7. Vital Signs

The incidence of post-baseline abnormality in vital signs and body weight in Study CS2, stratified by treatment group, is displayed in the table below. A larger percentage of inotersen subjects (25.9%) had a systolic blood pressure measurement <90 mm Hg, compared to placebo subjects (11.7%). A larger percentage of inotersen subjects (12.5%) had a diastolic blood pressure measurement <50 mm Hg, compared to placebo subjects (8.3%). Inotersen subjects also had a higher frequency of syncope or

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<sup>40</sup> Integrated Summary of Safety Table 2.47 (P.2409-2460)

<sup>41</sup> Integrated Summary of Safety Table 2.47 (P.2439-2440)

<sup>42</sup> Integrated Summary of Safety Table 2.47 (P.2446-2447)

<sup>43</sup> Normal range adult male 13.6 – 18.0 mg/dL; normal range adult female 12.0 – 16.0 mg/dL

<sup>44</sup> P. 22 420915-CR02 Study Report

<sup>45</sup> Study CS2 Clinical Study Report Table 4.40

presyncope adverse events in inotersen subjects (13%) compared to placebo (5%) (see Section 8.4.5.). Findings for other vital sign parameters do not indicate an adverse effect with inotersen.

**Table 19. Incidence of Post-Baseline Abnormality of Vital Signs and Body Weight. Study CS2 Safety Set**

Vital Signs and Body Weight	Category	Placebo (CS2) (N=60)	ISIS 420915 300 mg (CS2) (N=112)
Systolic Blood Pressure (mmHg)	n	60	112
	<90 mmHg	10 ( 16.7%)	29 ( 25.9%)
	>140 mmHg	30 ( 50.0%)	56 ( 50.0%)
	>160 mmHg	7 ( 11.7%)	12 ( 10.7%)
Diastolic Blood Pressure (mmHg)	n	60	112
	<50 mmHg	5 ( 8.3%)	14 ( 12.5%)
	>90 mmHg	27 ( 45.0%)	40 ( 35.7%)
	>100 mmHg	8 ( 13.3%)	10 ( 8.9%)
Pulse Rate (bpm)	n	60	112
	<60 bpm	22 ( 36.7%)	36 ( 32.1%)
	>100 bpm	13 ( 21.7%)	17 ( 15.2%)
Body Weight	n	59	110
	Decrease >=7.0% from Baseline	18 ( 30.0%)	22 ( 19.6%)
	Increase >=7.0% from Baseline	8 ( 13.3%)	15 ( 13.4%)
Temperature (°C)	n	60	112
	<36.0°C	40 ( 66.7%)	77 ( 68.8%)
	>38.0°C	0	1 ( 0.9%)
Respiratory Rate (breaths/min)	n	60	112
	<12 breaths/min	5 ( 8.3%)	7 ( 6.3%)
	>20 breaths/min	18 ( 30.0%)	30 ( 26.8%)

Source: P.2471-2471 Integrated Summary of Safety (Applicant Table 2.52)  
 ISIS 420915 = inotersen

### 8.4.8. Electrocardiograms (ECGs)

**This review section is provided by Dr. Christopher Breder.**

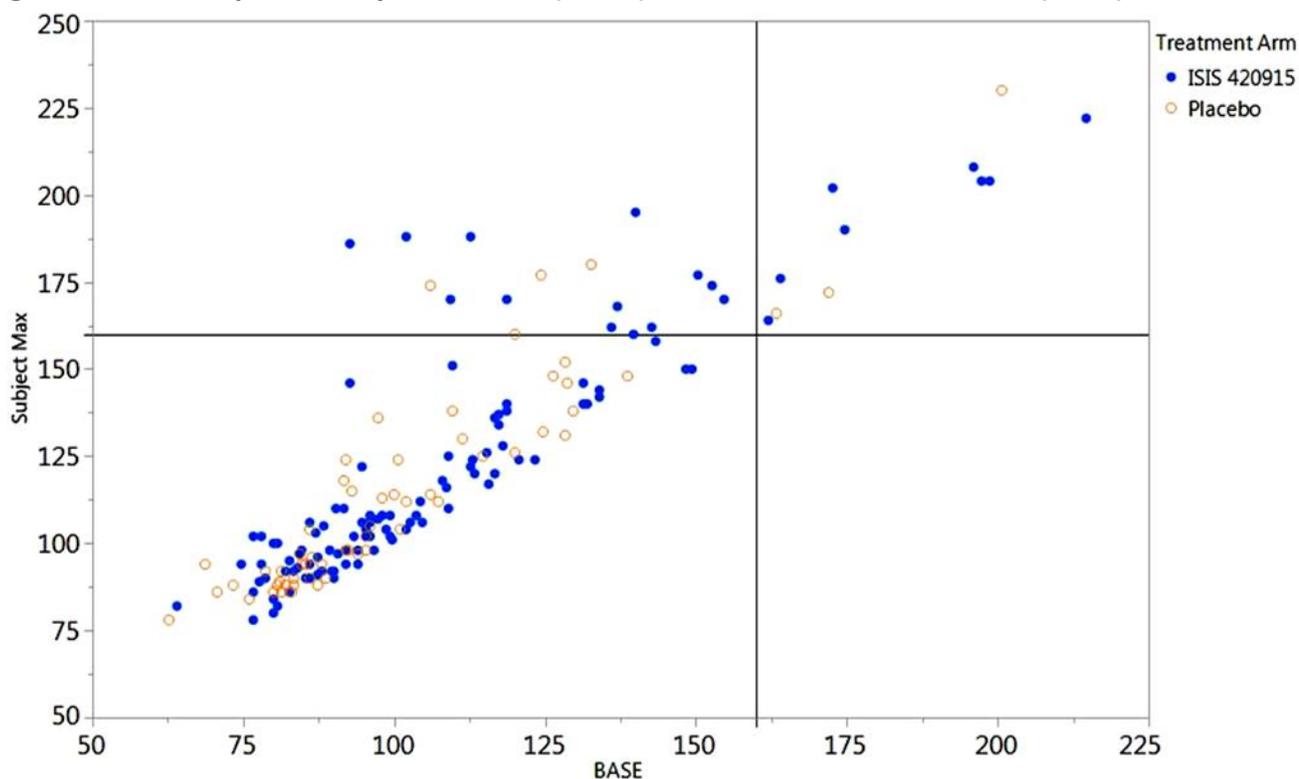
#### Screening the Electrocardiogram Database for Interval Changes

EKG intervals were screened for imbalances by treatment. For an initial screen, and in collaboration with the QT-IRT team, it was determined that there was an imbalance in patients with QRS widening, defined as a mean (by visit and time point) of greater than 160 msec and an increase of 25% from baseline. Six (5.4%) of INO patients and 1 (1.7%) PBO patients fulfilled these criteria for increased QRS duration.

Following this analysis, 16 patients with a median (by visit) QRS duration greater than or equal to 160 msec at baseline or screening were excluded from analysis [Eleven (9.8%) of INO patients and 5 (10%) PBO patients]. The remaining population included 101 INO patients and 55 PBO patients (ratio of 65/35). Eleven (11%) INO subjects and 3 (5.5%) of PBO patients in the remaining dataset had a QRS duration in any EKG on treatment greater than or equal to 160 msec. Eight (7.9 %) INO subjects and 2 (3.6%) of PBO patients had a median (by visit) QRS duration on treatment greater than or equal to 160 msec. Five (5 %) INO patients and 0 (0%) PBO patients had a greater than 50% increase in the median QRS duration. Four (4%) INO and 0 (0%) patients had both a median QRS duration on treatment greater than or equal to 160 msec and greater than 50% increase in the median QRS duration.

A scatterplot (see figure below) of the individual baseline versus the maximum values were also produced from the original EKG dataset (prior to removing patients with baseline QRS  $\geq$  160).

**Figure 1. A Scatterplot of Subject Baseline (x-axis) and Maximum QRS duration (msec)**



Reference lines are placed at 160 msec. Values in the upper left quadrant, where the yellow arrow is placed, are those where QRS has been prolonged from below the threshold value to above. Randomization to ISI 420915 and Placebo was in a 2:1 ratio.

**Medical Officer’s comments (Dr. Christopher Breder)** – These analyses demonstrate a treatment-related change in QRS duration (QRSd). Methodology for analysis of the QRSd are not so universally accepted as those for QTcF prolongation, which is described in guidance. Of the standard intervals collected in EKGs, changes in the QRS show the greatest association with decreased left ventricular systolic and diastolic function, and eventually to increased mortality [1]. According to a study by Desai, et al “... after adjustment in the Cox model for age, gender, and heart rate, the QRS duration score was a strong

independent predictor of cardiovascular mortality. For every 10-ms increase in QRS duration, there was an 18% increase in cardiovascular risk.” [2] With respect to the threshold of 160 msec, Hofmann et al., write that “...Kaplan-Meier plots show significantly different survival rates for patients with QRSd < 120 ms, QRSd 120–159 ms, or QRSd ≥160 ms (P = 0.0085). Multivariate analysis showed that QRSd was the only independent risk factor for all-cause mortality (P=0.008).” [3] In a trial in 58 patients with dilated cardiomyopathy, (80%) of patients with a QRS duration of > 160 ms (n = 10) compared with 13% in the remaining patients [4]. Outcomes are worse when the patient has a pre-existing diagnosis of heart failure or atrial fibrillation, as was the case in the CS2 study [5]. The exact threshold of significance for a change from baseline is not clear; however, considering the findings of Desai described above, a 50% change from baseline and a median QRSd ≥160 msec in patients starting below that value would be considered very meaningful.

There are limitations to these data. There was a high degree of variability in the EKGs. The median value for each day of assessments was used, rather than the mean, to minimize the bias from this source. Those with values above the 160 msec threshold at screening or baseline were removed from the final analysis, yet the results after removing patients with a QRSd ≥160 msec are consistent with analyses using the uncensored database.

The literature suggests the effect of prolonged QRS on mortality and ventricular function is more pronounced in the elderly and those with more severe heart disease. Patients with this disease are likely to have preexisting heart disease.

The sample size is limited, the finding was derived from a study not designed to test this hypothesis, and the background cardiac disease in hATTR amyloidosis patients all complicate the interpretation of these analyses. However, the data appear to suggest an association with inotersen treatment and QRS prolongation in Study CS2. Therefore, this finding should be descriptively presented in the product labeling.

#### References for Section 8.4.8:

1. Shamim, W., et al., Incremental changes in QRS duration in serial ECGs over time identify high risk elderly patients with heart failure. *Heart*, 2002. 88(1): p. 47-51.
2. Desai, A.D., et al., Prognostic Significance of Quantitative QRS Duration. *Am J Med*, 2006. 119(7): p. 600-6.
3. Hofmann, M., et al., Prognostic value of the QRS duration in patients with heart failure: a subgroup analysis from 24 centers of Val-HeFT. *J Card Fail*, 2005. 11(7): p. 523-8.
4. Xiao, H.B., et al., Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. *Int J Cardiol*, 1996. 53(2): p. 163-70.
5. Whitbeck, M.G., et al., QRS duration predicts death and hospitalization among patients with atrial fibrillation irrespective of heart failure: evidence from the AFFIRM study. *Europace*, 2014. 16(6): p. 803-11.

#### 8.4.9. QT

Drs. Christine Garnett and Lars Johannesen in their QT interdisciplinary review team (QT-IRT) consult review dated January 26, 2018 noted that the ECG data in CS2 were highly variable and difficult to interpret, citing an example of subject (b) (6) who had time points where QTc measurement varied more than 100 milliseconds (ms) within a triplicate measurement. Drs. Garnett and Johannesen suggested that ECG data collected in Study 420915-CS1 be reported in the label. In that study (n=14 for placebo, and n=51 or inotersen with doses from 50 mg to 400 mg), no increase in PR > 25% or new PR values > 250 ms and no increase in QRS > 25% or new PR > 100 ms were observed for either inotersen or placebo.

#### 8.4.10. Immunogenicity

**This review section is provided by Dr. Christopher Breder.**

A consult was provided by the Office of Biotechnology Products / Division of Biotechnology Review concluded 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. The assay can detect IgG predominantly. 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 (<1 month) of ADA is important in the evaluation. They also noted that the ADA assay is relatively sensitive, 6.28 ng/mL meeting the Guidance recommendation, so the ADA titer should be used to stratify patients when analyzing the ADA impact on safety and efficacy.

Antibodies to inotersen (INO) were formed in 30.4% of the patients with hATTR treated with inotersen in CS2 and the immunogenicity (IM) was characterized by a late onset (median onset 202.5 days) and low antibody titers (median peak titer 300). No consistent trend between duration of INO exposure or dose level and IM incidence was identified from the available data. ADA were generally sustained once formed, which was approximately 7 months post-initiation of treatment.

Plasma inotersen concentration-time profiles in the first 24 hours after dose administration were reported to be similar between ADA-negative (ADA-) and ADA-positive (ADA+) subjects on all examined days (Days 1, 240, and 449), suggesting ADA had a minimal effect on peak (C<sub>max</sub>) and total (AUC) plasma exposures.

Comparisons of the immunogenicity in relation to the adverse events, or tolerability, were performed by the Medical Reviewer using the CS2, placebo-controlled study database. There were 110 patients on INO (33 ADA+ / 77 ADA-) and 59 treated with placebo, who were determined NOT to be ADA+ at baseline, with only two patients who were ADA+ at baseline (b) (6) and one patient (b) (6) with an unknown ADA status; these three were not included in the calculations. Calculating the incidence of AEs by ADA status revealed several AEs occurring with a higher frequency (defined as ADA+ ≥10% ADA-) in the ADA+ population (see table below).

**Table 20. Adverse Events with an Incidence for ADA+ that was 10% greater than that in ADA- Patients (CS2 Population; ADA- at baseline)**

Preferred Term	N Pts	N (%) ADA+	N (%) ADA-	RR, %ADA+ / %ADA-	ADA+ minus ADA-
Fatigue	46	13 (39)	21 (15)	2.6	24
Injection site erythema	35	12 (36)	23 (17)	2.2	20
Presyncope	6	6 (18)	0 (0.4)	50	18
Myalgia	26	8 (24)	12 (8.8)	2.8	15
Influenza like illness	12	6 (18)	4 (2.9)	6.2	15
Syncope	12	6 (18)	4 (2.9)	6.2	15
Headache	35	9 (27)	18 (13)	2.1	14
Decreased appetite	12	6 (18)	6 (4.4)	4.2	14
Dyspnoea	14	6 (18)	6 (4.4)	4.2	14
Chills	24	7 (21)	14 (10)	2.1	11
Migraine	8	4 (12)	2 (1.5)	8.3	11
Nausea	46	10 (30)	27 (20)	1.5	11
Constipation	24	6 (18)	11 (8)	2.3	10
Vomiting	21	6 (18)	11 (8)	2.3	10

Abbreviations = ADA – antidrug antibody status on treatment, N – number of patients, RR – relative risk

CS3 Open-Label Extension Study

Seventy-four (74) patients who had been treated with INO in CS2 and 40 who had been treated with placebo were included in the immunogenicity analysis using the CS3 databases supplied by the applicant. Subject 420915-CS2/ (b) (6), whose ADA status was positive prior to CS2, participated in CS3 and was excluded from the analyses. The number of patients with a known ADA status is listed in **Error! Reference source not found.**1 by treatment.

**Table 21. Patient ADA status in the CS3 Open Label Study by Treatment in the CS2 study**

Treatment	ADA Status	N Pts
ISIS 420915	NEGATIVE	35
ISIS 420915	POSITIVE	31
Placebo	NEGATIVE	25 <sup>46</sup>
Placebo	POSITIVE	10

<sup>46</sup> excludes patient (b) (6) who was ADA+ before the CS2 study

Several AEs associated with INO treatment persist into the open label extension period (e.g., fatigue and various injection site reactions) or evolve later in that period of treatment (e.g., rash) (Table 22).

**Table 22. Adverse Events with an Incidence for ADA+ that was 10% Greater than that in ADA- in Patients Treated with Inotersen in the CS2 Trial (CS3 Population ADA- at CS2 baseline)**

Preferred Term	N, PTs	CS2 Inotersen-treated		
		N, %, ADA+	N, %, ADA-	CS3 ADA+ minus ADA-
Fatigue	21	11 (35)	5 (14)	21
Hypoaesthesia	6	5 (16)	0 (1)	15
Injection site erythema	12	7 (23)	3 (9)	14
Retching	5	4 (13)	0 (1)	11
Rash	6	4 (13)	0 (1)	11
Injection site bruising	6	4 (13)	0 (1)	11
Injection site pain	11	4 (13)	1 (3)	10

Table 23 lists AEs that emerge in the CS3 open label extension in patients previously treated with PBO; these are largely consistent with the AEs seen in INO-treated patients from the CS2 trial (Table 20).

**Table 23. Adverse Events with an Incidence for ADA+ that was 10% Greater than that in ADA- in Patients Treated with Placebo in the CS2 Trial (CS3 Population ADA- at CS2 baseline)**

Preferred Term	N Pts	N, %, ADA+	N, %, ADA-	ADA+ minus ADA-
Diarrhoea	19	7 (70)	4 (16)	54
Nausea	21	4 (40)	2 (8)	32
Myalgia	11	4 (40)	3 (12)	28
Chills	13	3 (30)	0 (2)	28
Syncope	10	3 (30)	0 (2)	28
Injection site rash	7	3 (30)	1 (4)	26
Fatigue	21	3 (30)	2 (8)	22
Injection site erythema	12	2 (20)	0 (2)	18
Injection site pain	11	3 (30)	3 (12)	18
Injection site swelling	4	2 (20)	0 (2)	18
Weight decreased	6	2 (20)	0 (2)	18
Blood creatinine increased	2	2 (20)	0 (2)	18
Laceration	2	2 (20)	0 (2)	18
Sciatica	2	2 (20)	0 (2)	18
Headache	7	2 (20)	1 (4)	16
Cough	7	2 (20)	1 (4)	16
Oedema peripheral	17	3 (30)	4 (16)	14
Fall	10	3 (30)	4 (16)	14
Vomiting	9	2 (20)	2 (8)	12
Thrombocytopenia	16	3 (30)	5 (20)	10

**Medical Reviewer comments (Dr. Christopher Breder):** Most AEs are notably more prevalent in ADA+ than ADA- patients (Tables 20, 22, and 23); a typical result for studies where the drug results in the generation of ADAs. The difference between ADA+ and – of  $\geq 10\%$  strengthens the plausibility of an association of the reported AEs and ADA status. Although the sample size is relatively small, the occurrence of a few severe AEs and more substantial numbers of moderate AEs supports a general reference to this information in labeling.

## 8.5. Analysis of Submission-Specific Safety Issues

### 8.5.1. Thrombocytopenia

Inotersen causes reductions in platelet count that can result in serious or life-threatening bleeding. The frequency of reduced platelet counts in Studies CS2 and CS3 is summarized in the table below.

**Table 24. Subjects with decreased platelet measurements (central and local laboratory values). Studies CS2 and CS3.**

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

Platelet measurement normal range:  $140 - 400 \times 10^9/L$

Nadir platelet counts in 4 subjects were consistent with laboratory errors and were corrected for the analyses in this table.<sup>47</sup> Data through Safety Update Report cut-off date, September 15, 2017.

Sources: Responses to FDA information requests submitted to NDA 211172 on March 12, 2018 and March 16, 2018.

<sup>47</sup> - Study CS2 inotersen-treated subject (b) (6) had a single platelet measurement of  $5 \times 10^9/L$ , for which the subject received no treatment. A repeat platelet count measured on the same day was  $109 \times 10^9/L$ . The subject's nadir platelet count, measured 4 months later, was  $98 \times 10^9/L$ . (Baseline platelet count was  $185 \times 10^9/L$ .)

- Study CS2 placebo-treated subject (b) (6) had a nadir platelet count of  $69 \times 10^9/L$ , which was occurred in the setting of platelet clumping and was not interpretable. This subject had a total of 5 platelet counts that were not interpretable because of a clumped sample. No antiplatelet antibody testing was performed in this subject. The subject's nadir platelet count, using interpretable blood samples, was  $140 \times 10^9/L$  (Narrative Study CS2 CSR p. 3496).

- Study CS3 Subject (b) (6) had a nadir platelet measurement of  $15 \times 10^9/L$ , which occurred in the setting of a hemolyzed sample. The subject's actual nadir platelet count was  $40 \times 10^9/L$ .

- Study CS3 Subject (b) (6) had a single platelet count of  $62 \times 10^9/L$ , which was likely a laboratory error. Two days later the subject's platelet count was  $176 \times 10^9/L$ , and all other platelet counts were normal.

In Study CS2, platelet counts  $<100 \times 10^9/L$  occurred in 28 of 112 (25.0%) of inotersen subjects, compared with 1 of 60 (1.7%) of placebo patients. Platelet counts  $<75 \times 10^9/L$  (the level below which primary hemostasis is generally considered to be impaired)<sup>48</sup> occurred in 16 of 112 (14.3%) inotersen subjects, compared to 0 placebo subjects. Three (2.7%) inotersen subjects had severe thrombocytopenia ( $<25 \times 10^9/L$ ), which can have potentially fatal bleeding complications, including spontaneous intracranial or intrapulmonary hemorrhage.

**Description of clinical cases**

Inotersen subjects with thrombocytopenia had a range of clinical presentations, which encompassed both types of thrombocytopenia described in the table below.

**Table 25. Thrombocytopenia with inotersen<sup>49</sup>**

Type	Thrombocytopenia	Clinical Manifestations
Rare	<ul style="list-style-type: none"> <li>• Rapid onset</li> <li>• Severe</li> </ul>	<ul style="list-style-type: none"> <li>• Catastrophic, fatal bleeding can occur</li> <li>• May present with mild or moderate bleeding</li> </ul>
Common	<ul style="list-style-type: none"> <li>• Gradual and slow decline</li> <li>• Often mild; can be moderate or severe</li> </ul>	<ul style="list-style-type: none"> <li>• Asymptomatic or can have bleeding (mild to severe)</li> </ul>

Clinical summaries for the 3 subjects<sup>50</sup> who experienced severe thrombocytopenia ( $<25 \times 10^9/L$ ) in the inotersen clinical development program are presented below. These subjects had an onset of thrombocytopenia that was precipitous and unpredictable, with normal platelet counts immediately prior to the nadir platelet counts. One subject died from intracranial hemorrhage, and the other two subjects improved with cessation of inotersen and corticosteroid treatment.

<sup>48</sup> Guidelines for the use of platelet transfusions. British Committee for Standards in Haematology, Blood Transfusion Task Force. *Br J Haematol.* 2003 Jul;122(1):10-23.

<sup>49</sup> Table based on a summary table of thrombocytopenia in antisense oligonucleotides (ASOs) by Qin Ryan, MD (FDA Division of Hematology Products)

<sup>50</sup> Subjects [REDACTED] (b) (6)

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 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  $<10 \times 10^9/L$ , 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.)

Reviewer comment: In the original Study CS2 protocol, platelet measurements were generally scheduled 2-6 weeks apart<sup>51</sup>. After this fatal event, the Study CS2 and CS3 protocols were amended to include weekly platelet measurements.

Figure 2. Subject (b) (6). Summary of Events.<sup>52</sup>

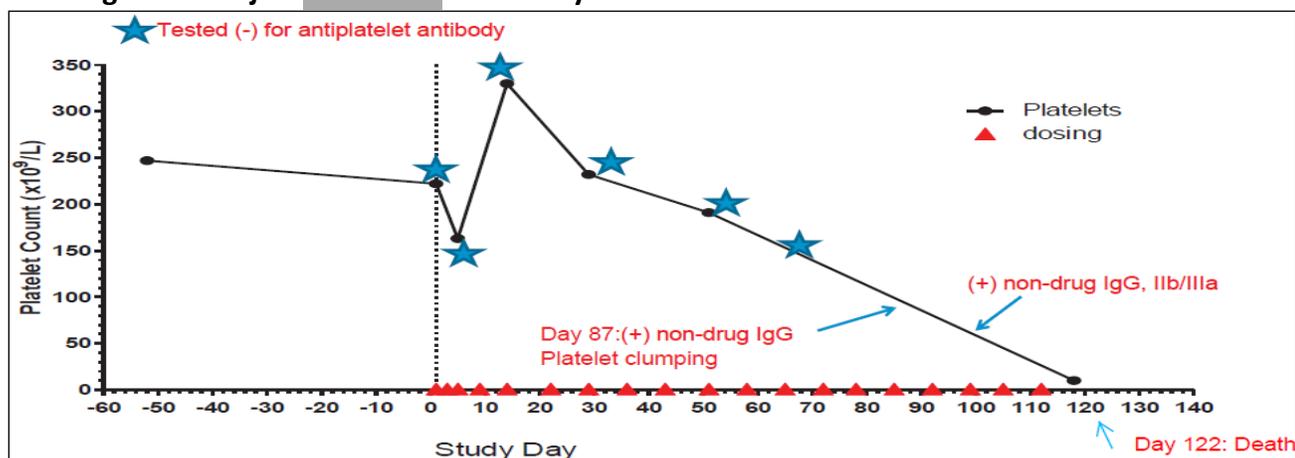


Table 26. Subject (b) (6) Platelet counts.<sup>53</sup>

Date (Study Day)	On/Off Inotersen	Platelet count (NR 140-400 x10 <sup>9</sup> /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

<sup>51</sup> Summary of platelet count rule changes. December 15, 2017 submission to NDA 211172.

<sup>52</sup> P. 1066 Sponsor response to FDA pre-submission safety requests. Module 1 November 6, 2017 NDA 211172.

<sup>53</sup> Narrative p. 3758 Study CS2 Clinical Study Report. Module 5 November 6, 2017 submission to NDA 211172.

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  $9 \times 10^9/L$ , 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.”<sup>54</sup> 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.

*Reviewer comment: This subject reported symptoms of thrombocytopenia before the low platelet count was identified with scheduled platelet measurements. If an inotersen-treated patient develops signs or symptoms of thrombocytopenia, platelet count should be measured as soon as possible, and inotersen dosing should be stopped until the platelet count is confirmed. Educating providers, patients, and caregivers on how to identify symptoms of thrombocytopenia will be an essential part of risk mitigation in the postmarketing setting.*

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<sup>54</sup> P. 21 420915-CR02 Study Report

Figure 3. Subject (b) (6). Summary of Events.<sup>55</sup>

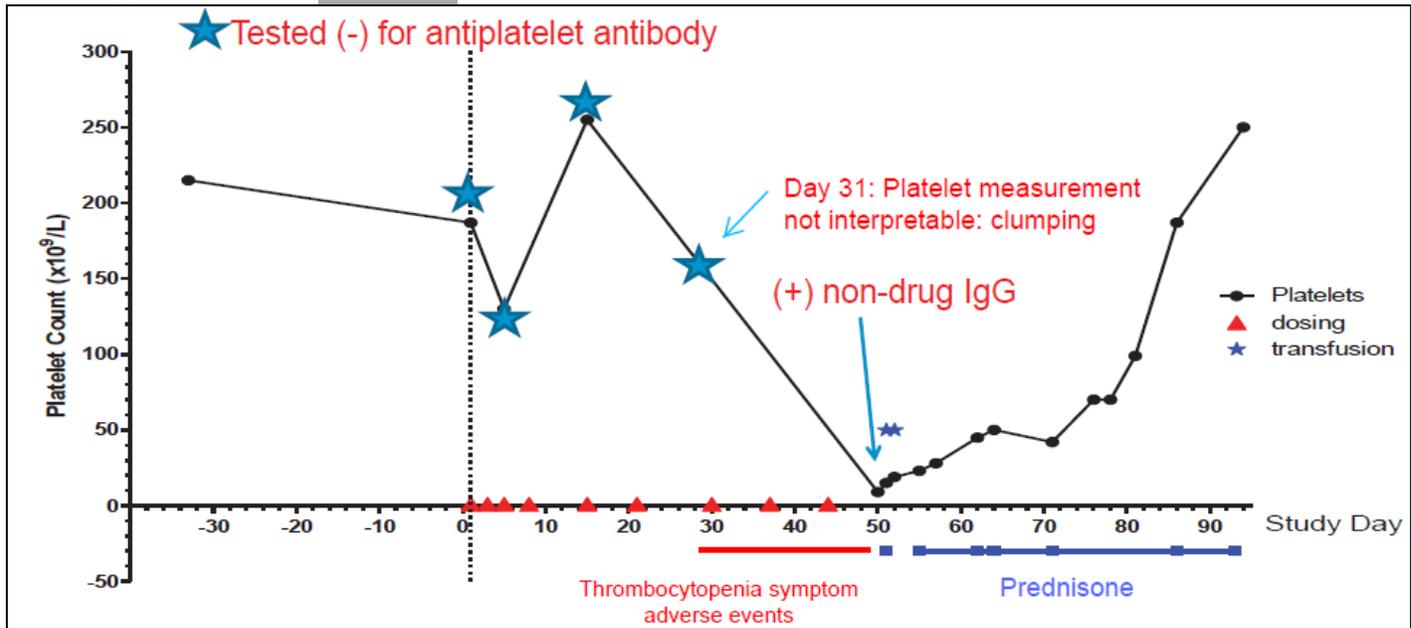


Table 27. Subject (b) (6). Summary of platelet counts and thrombocytopenia symptom adverse events.<sup>56</sup>

Date (Study Day)	On/Off Inotersen	Platelet count (NR 140-400 x10 <sup>9</sup> /L) Adverse events
(b) (6)	Off	215
(b) (6)	Off	187
(b) (6)	On	130
(b) (6)	On	255
(b) (6)	On	Heavy menstruation
(b) (6)	On	Lower limb hematomas
(b) (6)	On	Platelet count uninterpretable: clumping
(b) (6)	On	Hematoma finger left hand
(b) (6)	On	Gingival bleeding
(b) (6)	Off	9
(b) (6)	Off	24
(b) (6)	Off	66
(b) (6)	Off	42
(b) (6)	Off	72
(b) (6)	Off	187
(b) (6)	Off	250
(b) (6)	Off	227

NR = Normal range

<sup>55</sup> P. 1065 Sponsor response to FDA pre-submission safety requests. Module 1 November 6, 2017 NDA 211172.

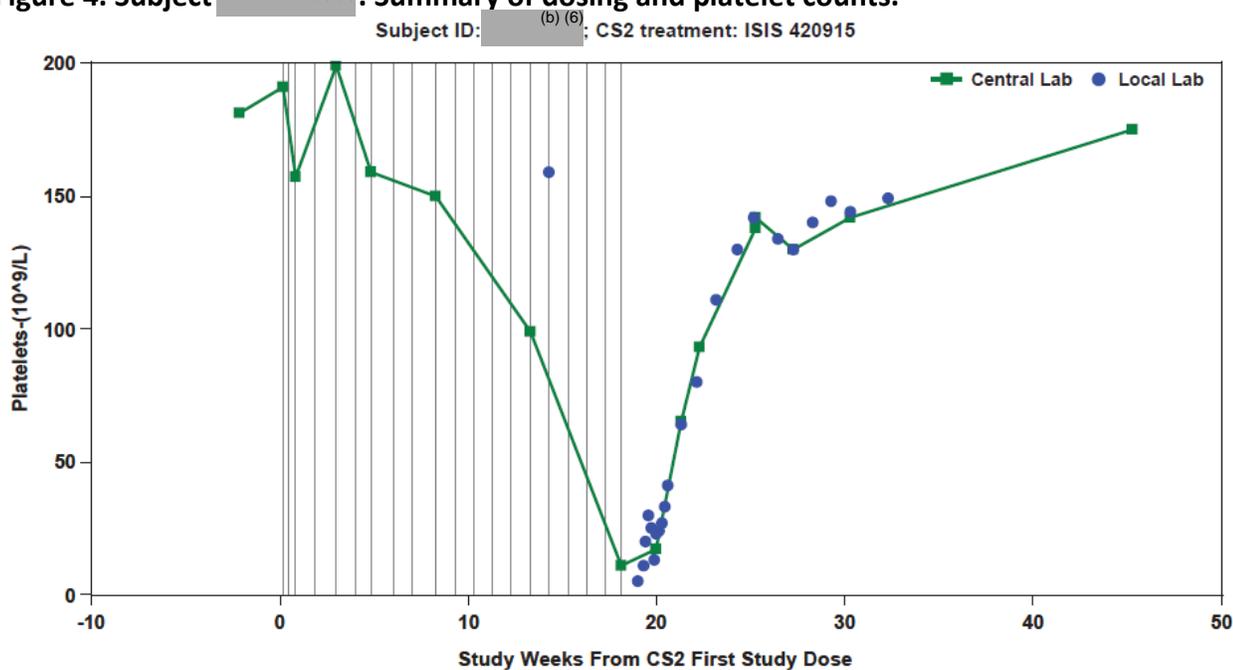
<sup>56</sup> Narrative p. 3748-3749 Study CS2 Clinical Study Report. Module 5 November 6, 2017 submission to NDA 211172.

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<sup>57</sup> (see graph and table below) until 4 months after the first dose of inotersen (Study Day 127), when he had a platelet count of  $11 \times 10^9/L$  and tested positive for IgG antiplatelet antibodies.<sup>58</sup> 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  $5 \times 10^9/L$ , and he was hospitalized. He was treated with intravenous methylprednisolone 1 g/day for 3 days, and his platelet count improved.

Reviewer comment: Like Subject (b) (6), this subject received an inotersen dose despite reporting a symptom of thrombocytopenia.

Figure 4. Subject (b) (6). Summary of dosing and platelet counts.<sup>59</sup>



Grey vertical lines represent the dosing records from CS2 study.

<sup>57</sup> On (b) (6) Study Day 93) the subject had a platelet count of  $99 \times 10^9/L$ , which was followed by a platelet count of  $159 \times 10^9/L$  1 week later.

<sup>58</sup> Antiplatelet antibody tests, performed at least monthly prior to Study Day 127, had been negative. Source: response to FDA information request submitted to NDA 211172 on February 12, 2018.

<sup>59</sup> ISS p. 2901

**Table 28. Subject (b) (6) Summary of dosing and platelet counts.<sup>60</sup>**

Date (Study Day)	On/Off Inotersen	Platelet count (NR 140-400 x10 <sup>9</sup> /L)
(b) (6)	Off	181
	Off	191
	On	157
	On	150
	On	99
	On	159
	On	11
	On	11 (NR not provided)
	On	10 (NR not provided)
	On	5 (NR 150-450)
	Off	11 (NR 150-450)
	Off	20 (NR 150-450)
	Off	30 (NR 150-450)
	Off	17
	Off	23 <sup>a</sup> (NR 150-450)
	Off	41 (NR 150-450)
	Off	65
	Off	64 <sup>a</sup> (NR 150-450)
	Off	93
	Off	111
	Off	142
	Off	142
	Off	138
Off	130	
Off	175	

<sup>a</sup> Local laboratory results

NR = Normal range

In contrast to the 3 subjects with platelet counts < 25 x 10<sup>9</sup>/L, some inotersen subjects had platelet declines that occurred over a longer time course (see the clinical course of Subjects (b) (6) and (b) (6) below). These subjects had nadir platelet levels ranging from mild to severe (as low as 29 x 10<sup>9</sup>/L). At the time of platelet nadir, Subject (b) (6) had a major bleeding event (hemoglobin decreased to 6.5 mg/dL, mental status change, and computed tomography (CT) scan findings of a possible intracerebral hemorrhage which resolved after dexamethasone treatment).

<sup>60</sup> Narrative p. 3809-3812 CS2 clinical study report.

Study CS2/CS3 Subject (b) (6)

At enrollment, this 61-year-old male from the United States had Stage 2 hATTR-PN. Platelet counts were normal at baseline and generally were normal in Study CS2.<sup>62</sup> In Study CS3 he had fluctuating and gradually decreasing platelet counts. He received his last inotersen dose on (b) (6), because the platelet count on that day was  $67 \times 10^9/L$ . Despite discontinuing dosing, his platelet count continued to decline (see table below). On (b) (6) the subject injured his right foot (abrasion and partial 1<sup>st</sup> toenail avulsion) and had bleeding that did not spontaneously stop. He was treated empirically with amoxicillin.

On (b) (6) the physician instructed the subject to go to the emergency room (ER) due to hematology laboratory results. On that day platelet count 29 (150-400 K/cu mm), hemoglobin 6.5 (13.75-17.5 g/dL), hematocrit 19.5 (41-53%), red blood cell count (RBC) 2.12 (4.50-6.0 M/cu mm), white blood cell count (WBC) 2.94 (3.50-10.80K/cu mm). This was the subject's nadir platelet count ( $29 \times 10^9/L$ ), which occurred 2 years and 2 months after his first inotersen dose (on Study Day 802).

In the ER, the subject did not report bleeding from his mucosa, hemoptysis, hematemesis or melena. The subject's wife reported that the subject had exhibited bizarre, manic behaviors, disorientation and some confusion for one week. Computed tomography (CT) of the head revealed a possible punctate left frontal lobe intraparenchymal hemorrhage, with no mass effect or midline shift. Treatment in the ER included one liter of normal saline and 10 mg Decadron (dexamethasone). No antiplatelet antibody testing was reported.

On (b) (6) treatment was started with dexamethasone 40 mg intravenous daily for 4 days, and he was transfused with one unit packed red blood cells. On (b) (6), a repeat CT of head revealed no acute intracranial abnormality, including no evidence of hemorrhage. The previously noted left frontal punctate hyperdensity was not identified; per the neuroradiologist, it may have resolved or represented artifact.

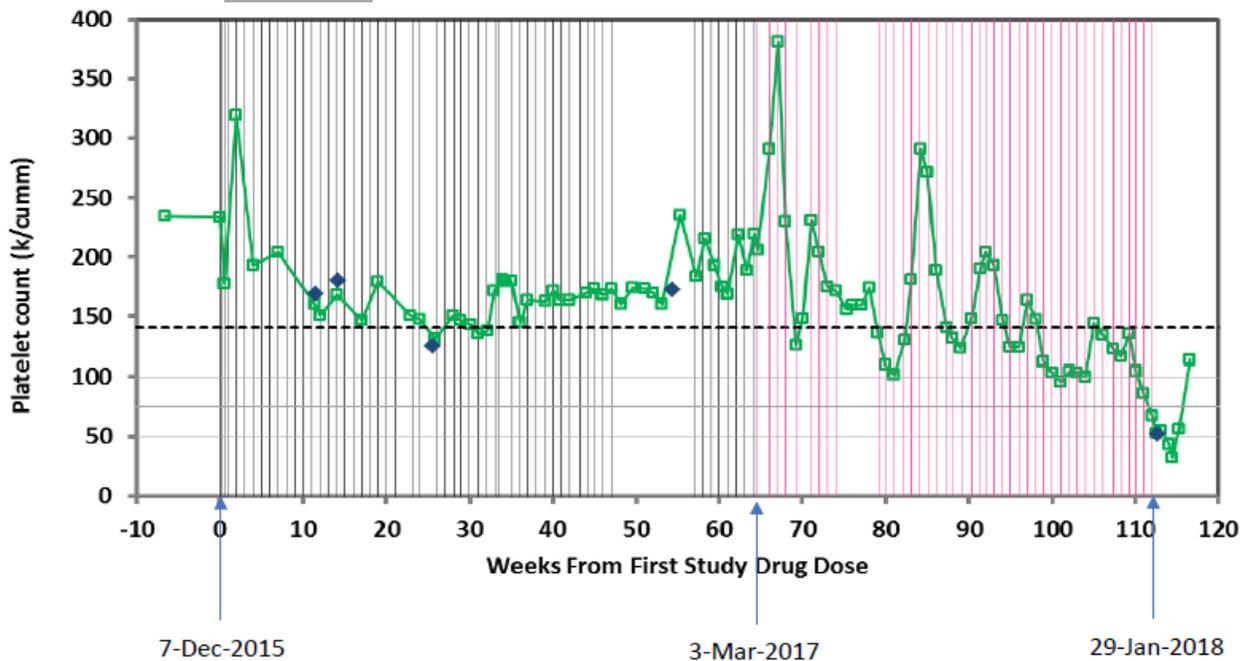
After treatment with dexamethasone and with continued cessation of inotersen dosing, the subject's platelet count improved to  $114 \times 10^9/L$  at the last reported measurement on (b) (6).

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<sup>61</sup> March 12, 2018 submission to NDA 211172. Serious bleeding in Subject (b) (6) was initially reported as part of the 120-day safety update report.

<sup>62</sup> Inotersen dosing was held during CS2 study weeks 49-57 because of decreased renal creatinine clearance in the setting of urinary retention and dehydration.

Figure 5. Subject (b) (6) Summary of dosing and platelet counts<sup>63</sup>



Grey and pink lines represent the dosing records from CS2 and CS3 studies, respectively.

<sup>63</sup> P. 27 March 12, 2018 submission to NDA 211172.

**Table 29. Subject (b) (6). Summary of dosing and hematology laboratory results.** (b) (6)

Study	Date	On/Off Inotersen (a)	Hemoglobin (g/dL) (RR 13.6-18.0)	Hematocrit (%) (RR 40-52)	WBC (10 <sup>3</sup> /uL) (RR 3.5-11.0)	Platelets (10 <sup>3</sup> /uL) (RR 140-400)
CS3	(b) (6)	On	11.0	34	4.1	100
CS3	(b) (6)	On	9.3	28	3.9	144
CS3	(b) (6)	On	9.5	29	3.6	134
CS3	(b) (6)	On	9.8	29	3.9	122
CS3	(b) (6)	On	9.6	29	4.4	116
CS3	(b) (6)	On	9.9	30	3.7	135
CS3	(b) (6)	On	9.3	28	3.2	104
CS3	(b) (6)	On	9.2	28	2.9	86
CS3	(b) (6)	On	8.9	27	2.9	67
CS3	(b) (6)	On	9.4	28	3.7	53
CS3	(b) (6)	On	n.d.	n.d.	n.d.	52 (RR 130-400)
CS3	(b) (6)	On	9.8	30	3.0	55
CS3	(b) (6)	Off	8.6	26	2.7	43
CS3	(b) (6)	Off	7.1	21.4		32
CS3	(b) (6)	Off	7.3	22	3.1	32
CS3	(b) (6)	Off	6.5 (RR 13.5-17.5)	19.5 (RR 41-53)	2.94 (RR 3.5-10.80)	29 (RR 150-400)
CS3	(b) (6)	Off	9.7 (RR 13.5-17.5)	29.1 (RR 41-53)	1.50 (RR 3.5-10.80)	31 (RR 150-400)
CS3	(b) (6)	Off	8.5 (RR 13.5-17.5)	25.1 (RR 41-53)	5.09 (RR 3.5-10.80)	40 (RR 150-400)
CS3	(b) (6)	Off	8.2	25	3.7	56
CS3	(b) (6)	Off	7.9 (RR 13.5-17.5)	23.2 (RR 41-53)	3.66 (RR 3.5-10.80)	50 (RR 150-400)
CS3	(b) (6)	Off	7.0 (RR 13.5-17.5)	20.6 (RR 41-53)	3.70 (RR 3.5-10.80)	75 (RR 150-400)
CS3	(b) (6)	Off	7.5 (RR 13.5-17.5)	22.3 (RR 41-53)	4.4 (RR 3.5-10.8)	79 (RR 150-400)
CS3	(b) (6)	Off	7.3	22	5.0	114
CS3	(b) (6)	Off	7.3 (RR 13.5-17.5)	22 (RR 41-53)	5.00 (RR 3.5-10.80)	114 (RR 150-400)

(a) Off inotersen is defined as ≥10 days from previous inotersen dose.

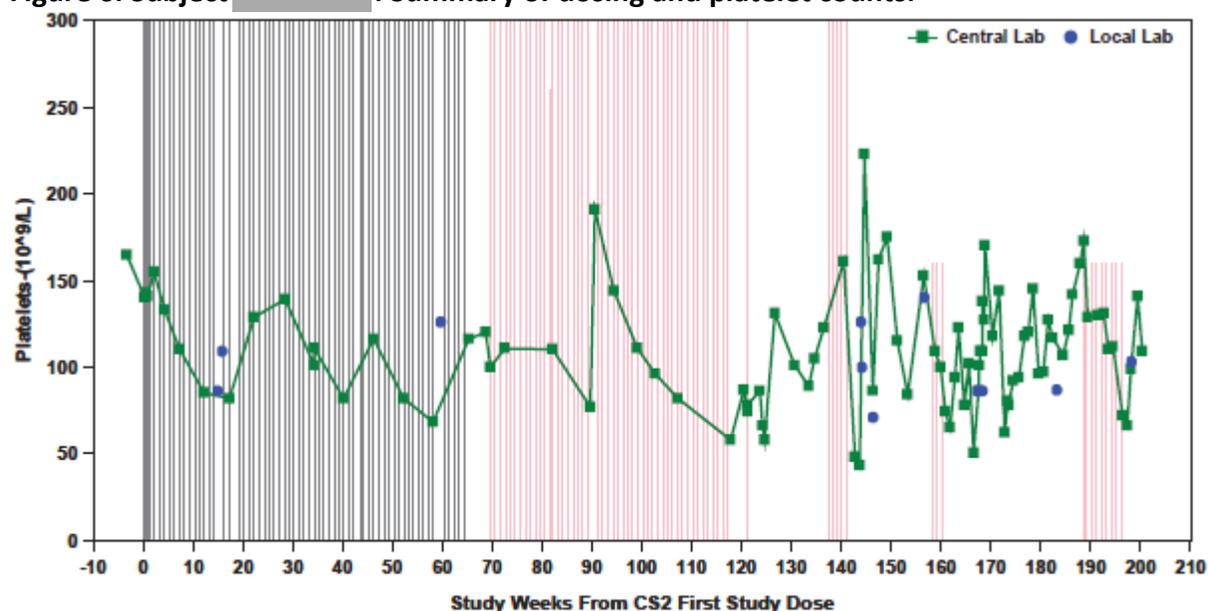
(b) RR = reference range

Study CS2/CS3 Subject (b) (6)

At enrollment, this 55-year-old male from the United States had Stage 1 hATTR-PN. 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). This subject tested positive for treatment-emergent antiplatelet antibodies (indirect assay) on Study Day 848.<sup>64</sup> The last full dose (inotersen 300 mg) was administered on Study Day 988, and then treatment was held because of low platelet counts. This subject's nadir platelet count ( $43 \times 10^9/L$ ) occurred 2 years and 9 months after his first inotersen dose (on 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.<sup>65</sup>

Reviewer comment: The efficacy of inotersen reduced dosing at 160 mg weekly has not been established.

Figure 6. Subject (b) (6). Summary of dosing and platelet counts.



Source: P. 2848 Integrated Summary of Safety

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.

<sup>64</sup> Dataset submitted to NDA 211172 on February 12, 2018.

<sup>65</sup> January 8, 2018 submission to NDA 211172.

**Table 30. Subject (b) (6) Summary of dosing and platelet counts.<sup>66</sup>**

Date (Study Day)	On/Off Inotersen	Platelet count (NR 140-400 x10 <sup>9</sup> /L)
(b) (6)	Off	165
	Off	140
	On	133
	On	85 (NR 140-400)
	On	86 (NR 150-450)
	Off	109 (NR 150-450)
	On	68 (NR 140-400)
	Off	126 (NR 150-450)
	Off	116 (NR 140-400)
	Off	120 (NR 140-400)
	Off	100 (NR 140-400)
	On	110 (NR 140-400)
	On	77 (NR 140-400)
	Off	191 (NR 140-400)
	On	82 (NR 140-400)
	On	58 (NR 140-400)
	Off	78 (NR 140-400) 74 (NR 140-400)
	Off	58 (NR 140-400)
	Off	123 (NR 140-400)
	On	161 (NR 140-400)
	Off	48 (NR 140-400)
	Off	43 (NR 140-400)
	Off	175 (NR 140-400)
	Off	153 (NR 140-400)
	On (160 mg)*	109 (NR 140-400)
	On (160 mg)*	100 (NR 140-400)
	On (160 mg)*	74 x10 <sup>9</sup> /L (NR 140-400)
	Off	50 (NR 140-400)
	Off	173 (NR 140-400)
	On (160 mg)*	129 (NR 140-400)
	On (160 mg)*	112 (NR 140-400)
	On (160 mg)*	Platelet clumps (NR 140-400)
Off	109 (NR 140-400)	

NR = Normal range

\* Dose reduced due to thrombocytopenia

### Time course of platelet changes

In Study CS2, there was a temporary decrease in platelet count with administration of 3 loading doses in the first week (see figure below). Subjects had decreased platelet counts at Study Days 3<sup>67</sup> and 5.<sup>68</sup> The

<sup>66</sup> P. 2966-2967 CS3 Clinical Study Report

<sup>67</sup> Change in platelet count from baseline at Day 3 [median (interquartile range)]: -19.00 (-28.75, -9.50) x 10<sup>9</sup>/L

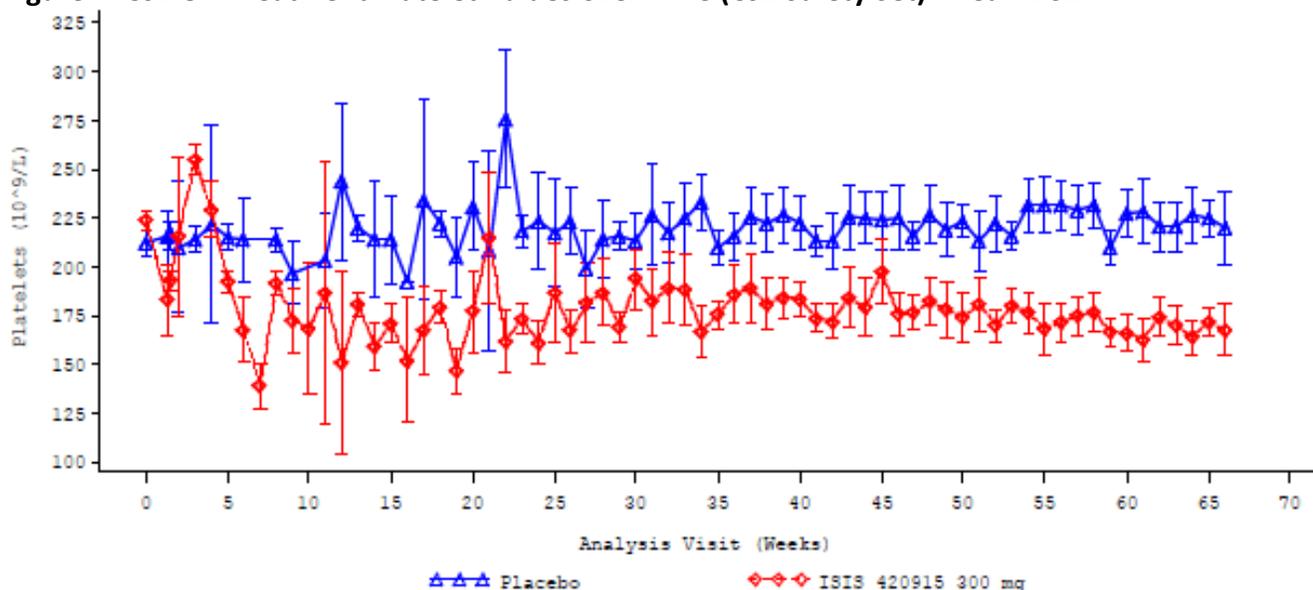
<sup>68</sup> Change in platelet count from baseline at Day 5 [median (interquartile range)]: -25.50 (-42.25, -11.50) x 10<sup>9</sup>/L

platelet decreases were not clinically significant. Most subjects' platelet counts increased to baseline or higher by Study Day 15 (Week 3)<sup>69</sup> (see figure below).

*Reviewer comment: The reduction and subsequent recovery in platelet count with loading dose administration is consistent with a short-term effect of inotersen on platelets that is correlated with plasma inotersen levels. [Peak plasma levels were observed within a few hours after dosing (median  $T_{max}$  ranging from 1.5 to 4 hours). Mean inotersen plasma concentrations decreased greater than 90% from the  $C_{max}$  by 24 hours after subcutaneous injections.]<sup>70</sup> The mechanism of these platelet changes is unclear.*

The nadir of mean values occurred between 2 and 4 months after the first inotersen treatment (see figure below). This time frame coincides with outlying platelet counts from the 3 cases of severe thrombocytopenia  $< 25 \times 10^9/L$ , which had a large influence on the mean platelet count calculations in that time frame.

**Figure 7. CS2 On-Treatment Platelet Values over Time (CS2 Safety Set). Mean  $\pm$  SE.**



Source: Summary of Clinical Safety Figure 3

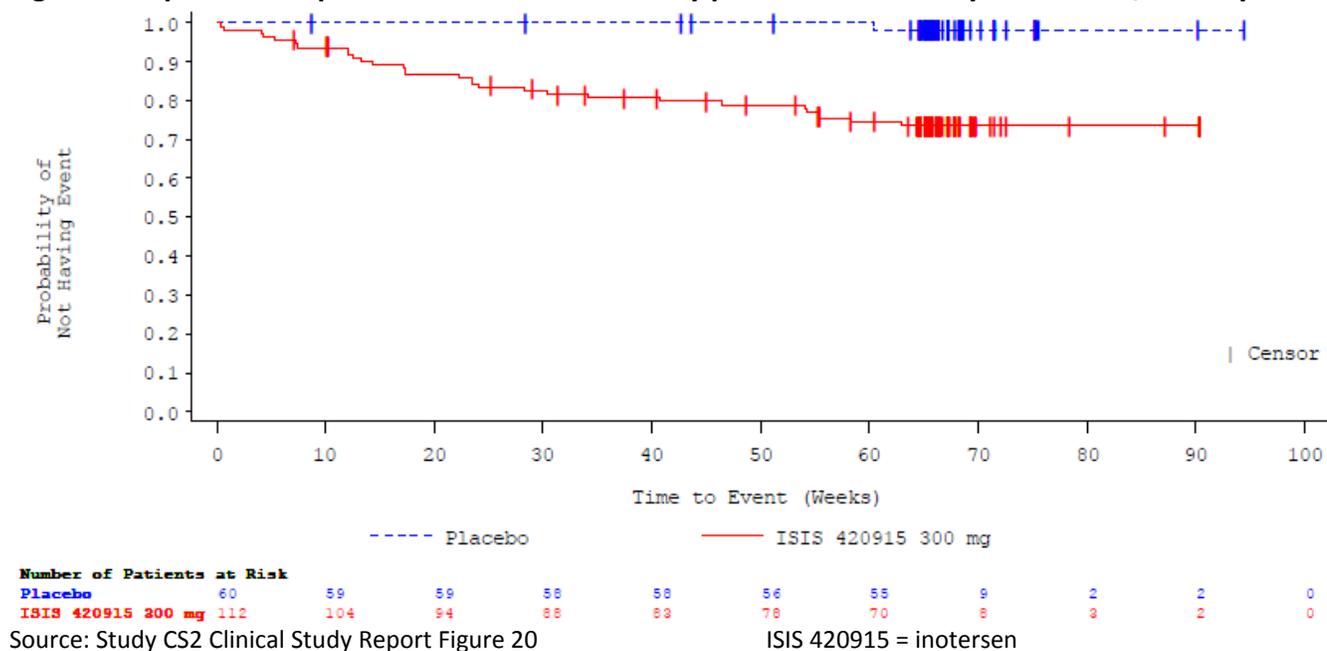
ISIS 420915 = inotersen

The figure below displays a Kaplan-Meier plot for the time to first on-study platelet abnormality  $< 100 \times 10^9/L$  in Study CS2, in which events occurred throughout the study period.

<sup>69</sup> Change in platelet count from baseline at Day 15 [median (interquartile range)]: 25.75 (7.75, 54.00)  $\times 10^9/L$

<sup>70</sup> Study CS1 pharmacokinetic study results. P. 20-21 Summary of Clinical Pharmacology

**Figure 8. Kaplan-Meier plot for time to first on-study platelet abnormality <math> < 100 \times 10^9/L </math>. Study CS2.**



### Antiplatelet antibody testing in inotersen clinical studies

A potential mechanism for the emergence of antiplatelet antibodies with inotersen is an increase in B lymphocyte levels.<sup>71</sup> In Study CS2, inotersen subjects had increases in IgG and IgM concentrations greater than the upper limit of normal at any time post-baseline more frequently (20.6% and 44.4%, respectively) than placebo subjects (7.7% and 0%, respectively).<sup>72</sup>

In clinical studies, the Sponsor evaluated for an immune mechanism for platelet declines by testing for antiplatelet antibodies. At a time when treatment allocation remained blinded in Study CS2, antiplatelet antibody testing was performed in most patients with platelet declines <math> < 100 \times 10^9/L </math>, as well as in some subjects with <math> < 30\% </math> reduction in platelets from baseline for comparison.<sup>73</sup> Antiplatelet antibody test results for Study CS2 subjects, as well as changes in platelet count, are summarized in the table below.

*Reviewer comment: Because antiplatelet antibody testing was performed in selected subjects, antiplatelet antibody test results are not representative of the entirety of either Study CS2 subject group. The Sponsor performed analyses in Study 420915-CR02, which included test results from (b) (4)*

<sup>71</sup> P. 22 420915-CR02 Study Report

<sup>72</sup> Study CS2 Clinical Study Report Table 4.40

<sup>73</sup> Response to FDA information request. Submitted to NDA 21172 on February 12, 2018.

(b) (4) but not the central laboratory (b) (4)<sup>74</sup> Tables 27 and 28 below include test results from both laboratories.

In Study CS2, all 9 inotersen subjects who developed treatment-emergent positive antiplatelet antibodies developed treatment-emergent thrombocytopenia (Table 27). Inotersen patients with no positive antiplatelet antibody test, as well as patients with positive antiplatelet antibody tests at baseline, had nadir platelet counts ranging from moderate thrombocytopenia to normal platelet levels.

*Reviewer comment: In Study CS2 subjects with a positive antiplatelet antibody test at baseline, all epitope testing was negative with the exception of HLA-Class I antibody positivity in 3 subjects (2 inotersen and 1 placebo) and GPIIb/IIIa-HPA5 positivity in 1 placebo subject. According to the Study 420915-CR02 study report, positivity to HLA and HPA-5b antibodies in these subjects is considered to not be clinically relevant, since these are alloantibodies.<sup>75</sup>*

**Table 31. Summary of antiplatelet antibody test results and changes in platelet count. Study CS2.**

	Nadir platelet count Median (Range)	Largest percent decrease in platelets from baseline Median (Range)
<b>Inotersen subjects (N=37)</b>		
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)
<b>Placebo subjects (N=18)</b>		
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<sup>9</sup>/L

Sources: Submissions to NDA 211172 on November 6, 1017 (dataset ADLB) and February 12, 2018.

In Studies CS2 and CS3, 23 of 152 (15.1%) inotersen subjects had treatment-emergent moderate to severe thrombocytopenia with a nadir platelet count <75 x 10<sup>9</sup>/L. (In Study CS2, no placebo-treated subjects had a nadir platelet count <75 x 10<sup>9</sup>/L.) Thirteen of 23 (56.5%) of subjects with a nadir platelet count <75 x 10<sup>9</sup>/L had a treatment-emergent positive antiplatelet antibody test result shortly before or at a time of platelet decline (see table below).

<sup>74</sup> Response to FDA information request. Submitted to NDA 211172 on February 12, 2018.

<sup>75</sup> P. 16 Study 420915-CR02.

Reviewer comment: In the table below, some subjects tested positive for drug-independent antiplatelet antibodies. Drug-dependent antibodies may be identified as drug-independent in cases where the drug-dependent antibody reacts only with a drug metabolite produced in vivo.<sup>76</sup>

**Table 32. Subjects with nadir platelet counts <75 x 10<sup>9</sup>/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 <sup>#</sup>	Yes	No
CS2		(b) (6)	9	Antiplatelet IgG - Drug Independent	Yes	No
CS2		(b) (6)	10	Antiplatelet IgG - Drug Independent Anti- GPIIb/IIIa <sup>#</sup>	Yes	No
CS3		(b) (6)	33	Antiplatelet IgM - Drug Dependent/ Antiplatelet IgG - Drug Dependent/ Antiplatelet IgG - Drug Independent/ *	Yes	No
CS3		(b) (6)	41	Antiplatelet IgG - Drug Dependent	Yes	No
CS3		(b) (6)	43	Platelet Antibodies, Indirect	Yes	No
CS3		(b) (6)	50	Antiplatelet IgM - Drug Dependent/ Antiplatelet IgG - Drug Independent/*	Yes	No
CS3		(b) (6)	56	Platelet Antibodies, Indirect	Yes	No
CS2		(b) (6)	58	Platelet Antibodies, Indirect	Yes	No
CS3		(b) (6)	59	Antiplatelet IgM - Drug Dependent/ Antiplatelet IgG - Drug Dependent/ Antiplatelet IgG - Drug Independent	Yes	No
CS2		(b) (6)	62	Antiplatelet IgG - Drug Independent/*	Yes	No
CS3		(b) (6)	66	Antiplatelet IgG - Drug Dependent	Yes	No
CS3		(b) (6)	69	Platelet Antibodies, Indirect	Yes	No

\*Subject also tested positive for antiplatelet antibodies with an indirect assay not specific to the type of antibodies present. The clinical study central laboratory used an indirect assay for antiplatelet antibodies. Some antiplatelet antibody testing was also performed at a separate laboratory (b) (4) which evaluated the antiplatelet antibody type.

<sup>#</sup> Epitope testing results (p. 18 420915-CR02 Study Report)

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

Data through the original NDA data cut-off dates: March 28, 2017 and February 28, 2017 for Studies CS2 and CS3, respectively.

<sup>76</sup> Aster RH. et al. *N Engl J Med* 2007; 357:580-587.

## Use of antiplatelet antibody testing in the evaluation of thrombocytopenia with inotersen

Antiplatelet antibody testing may be a useful in the evaluation of individual inotersen patients with thrombocytopenia. Additional research using antiplatelet antibody testing may provide insight into the mechanisms of thrombocytopenia seen with inotersen. However, the currently available data do not support antiplatelet antibody testing as a screening tool for thrombocytopenia with use of inotersen:

- Antiplatelet antibody testing can be technically demanding and is not always widely available.
- In the 3 inotersen subjects with severe thrombocytopenia, the emergence of antiplatelet antibodies occurred very close to or at the time of the severe platelet count decline.
- Antiplatelet antibody testing is reported to have suboptimal sensitivity.<sup>77</sup>
- As seen in Study 420915-CR02, some patients may have baseline antiplatelet antibodies that are not clinically relevant, which may complicate the interpretation of antiplatelet antibody testing.

## Mechanism of platelet count declines

### Cases of severe thrombocytopenia < 25 x 10<sup>9</sup>/L with inotersen

All 3 subjects who developed severe thrombocytopenia < 25 x 10<sup>9</sup>/L tested positive for treatment-emergent anti-platelet IgG antibodies detected shortly before, or at the time of the severe reduction in platelet count. Additional information supports an immune-mediated mechanism in these cases of severe thrombocytopenia:

- Subject (b) (6) 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.
- Subjects who received corticosteroids<sup>78</sup> had improved platelet counts with treatment.
- In 2 subjects,<sup>79</sup> the epitope was GPIIb/IIIa, which is a common target for antiplatelet antibodies in immune thrombocytopenia. (No epitope was identified in the third case.)

### Other cases of thrombocytopenia with inotersen

In cases of thrombocytopenia with inotersen, other than cases of severe thrombocytopenia < 25 x 10<sup>9</sup>/L, the etiologies may be multifactorial, and the causal mechanisms are not entirely clear. Some of these subjects tested positive for treatment-emergent antiplatelet antibodies, which may indicate an immune mechanism. However, approximately half of the Study CS2 and CS3 subjects with nadir platelet counts < 75 x 10<sup>9</sup>/L had no positive result with antiplatelet antibody testing.

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<sup>77</sup> Aster RH. et al. *N Engl J Med* 2007; 357:580-587.

<sup>78</sup> Subjects (b) (6)

<sup>79</sup> Subjects (b) (6)

In Study CS2, there was reduction and subsequent recovery in platelet count with loading dose administration, which is consistent with a short-term effect of inotersen on platelets that is correlated with plasma inotersen levels. The mechanism of this effect is unclear. A related mechanism may be a factor in thrombocytopenia over the course of inotersen treatment.

The Sponsor evaluated other possible causes of platelet count changes with inotersen, and the resulting conclusions are outlined in the figure below.

**Figure 9. Sponsor conclusions regarding excluded causes for platelet reductions with inotersen**

- 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 (C<sub>max</sub>) 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.

Source: P. 139 Summary of Clinical Safety

## Effect of Subject Baseline Characteristics on the Risk of Thrombocytopenia

### Body Weight

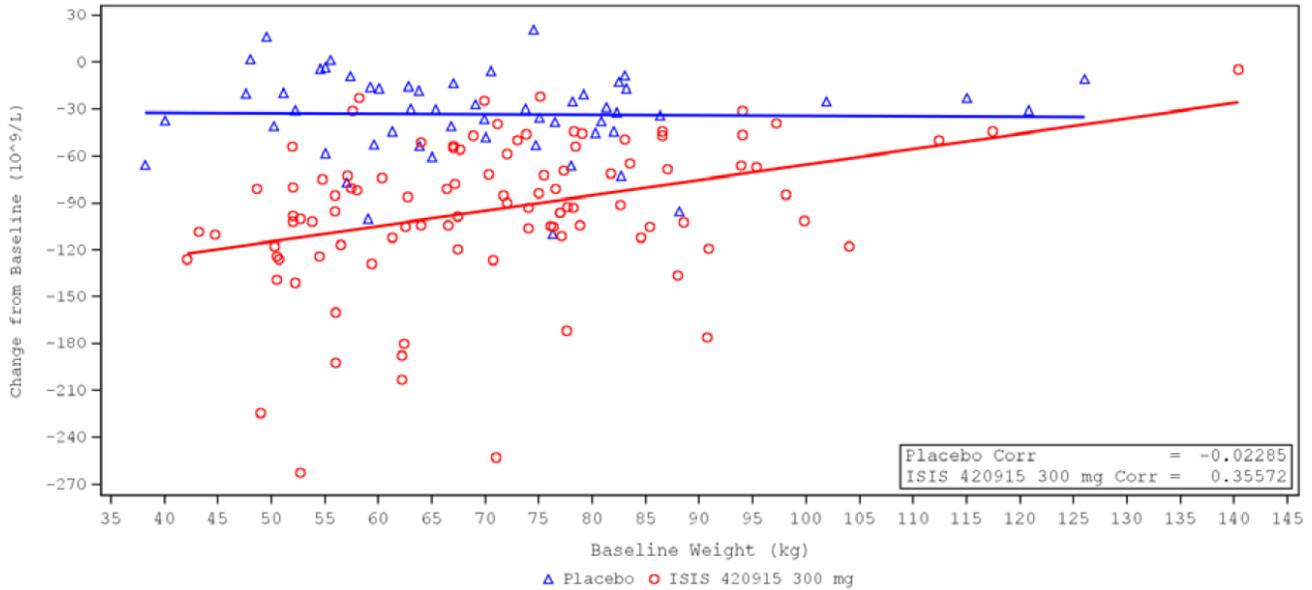
Analysis of the effect of body weight shows that overall, lower body weight is associated with larger absolute and percent reduction in platelet count (see figures below). However, body weight did not appear to have a significant impact on severe thrombocytopenia ( $<25 \times 10^9/L$ ), as the subjects with the lowest nadir platelet counts have body weights evenly distributed from 49 to 90 kg.<sup>80</sup>

*Reviewer comment: While there is an overall association between lower body weight and larger reduction in platelet count, analyses of platelet reduction stratified by baseline body weight did not reveal a specific group of subjects at increased risk.<sup>81</sup>*

<sup>80</sup> P. 54 Summary of Clinical Pharmacology

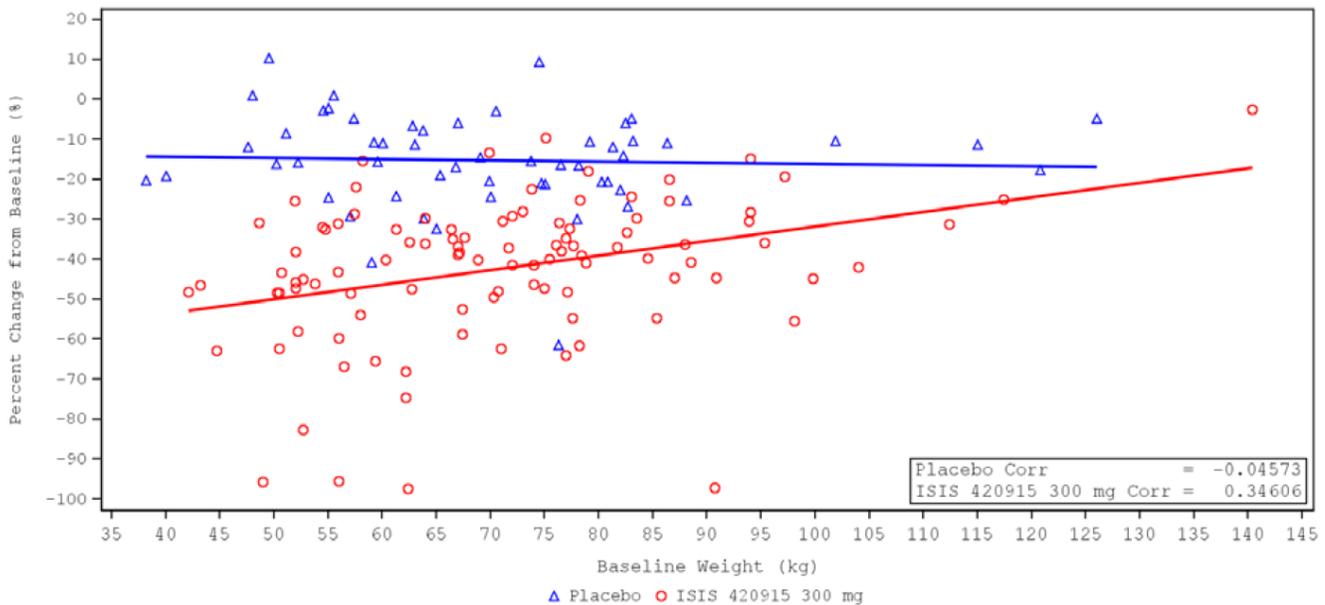
<sup>81</sup> March 9, 2018 information request response submitted to NDA 211172 on March 9, 2018.

**Figure 10. Scatter Plot for Maximum Change of Platelets from Baseline vs. Baseline Body Weight. Study CS2 (On-Treatment).**



Source: P. 27 420915-CR01 Study Report

**Figure 11. Scatter Plot for Maximum Percent Change of Platelets from Baseline vs. Baseline Body Weight. Study CS2 (On-Treatment).**



Source: P. 27 420915-CR01 Study Report

*Reviewer comment: As a possible strategy to reduce the frequency of thrombocytopenia with inotersen treatment, this reviewer recommends considering the evaluation of the efficacy and safety of lower doses of inotersen.*

Baseline platelet count

Analyses of post-baseline nadir platelets and dose exposure stratified by baseline platelet count in Study CS2 are displayed in the table below.

**Table 33. Post-baseline nadir platelets and dose exposure by baseline platelet count. Study CS2.**

	Inotersen Baseline Platelets <125 x 10 <sup>9</sup> /L (N=2)	Inotersen Baseline Platelets <150 x 10 <sup>9</sup> /L (N=10)	Inotersen Baseline Platelets <200 x 10 <sup>9</sup> /L (N=39)	Inotersen Baseline Platelets ≥200 x 10 <sup>9</sup> /L (N=73)	Inotersen All subjects (N=112)	Placebo (N=60)
<b>Number (%) Subjects with Nadir platelets &lt;75 x 10<sup>9</sup>/L*</b>	2 (100)	3 (30.0)	10 (25.6)	3 (4.1)	13 (11.6)	0
<b>Absolute Value of Nadir Platelets (10<sup>9</sup>/L) Median Range (Min, Max)</b>	65 (60, 70)	84 (60, 123)	93 (5, 172)	150 (9, 275)	130 (5, 275)	173 (69, 285)
<b>Change from Baseline of Nadir Platelets (10<sup>9</sup>/L) Median Range (Min, Max)</b>	-55 (-63, -47)	-54 (-73, -23)	-67 (-180, -5)	-102 (-263, -22)	-86 (-263, -5)	-30 (-110, -21)
<b>Percent Change from Baseline of Nadir Platelets Median Range (Min, Max)</b>	-46 (-51, -40)	-39 (-51, -16)	-40 (-97, -3)	-38 (-96, -10)	-39 (-97, -3)	-15 (-61, 10)
<b>Treatment Duration (Months) Median Range (Min, Max)</b>	9 (4, 15)	15 (4, 15)	15 (0, 15)	15 (0, 15)	15 (0, 15)	15 (1, 15)

\*A total of 13 subjects based on Maximum Toxicity Grade in ISS Table 2.31.

Platelet baseline is the average of pre-dose assessments

Source: Sponsor IR responses February 28, 2018 and March 9, 2018.

Data through the original NDA data cut-off dates: March 28, 2017 and February 28, 2017 for Studies CS2 and CS3, respectively.

There is little experience with inotersen treatment in patients with baseline platelets count < 125 x10<sup>9</sup>/L at baseline, as only 2 Study CS2 subjects<sup>82</sup> met this threshold. Patients with baseline platelet count < 125 x 10<sup>9</sup>/L were excluded from Studies CS2 and CS3.<sup>83</sup>

<sup>82</sup> Subjects (b) (6)

Compared to subjects with a baseline platelet count  $\geq 200 \times 10^9/L$ , subjects with a baseline platelet count  $< 200 \times 10^9/L$  had:<sup>84</sup>

- Lower nadir platelet counts
- Smaller change from baseline of nadir platelet counts
- Similar percent change from baseline of nadir platelet counts

The table below displays the frequency and relative risk of platelet count  $< 75 \times 10^9/L$  by baseline platelet count. Compared to subjects with baseline platelet counts  $\geq 200 \times 10^9/L$ , subjects with baseline platelet counts  $< 200 \times 10^9/L$  had 6.2 and 7.0 times the risk of having a nadir platelet count  $< 75 \times 10^9/L$  in Study CS2 and in the longitudinal safety set (Studies CS2 and CS3), respectively.

**Table 34. Frequency and relative risk of nadir platelet count  $< 75 \times 10^9/L$  by baseline platelet count**

	Inotersen Subjects Baseline Platelets $< 200 \times 10^9/L$ (N=39)	Inotersen Subjects Baseline Platelets $\geq 200 \times 10^9/L$ (N=73)	Relative Risk: Baseline platelet count $< 200 \times 10^9/L$ / Baseline platelet count $\geq 200 \times 10^9/L$
Nadir platelet count $< 75 \times 10^9/L$ Study CS2 n (%)	10 (25.6)	3 (4.1)	6.2
Nadir platelet count $< 75 \times 10^9/L$ Study CS2 and CS3 Longitudinal Safety Set n (%)	15 (38.5)	4 (5.5)	7.0

Source: Study CS2 and CS3 ADLB datasets

Data through the original NDA data cut-off dates: March 28, 2017 and February 28, 2017 for Studies CS2 and CS3, respectively.

*Reviewer comment: In Study CS2, 71% of subjects<sup>85</sup> had a  $\geq 30\%$  post-treatment decrease in platelet count from baseline. Subjects with subjects with baseline platelet count  $< 200 \times 10^9/L$  had less platelet count reserve, which resulted in a higher risk of post-treatment platelet counts  $< 75 \times 10^9/L$ , levels at which primary hemostasis is generally considered to be impaired.*

Baseline platelet count  $< 200 \times 10^9/L$  did not appear to be a risk factor for developing thrombocytopenia  $< 25 \times 10^9/L$ . (Baseline platelet counts in these subjects ranged from 181-235  $\times 10^9/L$ .)

<sup>83</sup> Baseline platelet count  $< 100 \times 10^9/L$  was exclusion criterion 2c in the original Study CS2 protocol. In CS2 Protocol versions 2-5 and in all versions of the CS3 study protocol, exclusion criterion 2c was a platelet count  $< 125 \times 10^9/L$ .

<sup>84</sup> Analyses of combined data from the Longitudinal Safety Set (subjects who received inotersen in Study CS2 and continued receive inotersen in Study CS3) resulted in findings similar to those displayed in Table 29. (March 9, 2018 submission to NDA 211172).

<sup>85</sup> Summary of Clinical Safety Table 69

### Other baseline subject characteristics

In analyses of Study CS2 changes in platelet count stratified by subject age, sex, or race, these subject characteristics were not found to be factors affecting the magnitude of platelet count reduction.<sup>86</sup>

### Continued inotersen dosing in subjects with thrombocytopenia

The 3 subjects who experienced thrombocytopenia  $< 25 \times 10^9/L$  permanently discontinued dosing and were not rechallenged with inotersen.

In Studies CS2 and CS3, a total of 27 subjects<sup>87</sup> paused dosing for platelet counts  $< 75 \times 10^9/L$ , and dosing remained paused until the platelet count recovered to at least  $100 \times 10^9/L$  (see table below). After the first dose pause due to low platelet count, 18 subjects received inotersen dosing at the full dose (300 mg every week); 6 of these subjects were not able to maintain full inotersen dosing and received less than 10 full doses. Twelve subjects received reduced inotersen doses of varying regimens (usually approximately half the full inotersen dose (150-160 mg) every week).

*Reviewer comment: The efficacy of these reduced doses has not been established in clinical studies. The*

[REDACTED] (b) (4)

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<sup>86</sup> P. 26 420915-CR01 study report

<sup>87</sup> 120-Day Safety Update Report

<sup>88</sup> March 28, 2017 for Study CS2 and February 28, 2017 for Study CS3

**Table 35. Subjects who paused dosing due to platelet count < 75 x 10<sup>9</sup>/L**

Subject	Number of Full Doses after First Dose Pause	Number of Reduced Doses after First Dose Pause	Reduced Dose Regimen
CS2 <sup>a</sup>			
(b) (6)	0	0	
	0	0	
	0	0	
	0	0	
	3	104	160 mg/week
	8	14	150 mg every 2 weeks
	19	0	
	20	29	150 mg/week
	42	47	160 mg/week
	50	0	
	58	16	160 mg/week
	106	0	
	106	56	150 mg/week
	146	5	160 mg/week
	CS3: Inotersen-Inotersen <sup>b</sup>		
0	0		
0	8	160 mg every 2 weeks	
0	19	160 mg/week (Weeks 78-86) 80 mg/week (Weeks 78-86) 80 mg every 2 weeks (Weeks 116, 122-128)	
0	46	160 mg/week	
2	0		
6	2	150 mg/week	
CS3 Placebo-Inotersen <sup>c</sup>			
0	40	160 mg/week	
1	0		
1	0		
16	0		
17	0		
25	0		
39	0		

\* Cases of severe thrombocytopenia <25 x 10<sup>9</sup>/L

<sup>a</sup> First dose pause due to platelet count < 75 x 10<sup>9</sup>/L occurred in Study CS2. Subsequent doses were administered in Study CS2, and in some cases Study CS3.

<sup>b</sup> First dose pause due to platelet count < 75 x 10<sup>9</sup>/L, as well as subsequent doses, occurred in Study CS3. Subjects received inotersen in both Studies CS2 and CS3.

<sup>c</sup> First dose pause due to platelet count < 75 x 10<sup>9</sup>/L, as well as subsequent doses, occurred in Study CS3. Subjects received placebo in Study CS2 and inotersen in Study CS3.

Sources: 120-Day Safety Update Report submitted March 6, 2018 and the response to FDA information request submitted to NDA 211172 on March 12, 2018. Data cut-off September 15, 2017.

In Studies CS2 and CS3, 11 subjects had a fall in platelet count from  $\geq 100 \times 10^9/L$  to a platelet count  $< 75 \times 10^9/L$ <sup>89</sup> within 1-2 weeks. In one example, Study CS2 Subject (b) (6) had a platelet count reduction from  $100 \times 10^9/L$  to  $40 \times 10^9/L$  in one week;<sup>90</sup> dosing was stopped, and the next weekly platelet count improved.

In clinical studies, many of these subjects received platelet measurements once weekly. (b) (4)

Based on this clinical study experience, platelet monitoring every 2 weeks and inotersen dosing weekly would result in continued dosing in patients with undetected low platelet counts.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

In Study CS3, 24 of 114 (24%)

<sup>89</sup> Inotersen subject (b) (6) had an isolated low platelet count that improved within 3 days and appears to be a laboratory error. Placebo subject (b) (6) also had a drop in platelet count that improved within 3 days. These 2 subjects were not included in the count of 11 subjects. *Reviewer comment: This reviewer agrees with the exclusion of these 2 subjects.*

<sup>90</sup> Study CS2 CSR p. 3682

<sup>91</sup> P. 3 response to FDA information request. Submitted to NDA 21172 on January 8, 2018.

subjects had at least one dose held because no platelet value was available in the last 14 days. (Platelet monitoring was scheduled weekly.) Reasons included missed lab assessments or uninterpretable sample.

### **Uninterpretable platelet counts due to platelet clumping**

Inotersen subjects had uninterpretable platelet counts due to platelet clumping more frequently than placebo subjects. In Study CS2, 26 of 112 (23%) inotersen subjects had at least 1 clumped platelet sample, compared to 8 of 60 (13%) placebo subjects.<sup>92</sup> In 2 cases of severe thrombocytopenia  $< 25 \times 10^9/L$ , one of which resulted in death, clumped platelet samples caused a delay in diagnosis and treatment (see Figures 1 and 2). Both subjects had tested positive for treatment-emergent anti-platelet IgG antibodies detected shortly before, or at the time of the severe reduction in platelet count.

While platelet clumping can have a variety of causes (e.g., incompletely mixed or inadequately anticoagulated samples), platelet clumping can be caused by a reaction between antiplatelet antibodies and ethylenediaminetetra-acetic acid (EDTA).<sup>93</sup> In Study CS2, 7 of the 9 inotersen subjects with treatment-emergent positive antiplatelet antibody testing had at least 1 clumped platelet sample. One of the 6 inotersen subjects with baseline positive antiplatelet antibody testing also had a clumped platelet sample.

*Reviewer comment: Inotersen subjects had an increased frequency of uninterpretable platelet counts due to platelet clumping, which can add to the difficulty of assessing platelet counts.*

If a platelet count is uninterpretable, patients and prescribers should obtain a repeat measurement as soon as possible. Because the mechanism of platelet clumping can involve EDTA, a different anticoagulant (e.g., citrate, heparin) can be used with repeat testing.

### **Patient self- administration: Practical considerations**

As described in the Sponsor's proposed labeling, inotersen is intended to be administered by a patient or caregiver via subcutaneous injection.<sup>94</sup> Patients will also be responsible for obtaining platelet monitoring, which is the main way of mitigating the risk of serious, potentially fatal bleeding from thrombocytopenia. A summary of patient and provider responsibilities related to inotersen platelet monitoring and dosing is displayed in the figure below.

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<sup>92</sup> Response to FDA information request. Submitted to NDA 211172 on February 12, 2018.

<sup>93</sup> Lippi G, Plebani M. EDTA-dependent pseudothrombocytopenia: further insights and recommendations for prevention of a clinically threatening artifact. *Clin Chem Lab Med*. 2012 Aug;50(8):1281-5. doi: 10.1515/cclm-2012-0081.

<sup>94</sup> Sponsor proposed labeling. Submitted to NDA 211172 on November 6, 2017.

**Figure 12. Patient and health care provider responsibilities related to inotersen platelet monitoring and dosing**

Patient Responsibilities	Health Care Provider Responsibilities
<ul style="list-style-type: none"> <li>• Administer inotersen (if dosing is recommended).</li> <li>• Keep detailed and accurate dosing records.</li> <li>• Obtain scheduled platelet measurements.</li> <li>• Be vigilant for symptoms of thrombocytopenia and seek medical help for any concerns. If symptoms of thrombocytopenia occur, hold inotersen dosing until the health care professional provides instructions.</li> <li>• Obtain unscheduled platelet measurements, as needed, if symptoms of thrombocytopenia occur or if a platelet measurement is not interpretable.</li> <li>• Receive and understand monitoring and dosing instructions from the health care provider prior to dosing.</li> </ul>	<ul style="list-style-type: none"> <li>• Order platelet measurements.</li> <li>• Review platelet results</li> <li>• Provide instructions for dosing and monitoring based on most recent platelet count and whether any thrombocytopenia symptoms are present.</li> </ul>

*Reviewer comment: If the health care provider does not provide laboratory results and dosing instructions prior to an inotersen dose, there is an increased risk of a dosing error. I recommend providing prescribers with a dosing decision tool, which can summarize dosing and monitoring recommendations, as well as symptoms of thrombocytopenia. This tool can be used in the medical record and can facilitate the communication of dosing decisions with patients.*

### 8.5.2. Glomerulonephritis and Renal Toxicity

#### **Transthyretin amyloidosis-related kidney disease**

Amyloid renal deposits can occur with transthyretin amyloidosis (ATTR). Chronic renal failure and proteinuria are clinical features of ATTR-related kidney disease,<sup>95</sup> which may complicate or delay the diagnosis of renal toxicity related to inotersen.

<sup>95</sup> Transthyretin amyloidosis and the kidney. Lobato L, Rocha A. *Clin J Am Soc Nephrol*. 2012 Aug;7(8):1337-46.

**Renal Impairment: Adverse Events**

Accumulation of antisense oligonucleotides in proximal tubule cells of the kidney, sometimes leading to increased tubular proteinuria, has been described in preclinical studies.<sup>96-97</sup> Glomerulonephritis, considered a proinflammatory effect, has also been described in preclinical and clinical studies of antisense oligonucleotides.<sup>98,99,100,101</sup>

In placebo-controlled study CS2, 23 of 112 (20.5%) inotersen subjects had a treatment-emergent renal impairment adverse event, compared to 6 of 60 (10.0%) placebo subjects (see table below). In Study CS3, 9 of 114 (7.9%) subjects had a treatment-emergent renal impairment adverse event (see table below).

**Table 37. Study CS2. Treatment-Emergent Renal Impairment Adverse Events**

	Inotersen 300 mg N=112	Placebo N=60
	Subjects, n (%)	Subjects, n (%)
<b>Renal impairment</b>	<b>23 (20.5)</b>	<b>6 (10.0)</b>
Acute kidney injury	3 (2.7)	0
Albuminuria	2 (1.8)	1 (1.7)
Blood creatinine increased	2 (1.8)	1 (1.7)
Blood urea increased	3 (2.7)	0
Creatinine renal clearance decreased	2 (1.8)	0
Glomerular filtration rate decreased	6 (5.4)	2 (3.3)
Glomerulonephritis	2 (1.8)	0
Nephrotic syndrome	0	1 (1.7)
Protein urine present	1 (0.9)	0
Proteinuria	7 (6.3)	2 (3.3)
Renal failure	3 (2.7)	0
Renal impairment	4 (3.6)	0
Tubulointerstitial nephritis	1 (0.9)	0
Urine output decreased	1 (0.9)	0

Source: Summary of Clinical Safety Table 72

<sup>96</sup> Rappaport J, et al. Transport of phosphorothioate oligonucleotides in kidney: implications for molecular therapy. *Kidney Int.* 1995 May;47(5):1462-9.

<sup>97</sup> Henry, S. P., et al. (2008). Toxicologic properties of 20-methoxyethyl chimeric antisense inhibitors in animals and man. In *Antisense Drug Technology: Principles, Strategies and Applications*, 2nd ed. (S. T. Crooke, ed.), pp. 327–63. CRC Press, Carlsbad, CA.

<sup>98</sup> Antisense Oligonucleotide Therapies: The Promise and the Challenges from a Toxicologic Pathologist’s Perspective. Frazier KS. *Toxicologic Pathology*, 43: 78-89, 2015.

<sup>99</sup> A randomized placebo-controlled phase 3 trial of an antisense oligonucleotide, drisapersen, in Duchenne muscular dystrophy. Goemans N, et al. *Neuromuscul Disord.* 2018 Jan;28(1):4-15.

<sup>100</sup> Antisense Oligonucleotide Therapies: The Promise and the Challenges from a Toxicologic Pathologist’s Perspective. Frazier KS. *Toxicologic Pathology*, 43: 78-89, 2015.

<sup>101</sup> Acute Kidney Injury During Therapy with an Antisense Oligonucleotide Directed Against PCSK9. Van Poelgeest EP, et al. *Am J Kidney Dis.* 62(4):796-800.

*Reviewer comment: This reviewer evaluated the Sponsor’s search terms for adverse events of Renal Impairment. Events coded to the PTs Glomerulonephritis and Nephrotic syndrome were added to the Sponsor analyses and are included in the table above. In addition to the 2 cases of glomerulonephritis listed in the table, Subject (b) (6) had biopsy-proven glomerulonephritis, which was coded as Acute kidney injury by the Sponsor.*

**Table 38. Study CS3. Renal Impairment Treatment-Emergent Adverse Events**

Category Preferred Term	Placebo-Inotersen (N=40)	Inotersen-Inotersen (N=74)	Total (N=114)
	Subjects, n (%)	Subjects, n (%)	Subjects, n (%)
Renal impairment	5 (12.5)	4 (5.4)	9 (7.9)
Proteinuria	0	3 (4.1)	3 (2.6)
Albuminuria	0	1 (1.4)	1 (0.9)
Renal impairment	1 (2.5)	1 (1.4)	2 (1.8)
Blood creatinine increased	2 (5.0)	0	2 (1.8)
Blood urea increased	2 (5.0)	0	2 (1.8)
Urine output decreased	1 (2.5)	0	1 (0.9)

Source: Summary of Clinical Safety Table 73

**Cases of biopsy-proven glomerulonephritis**

In Study CS2, 3 of 112 (3%) inotersen subjects had biopsy-confirmed glomerulonephritis, compared to 0 of 60 placebo subjects. The cases of biopsy-confirmed glomerulonephritis are summarized below.

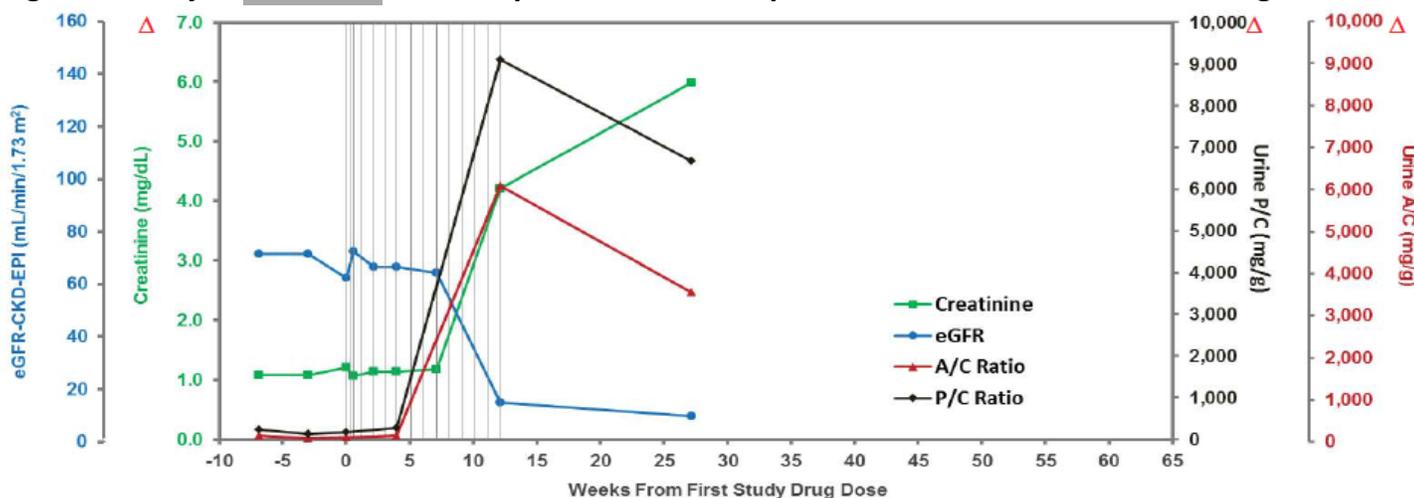
Subject (b) (6)

- The subject is a 67-year-old male who had a normal baseline estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m<sup>2</sup>.
- At Week 8, estimated GFR was normal, and urine protein to creatinine ratio (UPCR) was 270 mg/g. At the next lab check (Week 13; 3 months after starting inotersen), eGFR was 14 mL/min/1.73m<sup>2</sup>, and UPCR was 9102 mg/g (normal range <200 mg/g), and he received his last inotersen dose.
- At Week 14 he was hospitalized with shortness of breath, edema, 20-pound weight gain, that had developed over the past several weeks. He started hemodialysis 1 week after hospitalization and remained dialysis-dependent.
- Kidney biopsy showed fibrillary glomerulonephritis with sclerosing crescentic changes; amyloidosis, transthyretin type involving vessels and interstitium but not glomeruli; and severe interstitial fibrosis. The biopsy showed a silver-positive “matrix-like material seen distorting the glomerular architecture [that] has not been described in relation to transthyretin (familial) type

amyloidosis in the literature to date.” IgG and C3 deposition was seen within mesangial regions and capillary loops in 3+ amounts. (See Appendix 13.5 for the kidney biopsy report.)

- The subject did not receive immunosuppressive treatment for glomerulonephritis. His UPCR remained elevated at 6661 mg/g 3.5 months after the last dose of inotersen was administered.

**Figure 13. Subject (b) (6). Summary of renal laboratory measurements and inotersen dosing.**<sup>102</sup>



Grey vertical lines represent the dosing records from CS2 study.

Creatinine = serum creatinine; eGFR = estimated glomerular filtration rate; CKD-EPI = CKD-EPI Creatinine Equation (Levey 2009)  
 A/C Ratio = Urine AC (mg/g) = urine albumin to creatinine ratio; P/C Ratio = Urine P/C (mg/g) = urine protein to creatinine ratio

*Reviewer comment: Immunosuppressive treatment for glomerulonephritis may be contraindicated in patients with ongoing infection. Subject (b) (6) did not receive immunosuppressive treatment for glomerulonephritis. The subject developed bacteremia (attributed to the subject’s dialysis catheter), which may have contributed to the decision to avoid immunosuppression.<sup>103</sup> Infection adverse events were common in Studies CS2 and CS3; 15.5%<sup>104</sup> and 68.3%<sup>105</sup> had SAEs and AEs coded to the Infections and infestations SOC, respectively. Patients with active infection requiring systemic antiviral or antimicrobial therapy were excluded from inotersen clinical studies.*

*Hemodialysis can be difficult to manage in the setting of hATTR and its manifestations (e.g., cardiac involvement, autonomic dysfunction with hypotension, diarrhea), as it involves large shifts in intravascular volume. In hATTR patients who require hemodialysis, recurrent symptomatic intradialytic hypotension and a generally poor prognosis have been reported.<sup>106</sup>*

<sup>102</sup> P. 479 Sponsor response to FDA pre-submission safety requests. November 6, 2017 submission to NDA 211172.

<sup>103</sup> Reasons for not initiating immunosuppression were not specifically discussed in the subject records.

<sup>104</sup> Table 17 120-Day Safety Update Report

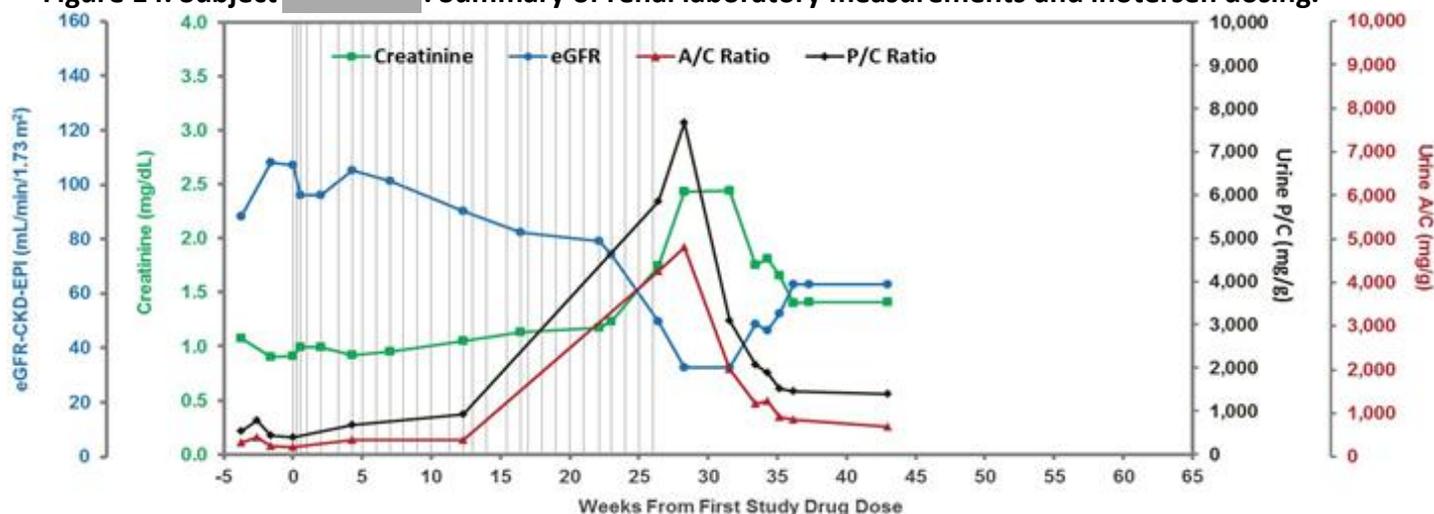
<sup>105</sup> Table 10 120-Day Safety Update Report

<sup>106</sup> End-stage renal disease and dialysis in hereditary amyloidosis TTR V30M: presentation, survival and prognostic factors. Lobato LB, et al. *Amyloid*. 2004 Mar;11(1):27-37.

Subject (b) (6)

- The subject is a 37-year-old male who had a normal baseline estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m<sup>2</sup> on (b) (6)
- On (b) (6) (Study Week 13), his UPCR was 918 mg/g (similar to a pre-treatment UPCR of 780 mg/g), and eGFR was normal. Lower limb edema was noted on (b) (6). Last inotersen dose was administered on (b) (6) (Study Week 26). On (b) (6) (6 months after starting inotersen), UPCR was 5850 mg/g, serum creatinine was 1.74 mg/dL, and eGFR was 32 mL/min/1.73m<sup>2</sup>.
- Despite cessation of inotersen, the subject's renal laboratory measurements continued to worsen. On (b) (6) (Study Week 28) he had nephrotic range proteinuria (6270 mg/24 hours), UPCR 7678 mg/g, serum creatinine 2.43 mg/dL, and eGFR 32 mL/min/1.73m<sup>2</sup>.
- On (b) (6) (Study Week 29) kidney biopsy showed fibrillary glomerulonephritis with crescents, crosshatched fibrillary material causing extensive capillary loop widening and mesangial expansion, interstitial fibrosis, and amyloidosis, TTR type. IgG was markedly positive in the mesangial regions. C3 staining was not done. (See Appendix 13.6 for the kidney biopsy report for Subject (b) (6)) That day, treatment started with oral prednisolone 60 mg once daily.
- Peak serum creatinine was 2.73 mg/dL on (b) (6) (eGFR 28 mL/min/1.73m<sup>2</sup>).
- He was treated with oral cyclophosphamide 100 mg daily from (b) (6) (Study Week 30) to (b) (6) (Study Week 38) and intravenous cyclophosphamide 500 mg IV every 3-4 weeks. Tapering of the prednisolone started in (b) (6), and treatment with prednisolone 10 mg daily was ongoing at study termination in (b) (6). After immunosuppressive treatment, the subject's renal parameters improved (UPCR 702 mg/g and eGFR 71 mL/min/1.73m<sup>2</sup> at last measurement on (b) (6)).

Figure 14. Subject (b) (6). Summary of renal laboratory measurements and inotersen dosing.<sup>107</sup>



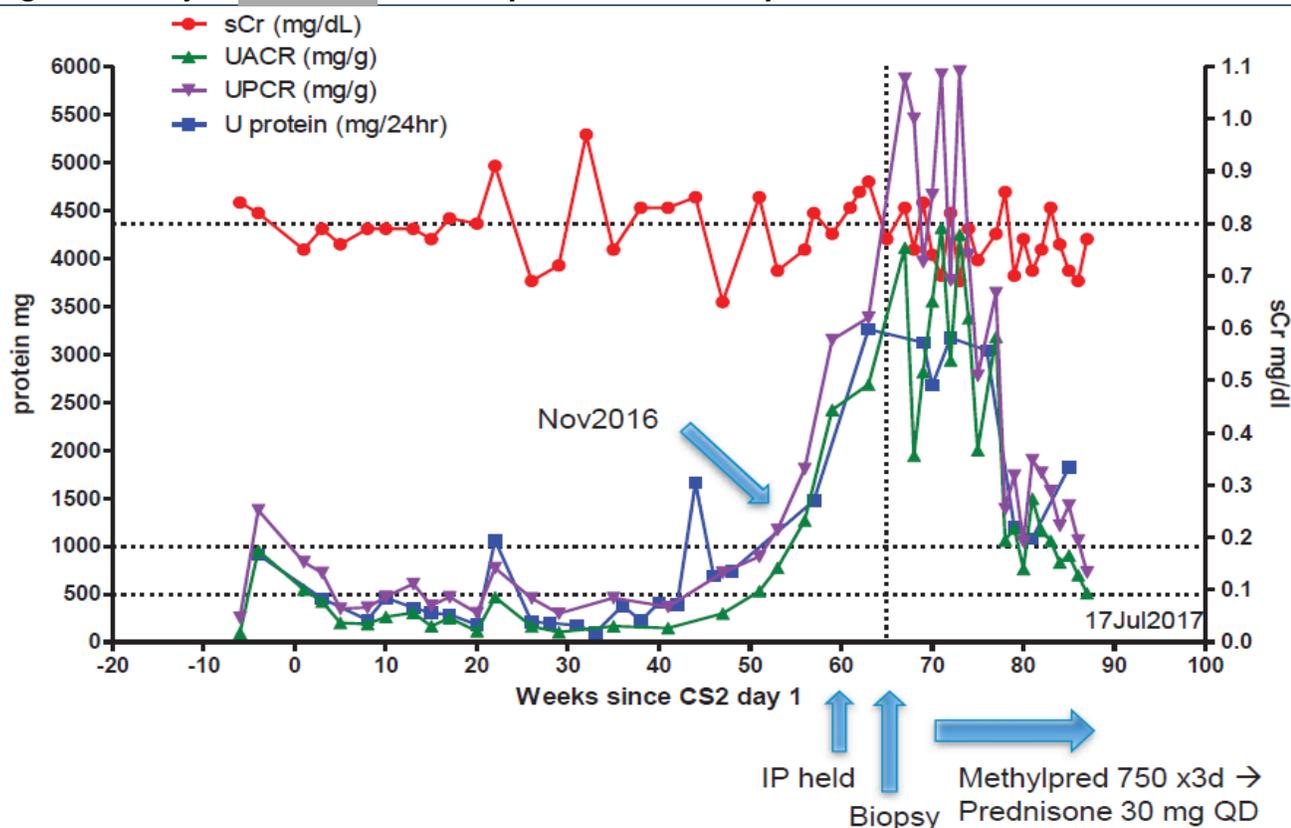
Grey vertical lines represent the dosing records from CS2 study.  
 Creatinine = serum creatinine; eGFR = estimated glomerular filtration rate; CKD-EPI = CKD-EPI Creatinine Equation (Levey 2009)  
 A/C Ratio = Urine AC (mg/g) = urine albumin to creatinine ratio; P/C Ratio = Urine P/C (mg/g) = urine protein to creatinine ratio

<sup>107</sup> P. 465 Sponsor response to FDA pre-submission safety requests. Module 1 November 6, 2017 submission to NDA 211172.

Subject (b) (6)

- The subject is a 35-year-old female from Brazil who had a normal baseline estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m<sup>2</sup>. Urine protein to creatinine ratio (UPCR) prior to treatment was variable, and the baseline UPCR was elevated at 1376 mg/g.
- The subject’s UPCR increased to 1807 mg/g on (b) (6) (Study Week 55; 13 months after first inotersen dose). Last dose of inotersen was administered on (b) (6) (Study Week 60). On (b) (6) UPCR increased to 3383 mg/g.
- Kidney biopsy on (b) (6) (Study Week 65) showed immune complex-mediated glomerulonephritis with focal crescents. (See Appendix 13.7 for the kidney biopsy report for Subject (b) (6))
- Despite stopping inotersen in (b) (6), UPCR increased to 5874 mg/g on (b) (6) and remained in that range until (b) (6). Serum creatinine remained normal.
- The subject was treated with corticosteroids (intravenous methylprednisolone 750 mg daily from (b) (6) and then oral prednisone 30 mg once daily through (b) (6) tapered until discontinuation in (b) (6)). Proteinuria improved after corticosteroid treatment. At last measurement on (b) (6) UPCR was 219 mg/g.

Figure 15. Subject (b) (6). Summary of renal laboratory measurements and clinical events.



IP = investigational product = inotersen; sCr = serum creatinine; UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio; U protein = urine protein

Source: P. 1574 Sponsor response to FDA pre-submission safety requests. November 6, 2017 submission to NDA 211172.

## Treatment of inotersen-related glomerulonephritis

In the 3 clinical study cases, immunosuppressive medication was required for improvement, and cessation of inotersen alone was not sufficient to resolve manifestations of glomerulonephritis:

- Subject (b) (6) did not receive immunosuppressive treatment for glomerulonephritis. He remained dialysis-dependent, and his UPCR remained elevated at 6661 mg/g 3.5 months after the last dose of inotersen was administered.
- Subject (b) (6) last inotersen dose was administered on (b) (6). On (b) (6), UPCR was 5850 mg/g, serum creatinine was 1.74 mg/dL, and eGFR was 32 mL/min/1.73m<sup>2</sup>. On (b) (6) (Study Week 28) he had nephrotic range proteinuria (6270 mg/24 hours), UPCR 7678 mg/g, serum creatinine 2.43 mg/dL, and eGFR 32 mL/min/1.73m<sup>2</sup>. Peak serum creatinine was 2.73 mg/dL on (b) (6). Immunosuppressive treatment was started on (b) (6) with subsequent improvement in the subject's renal parameters.
- Subject (b) (6) last dose of inotersen was on (b) (6). On (b) (6) UPCR was 3383 mg/g. UPCR increased to 5874 mg/g on (b) (6) and remained in that range until (b) (6). Corticosteroid treatment started on (b) (6), and the subject's proteinuria subsequently improved. At last measurement on (b) (6), UPCR was 219 mg/g.

*Reviewer comment: An additional case of immune-mediated renal toxicity occurred in Study CS3 Subject (b) (6), who had systemic antineutrophil cytoplasmic autoantibody (ANCA)-positive vasculitis with renal, articular, and skin involvement (see Section 8.5.3).*

## Nephrotic Syndrome

The 3 inotersen subjects with biopsy-proven glomerulonephritis were accompanied by nephrotic syndrome.<sup>108</sup> Complications of nephrotic syndrome include edema, hypercoagulability with venous or arterial thrombosis,<sup>109</sup> increased susceptibility to infection, protein malnutrition, hypovolemia, urinary loss of hormones, and hyperlipidemia.<sup>110</sup>

In a clinical study (DMD114044) of drisapersen, an antisense oligonucleotide developed for treatment of Duchenne muscular dystrophy, Subject (b) (6) developed life-threatening thromboses (renal vein and inferior vena cava thrombi with bilateral pulmonary emboli) in the setting of glomerulonephritis and nephrotic syndrome.<sup>111</sup> Like the inotersen subjects diagnosed with glomerulonephritis, proteinuria in

<sup>108</sup> P. 205 March 12, 2018 submission to NDA 211172.

<sup>109</sup> Parag KB, et al. Arterial thrombosis in nephrotic syndrome. *Am J Kidney Dis.* 1990 Feb;15(2):176-7.

<sup>110</sup> Crew RJ, et al. Complications of the nephrotic syndrome and their treatment. *Clin Nephrol* 2004; 62:245.

<sup>111</sup> P. 240 FDA briefing document. Peripheral and Central Nervous System Drugs Advisory Committee Meeting. November 24, 2015. Accessed on March 17, 2018 at:

<https://www.fdanews.com/ext/resources/files/11-15/11-20-FDA-DMD-Briefing.pdf?1520841005>

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Subject (b) (6) continued to worsen after cessation inotersen; thromboses occurred 1 month after cessation of drisapersen.

*Reviewer comment: In addition to treatment to preserve renal glomerular function, inotersen patients with glomerulonephritis will require monitoring and treatment for nephrotic syndrome and its manifestations.*

**Renal Impairment: Serious or Severe Treatment-Emergent Adverse Events**

Adverse events of renal impairment categorized as serious or severe in Studies CS2 and CS3 are summarized in the table below. In Study CS2, 7 of 112 (6.2%) inotersen subjects had a renal impairment event in these categories, compared to 1 of 60 (1.7%) placebo subjects. The 7 inotersen cases included 3 cases of biopsy-confirmed glomerulonephritis, 2 cases with baseline elevated urine protein that were unlikely related to inotersen,<sup>112</sup> and 2 cases that were possibly related to inotersen.<sup>113</sup>

*Reviewer comment: Accumulation of antisense oligonucleotides in proximal tubule cells of the kidney, sometimes leading to increased tubular proteinuria, has been described in preclinical studies. In individual subjects, it is difficult to assess of whether increased protein is related to inotersen, because proteinuria can be a clinical feature of hATTR-related kidney disease.*

**Table 39. Serious or Severe Treatment-Emergent Renal Impairment Adverse Events: Studies CS2 and CS3**

Subject Number	Study Treatment Group	Age <sup>a</sup> (Yr)/ Sex/ Mutation/ Baseline UPCR	Preferred Term(s)	Serious (Y/N) Sponsor Severity Assessment	Time From first inotersen dose to AE onset (months)	Biopsy (Y/N)	Comments and Reviewer Assessment of Causality
(b) (6)	CS2 Inotersen	67/ Male/ VAL30MET 229 mg/g	Acute kidney injury	Y Severe	3	Y	Fibrillary glomerulonephritis with crescent formation. <i>Related to inotersen.</i>
(b) (6)	CS2 Inotersen	37/ Male/ VAL30MET 540 mg/g	Glomerulonephritis Tubulointerstitial nephritis	Y Severe	6	Y	Fibrillary glomerulonephritis with extensive crescent formation. <i>Related to inotersen.</i>
(b) (6)	CS2 Inotersen	35/ Female/ VAL30MET 1376 mg/g	Glomerulonephritis	Y Moderate	13	Y	Immune complex-mediated glomerulonephritis with focal crescents. <i>Related to inotersen.</i>

<sup>112</sup> Subjects (b) (6)

<sup>113</sup> Subjects (b) (6)

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Subject Number	Study Treatment Group	Age <sup>a</sup> (Yr)/ Sex/ Mutation/ Baseline UPCR	Preferred Term(s)	Serious (Y/N) Sponsor Severity Assessment	Time From first inotersen dose to AE onset (months)	Biopsy (Y/N)	Comments and Reviewer Assessment of Causality
(b) (6)	CS2 Inotersen	78/ Female/ VAL30MET 116 mg/g	Renal failure	Y Severe	13	N	The subject had an increase in serum creatinine from 0.88 mg/dL at baseline to 1.6 mg/dL 14 months later. Hospitalized for renal failure and treated with increased hydration, as well as fosfomycin for suspected UTI. After inotersen discontinuation, serum creatinine returned to baseline level (0.91 mg/dL). <i>Possibly related to inotersen.</i>
	CS2 Inotersen	68/ Male/ VAL30MET 1878 mg/g	Renal impairment	Y Severe	< 1	N	Proteinuria and decreased eGFR at baseline. Continued decline with inotersen treatment. Progression to end-stage renal disease requiring dialysis after inotersen cessation. <i>Consistent with renal disease related to TTR amyloidosis, but a role of inotersen cannot be ruled out.</i>
	CS2 Inotersen	34/ Female/ VAL30MET 1552 mg/g	Acute kidney injury	Y Moderate	<1	N	Acute renal failure likely related to urinary tract infection in the setting of diuretic and angiotensin receptor blocker use. <i>Unlikely related to inotersen.</i>
	CS2 Inotersen	50/ Female/ VAL30MET 492 mg/g	Renal impairment	N Severe	5	N	Started inotersen in (b) (6). Developed decreased renal function, proteinuria, and edema in (b) (6). Inotersen was discontinued, but renal impairment continued. The subject had advanced hATTR-PN and died in (b) (6). The Sponsor attributed her death to cachexia. Renal dysfunction may have contributed to her death. <i>Possibly related to inotersen.</i>
	CS2 Placebo	55/ Female/ VAL30MET 716 mg/g	Proteinuria	N Severe	< 1	Y	Placebo-treated subject with biopsy-confirmed progression of renal disease related to TTR amyloidosis.
	CS3 Inotersen-Inotersen	27/ Male/ VAL30MET 74 mg/g	Renal impairment	N Severe	7	Y	Progressive renal decline. Biopsy showed renal disease relate to TTR amyloidosis. <i>Unrelated to inotersen.</i>
	CS3 Inotersen-Inotersen	60/ Male/ THR60ALA 216 mg/g	Haematuria	Y Mild	19	N	Hematuria in the setting of initiation of anticoagulation with rivaroxaban. <i>Unrelated to inotersen.</i>

Source: Summary of Clinical Safety Table 76 and patient narratives  
 UPCR = urine protein to creatinine ratio; TTR = transthyretin

**Renal Impairment: Laboratory Data**

In Study CS2, inotersen subjects had more frequent decreases in eGFR, as well as more frequent increases in urine protein to creatinine ratio and in serum creatinine (see table below).

**Table 40. Subjects with Renal Parameter Abnormalities**

	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=49)	Inotersen- Inotersen (N=85)	Inotersen 300 mg (N=112)	Inotersen 300 mg (N=161)
<b>Subjects with any renal parameter abnormalities, n (%)</b>	<b>49 (81.7)</b>	<b>94 (83.9)</b>	<b>38 (77.6)</b>	<b>74 (87.1)</b>	<b>101 (90.2)</b>	<b>139 (86.3)</b>
Creatinine clearance by CKD-EPI, n (%)						
<90 mL/min/1.73 m <sup>2</sup>	42 (70.0)	84 (75.0)	34 (69.4)	70 (82.4)	92 (82.1)	126 (78.3)
<60 mL/min/1.73 m <sup>2</sup>	16 (26.7)	29 (25.9)	11 (22.4)	29 (34.1)	43 (38.4)	54 (33.5)
<30 mL/min/1.73 m <sup>2</sup>	0	3 (2.7)	1 (2.0)	3 (3.5)	6 (5.4)	7 (4.3)
<15 mL/min/1.73 m <sup>2</sup>	0	2 (1.8)	0	1 (1.2)	3 (2.7)	3 (1.9)
≥25% decrease from Baseline (CS2 and Longitudinal data)/Inotersen Baseline (CS3 data)	6 (10.0)	32 (28.6)	7 (14.3)	36 (42.4)	52 (46.4)	59 (36.6)
≥50% decrease from Baseline (CS2 and Longitudinal data)/Inotersen Baseline (CS3 data)	0	8 (7.1)	1 (2.0)	5 (5.9)	13 (11.6)	14 (8.7)
n (%)						
Urine P/C ratio >5 x ULN	5 (8.3)	17 (15.2)	1 (2.0)	8 (9.4)	22 (19.6)	23 (14.3)
Urine A/C ratio >5 x ULN	14 (23.3)	32 (28.6)	13 (26.5)	22 (25.9)	41 (36.6)	54 (33.5)
Serum creatinine increase >44.2 μmol/L (0.5 mg/dL) from Baseline (CS2 and Longitudinal data)/Inotersen Baseline (CS3 data)	1 (1.7)	12 (10.7)	3 (6.1)	13 (15.3)	22 (19.6)	25 (15.5)

Includes all laboratory values (central and local) through the Safety Update Report cut-off date September 15, 2017.

Baseline = Results from evaluations performed before the first dose of inotersen.

Inotersen Baseline = Results from evaluations performed before the first dose of inotersen.

Source: P. 5 Response to FDA IR submitted to NDA 211172 on March 29, 2018

### Renal Impairment: Prescribing Information Recommendations

In the proposed labeling submitted with the NDA, the Sponsor includes instructions to not initiate inotersen treatment in patients with a urine protein to creatinine ratio  $\geq 1$  g/g (1000 mg/g).

The Sponsor's labeling recommendation for renal parameter monitoring is copied below.

#### Figure 16. Sponsor Proposed Labeling: Renal Parameter Monitoring



#### Reviewer comments:

*The Sponsor does not provide a specific proposal for the frequency of renal parameter monitoring. Based on the potential for rapid onset and progression of glomerulonephritis, this reviewer recommends monitoring urinalysis, quantitative urine protein, and serum creatinine every 2 weeks. Cases of glomerulonephritis in inotersen subjects did not resolve unless immunosuppressive treatment was administered. Prompt diagnosis of glomerulonephritis is necessary to facilitate timely treatment. Obtaining a renal biopsy to establish the diagnosis of glomerulonephritis can sometimes add to the time from initial evaluation to the start of treatment. In clinical study subjects<sup>114</sup> who received immunosuppressive treatment for glomerulonephritis, the time from first nephrotic-range proteinuria to the start of immunosuppressive treatment was 1-2 months.*

*The Sponsor proposes the confirmed diagnosis of acute glomerulonephritis as a criterion for stopping inotersen treatment.* (b) (4)

*The protocols for Studies CS2 and CS3 say that the drug will be stopped for 24-hour urine protein levels  $> 3.5$  g. However, the decision to stop inotersen based on renal parameters was determined by investigators and the Study Medical Monitor, often in consultation with a nephrologist.<sup>115</sup> Generally, inotersen was discontinued in study subjects with a urine protein to creatinine ratio (UPCR)  $> 1000$  mg/g,<sup>116</sup> which is consistent with the Sponsor's recommendation to avoid starting inotersen in patients with UPCR  $> 1000$  mg/g at*

<sup>114</sup> Subjects (b) (6)

<sup>115</sup> Appendix 2. Response to FDA pre-submission safety requests. NDA 211172 submitted November 6, 2017.

<sup>116</sup> Review of narratives submitted to NDA 211172 on February 5, 2018 in response to an FDA information request.

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*baseline. This reviewer recommends stopping inotersen in patients who develop UPCR >1000 mg/g during inotersen treatment.*

### 8.5.3. Inflammatory and Immune Effects

Inflammatory and immune changes are recognized as a class effect of antisense oligonucleotides.<sup>117</sup>

In a 39-week study of inotersen in monkeys,<sup>118</sup> vasculitis (perivascular mixed cell infiltration composed of neutrophils, macrophages, and lymphocytes) in multiple organs (e.g., cecum, cervix, colon, gallbladder, heart, injection site, kidneys, knee joint, liver, lung, pancreas, skeletal muscle, stomach, urinary bladder, uterus, and vagina) was seen in 6 of 32 inotersen-exposed monkeys and 0 of 8 control monkeys. These changes were not seen in the highest dose group and were sporadic within the dose groups in which they were observed. These pro-inflammatory organ changes were accompanied by significant increases of various plasma cytokines/chemokines.<sup>119</sup> In addition, mononuclear cell infiltrates in the choroid plexus were seen in 19 of 32 inotersen-exposed monkeys, compared to 0 of 8 control monkeys.<sup>120</sup>

In clinical studies, inotersen caused increases in B lymphocyte levels in Study CS2 subjects.<sup>121</sup> In inotersen clinical study subjects, conditions consistent with an inflammatory or immune etiology include:

- Immune thrombocytopenia (see Section 8.5.1)
- Glomerulonephritis (see Section 8.5.2)
- Neurologic toxicity\*
  - Carotid dissection and stroke
  - Myelopathy
  - Encephalitis
- Vasculitis\*
- Autoimmune hepatitis/Primary biliary cirrhosis (see Section 8.5.4)

\* Conditions marked with an asterisk are discussed in this review section.

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<sup>117</sup> Senn JJ, et al. Non-CpG-Containing Antisense 2'-Methoxyethyl Oligonucleotides Activate a Proinflammatory Response Independent of Toll-Like Receptor 9 or Myeloid Differentiation Factor 88. *Journal of Pharmacology and Experimental Therapeutics* September 2005, 314 (3) 972-979.

<sup>118</sup> Study 420915-AS08

<sup>119</sup> P. 588 Study 420915-AS08 final report

<sup>120</sup> Table 2 of Applicant response to FDA information request. Submitted to NDA 211172 on May 14, 2018.

<sup>121</sup> P. 22 420915-CR02 Study Report

## Inflammatory and Immune Effects of Inotersen: Neurologic Toxicity

In clinical studies of inotersen, neurologic serious adverse events consistent with the effects of vascular inflammation included:

- Stroke and Carotid Dissection
- Myelopathy
- Encephalitis

### Study CS2 Subject (b) (6) Stroke and Carotid Dissection

At enrollment, this 53-year-old female subject from the United States had Stage 2 hATTR-PN and cardiomyopathy with NYHA class II heart failure. Other relevant past medical history includes hypertension and evidence of myocardial infarction on baseline EKG.

- (b) (6) (Study Day 1): Pre-treatment vital signs included blood pressure 110/63 and heart rate 68 bpm. The subject received the first inotersen dose. (No additional inotersen doses were administered.) After dosing, the subject had AEs of ecchymosis, muscular/leg weakness, muscle spasms, injection site reaction and pain, nausea, vomiting, dry mouth, total body pain, anal incontinence, and productive cough.  
*Reviewer comment: The subject's post-treatment symptoms on Study Day 1 are consistent with cytokine release syndrome.*
- (b) (6) (Study Day 2): The subject had continued symptoms from Day 1, as well as inability to move her eyes, a 10-minute episode of screaming "gibberish," a diffuse headache, and difficulty eating (gagging).
- (b) (6) (Study Day 3): The subject was seen in the clinic. Some symptoms from Study Days 1 and 2 were reported as resolved. Vital signs included a blood pressure of 100/70, heart rate of 76 bpm, and temperature 100.4. ECG was not meaningfully different from baseline.
- (b) (6) (Study Day 7): The subject had trouble getting out of the car and her speech was incoherent. Her condition worsened, and she fell from the bed to the floor and was unable to move.
- (b) (6) (Study Day 9): The subject was hospitalized for cognitive dysfunction with possible seizure activity. Upon admission, the family reported a 1-week history of loss of speech, facial expression, and overall movement, as well as needing help ambulating, drowsiness, and fatigue.
- (b) (6) (Study Day 10):
  - A non-contrast computed tomography (CT) scan of the head revealed a hypoattenuating lesion with mass effect involving the left basal ganglia and anterior limb of the internal capsule. A neurology consultation concluded that the lesion likely represented a subacute infarct.  
*Reviewer comment: The 1-week history of symptoms on admission and the subacute infarct on CT scan indicate that the stroke occurred on approximately Study Day 2.*

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- CT angiogram of the head and neck showed mild stenosis of the distal horizontal left middle cerebral artery (MCA) segment. Suspected focal dissection at the left carotid artery bifurcation extending approximately 1 cm into the left internal carotid artery. An apparent small dissection flap was seen at the posterolateral aspect of the most distal common carotid artery.<sup>122</sup> There was no significant atherosclerotic disease seen at this level.
- A carotid and transcranial Doppler showed no evidence of atherosclerotic plaque or obstruction to flow at either carotid bifurcation. Transcranial Doppler mean flow velocities were normal in the middle cerebral, vertebral and basilar arteries. There were no embolic signals detected.
- There was no evidence of atrial fibrillation on interrogation of automatic internal cardiac defibrillator (AICD) and no events on telemetry.
- Treatment with heparin was initiated.
- (b) (6) (Study Day 11): A transesophageal echocardiography showed no evidence of thrombus in the left atrium and was consistent with past transthoracic echocardiography. Ejection fraction was 38%.
- (b) (6) (Study Day 15): Carotid cerebral angiogram was normal. Visualization of the cervical vessels did not demonstrate evidence of dissection of the left internal carotid artery.
- (b) (6) (Study Day 16): Whole-body scan showed no evidence of diffuse leptomeningeal amyloid deposition.

*Reviewer comment:*

*In this reviewer's assessment, this subject had left carotid artery dissection and embolic stroke (left middle cerebral artery) that is likely related to inotersen. Other than the left carotid artery dissection, no other embolic source was found:*

- *There was no evidence of atrial fibrillation on interrogation of automatic internal cardiac defibrillator (AICD) and no events on telemetry. The subject did not have a known history of atrial fibrillation.*
- *No thrombus was seen on transesophageal echocardiogram*
- *No leptomeningeal amyloid deposition was seen on whole-body scan*
- *CT angiogram and Doppler showed no significant atherosclerosis of the carotid arteries*

*Left carotid artery dissection was seen in CT angiogram on Study Day 10. Carotid cerebral angiogram (5 days later) on Study Day 15 was normal, which may be a result of healing of the injury. (The carotid cerebral angiogram was done approximately 2 weeks after the onset of stroke symptoms.) Healing of carotid artery injury with a raised intimal flap or intraluminal*

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<sup>122</sup> P. 60 Response to FDA information request submitted to NDA 211172 on August 8, 2018.

*thrombus on follow-up angiography after 7-10 days has been described in the published literature.*<sup>123</sup>

*In this subject, stroke and arterial dissection occurred shortly after a single dose of inotersen. There is no way to predict, prevent, or mitigate the occurrence of similar events. Stroke is a medical emergency, and thrombolytic therapy generally must start within 3-4.5 hours from the onset of symptoms. Thus, patient and prescriber education regarding this risk is essential.*

*Carotid dissection and embolic stroke occurred after symptoms consistent with cytokine release syndrome and increased inflammation. Pre-treatment high-sensitivity C-reactive protein (hsCRP) on Study Day 1 was 0.2 mg/L (reference range 0-3 mg/L), compared to 108 mg/L post-treatment on Study Day 3.<sup>124</sup> On Study Day 13 C-reactive protein was 8.3 mg/L (reference range 0.0-5.0 mg/L).*

*Cases of neurotoxicity have been reported in the setting of cytokine release with other therapies. In chimeric antigen receptor T cell (CAR-T) therapies, inflammatory cytokines can increase the permeability of the blood brain barrier, which can lead to high concentrations of serum cytokines.<sup>125</sup> This process can cause vascular disruption, with cerebral edema, hemorrhage, infarction, and necrosis, and neuronal death as observed in autopsy studies of 2 patients who had fatal neurotoxicity.<sup>126</sup>*

#### Study CS2 Subject (b) (6): Myelopathy

At enrollment, this 52-year-old female subject from Portugal had Stage 1. Other relevant past medical history includes pacemaker insertion (b) (6), positional vertigo (b) (6), and hypertension (b) (6). The subject first received inotersen on (b) (6) (Study Day 1).

- (b) (6) (Study Day 75): The subject had an AE of gait disturbance.
- (b) (6) (Study Day 226): Walking imbalance, reported as serious adverse event Preferred Term Myelopathy. Inotersen treatment was continued.
- Unspecified date in (b) (6): The subject experienced paraparesis, which began with a sudden episode of lumbar pain, a sensation of running water in the lower limbs, and worsening gait. At that time, a focal protrusion of the L4-L5 disc and mild,

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<sup>123</sup> Biffi WL, et al. Blunt carotid arterial injuries: implications of a new grading scale. *J Trauma*. 1999 Nov;47(5):845-53.

<sup>124</sup> Cytokines were not measured in Study CS2. See Section 8.4.6 for additional information regarding cytokine levels with inotersen use.

<sup>125</sup> Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov*. 2017;7:1404-19.

<sup>126</sup> Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomark Res*. 2018 Jan 22;6:4

diffuse disc prolapse at L3-L4 were identified, but no definitive etiology for the paraparesis was identified.

- (b) (6) (Study Day 270): The subject had worsening ataxia and pyramidal signs and was hospitalized with left vestibular neuritis and for evaluation of myelopathy. Weeks 40-42 doses of inotersen were not administered during the hospitalization.
- (b) (6) (Study Day 277): Lumbar puncture cerebrospinal fluid (CSF) examination: clear and colorless with 6.0 cells/mm<sup>3</sup> with prevalence of lymphocytes. CSF protein mildly elevated (51.5 mg/dL). CSF glucose 49 mg/dL. CSF bacteriology test negative. No evidence of neoplastic cells on CSF cytopathology test. Syphilis serology, brucellosis, and Lyme disease in CSF were negative.<sup>127</sup>
- (b) (6) (Study Day 284): Results from a magnetic resonance imaging (MRI) scan of the cervical/dorsal/lumbosacral spine were inconclusive. There was reported mild ectasia of the central canal in the ependymal, more evident in the inferior dorsal region. There was no diffuse leptomeningeal enhancement on contrast MRI.
- (b) (6) (Study Day 291): The subject was discharged from the hospital. The myelopathy and neuralgia remained ongoing. It was noted that prior to these events, the subject was very active and working full-time. According to the discharge note, the paraparesis was extensively investigated with no definitive diagnostic conclusion.<sup>128</sup>
- The subject restarted inotersen treatment and received doses for Weeks 43-45. Three days after the Week 45 dose, the subject the subject experienced an exacerbation of the paraparesis characterized by decreased muscle strength after awaking in the morning, significant functional impairment, and the inability to walk (Study Day 312). The subject had bilateral thigh edema and was found to have bilateral femoral deep vein thromboses (DVT). The subject subsequently developed pulmonary embolism. Laboratory evaluations did not indicate systemic rheumatic disease or a specific cause of thrombophilia.
- Inotersen was discontinued after administration of the Week 46 dose on (b) (6)

*Reviewer comment: This subject's progressive myelopathy is consistent with vasculitis. In a study of inotersen exposure in monkeys, vasculitis was seen in multiple organs. Symptoms of central nervous system vasculitis are nonspecific, and neither neuroradiological nor laboratory tests can provide a definite diagnosis, for which the gold standard is biopsy confirmation.<sup>129</sup> The evaluation of this condition involves systematic evaluation and exclusion of other disorders. This subject's paraparesis was extensively investigated with no definitive diagnostic conclusion.*

<sup>127</sup> P. 116 Applicant response to FDA information request submitted to NDA 211172 on August 8, 2018.

<sup>128</sup> P. 120 Applicant response to FDA information request submitted to NDA 211172 on August 8, 2018.

<sup>129</sup> Berlitz P. Diagnosis and treatment of cerebral vasculitis. *Ther Adv Neurol Disord*. 2010 Jan; 3(1): 29-42.

*Given the proinflammatory effects of inotersen, in this reviewer's assessment, this case is likely related to inotersen. The subject had a positive rechallenge with exacerbation of paraparesis 3 days after restarting inotersen (Study Day 312).*

*The Applicant says that "myelopathy secondary to degenerative spinal changes with spinal canal encroachment is a plausible alternate etiology in the view of the Applicant."<sup>130</sup> However, The Applicant acknowledges that CT scan evaluation of the spine performed after the onset of myelopathy showed no obvious sign of spinal cord compression.*

Study CS2 Subject (b) (6): Encephalitis

- At enrollment, this 46-year-old male subject from the Brazil had Stage 1 hATTR-PN and cardiomyopathy with NYHA class II heart failure. First dose of inotersen was administered on (b) (6) (Study Day 1). In (b) (6), inotersen dosing was held on and off because of proteinuria. Inotersen was restarted (b) (6).
- At the end of (b) (6) the subject had progressive, intermittent right-sided lumbar pain that increased over the following days and was associated with anorexia (weight loss of 20 pounds) and asthenia. There was no fever, loss of strength, or radiation.
- The Subject had a SAE of vomiting from (b) (6)
- Inotersen dosing was held from (b) (6) because of SAEs of Vomiting and Encephalitis.
- On (b) (6) (Study Day 246), the subject had acute worsening of lumbar pain, headache, and vomiting. He was treated symptomatically at a regional hospital for 48 hours and sent home.
- In (b) (6) his lumbar pain and headache continued to worsen. On (b) (6) (Study Day 266), the subject presented to the emergency department with lumbar pain, headache, and sudden onset of impaired speech described as "trouble finding words" and being "tongue-tied". There was no rigidity in the neck or signs of meningeal inflammation. Computerized tomography of the head, spine, chest, abdomen, and pelvis were all normal. On admission, a lumbar puncture revealed 20 white blood cells (77% lymphocytes; 22% monocytes; 1%macrophages), protein 303, glucose 35, SPE gamma globulin peak/fungus negative, and acid fast bacillus test was negative.<sup>131</sup>  
*Reviewer comment: CSF analyses are notable for high protein levels and lymphocyte-predominant pleocytosis. No positive culture results were reported.*
- On (b) (6) (Study Day 267), a serum analysis was negative for chronic hepatitis, HIV, and cytomegalovirus. The subject received intravenous (IV) ceftriaxone 2 g twice daily and IV ampicillin 2 g four times daily (b) (6). The subject received IV dexamethasone 10 mg four times daily (b) (6).

<sup>130</sup> P. 6 Applicant response to FDA information request submitted to NDA 211172 on August 8, 2018.

<sup>131</sup> Units of measure and reference ranges were not provided.

- Encephalitis resolved on [REDACTED] (b) (6) (Study Day 284).
- Inotersen dosing was restarted on [REDACTED] (b) (6) and has continued since last follow-up in [REDACTED] (b) (6). The subject has not had a recurrence of symptoms.

*Reviewer comment: This subject had progressive lumbar pain, headache, vomiting,<sup>132</sup> and sudden onset of language deficits. CSF analyses showed high protein levels and lymphocyte-predominant pleocytosis with no evidence of infection. Symptoms resolved after empiric treatment that included high dose steroids. This reviewer considers this subject's findings to be consistent with central nervous system inflammation.*

*Given the proinflammatory effects of inotersen, in this reviewer's assessment, this case is possibly related to inotersen. The inflammatory effects of inotersen can be idiosyncratic. It is possible that inotersen, in the presence of other contributing factors, may have led to this subject's central nervous system inflammation.*

### **Inflammatory and Immune Effects of Inotersen: ANCA-Positive Systemic Vasculitis**

Study CS3 Subject [REDACTED] (b) (6) was diagnosed with systemic antineutrophil cytoplasmic autoantibody (ANCA)-positive vasculitis with renal, articular, and skin involvement.

At enrollment, this 58-year-old male from Portugal had Stage 2 hATTR-PN. He first received inotersen in Study CS2 on [REDACTED] (b) (6). He completed treatment in Study CS2 and started treatment in Study CS3. He received a dose of inotersen on [REDACTED] (b) (6). The subject went on a vacation to Cuba for 2 weeks. After returning to Portugal on [REDACTED] (b) (6), the patient reported hand, feet, knee, and shoulder "arteritis" starting during travel, followed by erythematous cutaneous lesions in the lower limbs. The patient was diagnosed with PR3-ANCA-positive systemic vasculitis with renal, cutaneous and articular involvement.

The subject received a prednisolone 60 mg taper between [REDACTED] (b) (6) and [REDACTED] (b) (6) for the skin manifestations. By [REDACTED] (b) (6) the patient's skin and joint issues had improved but creatinine and proteinuria increased to 1.6 mg/dL and 1182 mg/g respectively (baseline CS3 creatinine was 1.2 mg/dL; UPCR was 104 mg/g). On [REDACTED] (b) (6) test results included: "C3 138, C4 14, IgG 1215, IgA 217, IgM 309 (<230), haptoglobin 283 (<200), anti streptolysin O 36, anti-HIV negative, HbsAg negative, Anti-HbsAg positive, Anti-HCV negative; Anti GBM, Anti DS-DNA, ANA negative; P-ANCA negative, and proteinase 3 antineutrophil cytoplasmic autoantibody (PR3-ANCA) 714 (reference range <20)."<sup>133</sup>

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<sup>132</sup> Vomiting can be a manifestation of central nervous system inflammation/vasculitis.

Salvarani C, et al. *Rheumatology* 2011;50:349–358

<sup>133</sup> Initial case report in applicant response to FDA information request submitted to NDA 211172 on August 8, 2018. Units of measure and reference ranges were not provided.

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Kidney biopsy was done on (b) (6). According to the local pathologist, biopsy findings likely represented a crescentic pauci-immune glomerulonephritis in the kidney with minor amyloid deposits.<sup>134</sup> Biopsy specimens were also sent to a central laboratory, which concluded that there was interstitial fibrosis with no evidence of crescentic glomerulonephritis.

*Reviewer comment: The investigator confirmed that although there is not a consensus on whether the kidney biopsy shows crescentic glomerulonephritis or interstitial nephritis, both can be related to an ANCA-mediated systemic vasculitis.*<sup>135</sup>

The subject was treated with prednisolone and subsequently developed severe hyperglycemia (glucose 711 mg/dL). Steroid dose was reduced, and the subject received treatment with IV pulse cyclophosphamide. On (b) (6), the subject's eGFR was 64 ml/min (normal range >60), urine protein was 42 mg/mL (normal range <12 mg/mL), and ANCA was negative. The subject continued treatment with azathioprine 150 mg and prednisolone 5 mg.

Other than exposure to inotersen, the subject had no systemic diseases or exposures associated with ANCA-positive vasculitis. While the subject was in Cuba there were no signs or symptoms of any kind of infection. Other than paracetamol taken at the start of the articular pain and swelling, the subject took no additional medications.

*Reviewer comment: In this reviewer's assessment, this case of ANCA-positive vasculitis is likely related to inotersen. This subject had no systemic diseases or exposures (e.g., drugs, infections) associated with ANCA-positive vasculitis, and inotersen has known proinflammatory effects.*

#### 8.5.4. Liver Effects

The liver is a major site of accumulation of antisense oligonucleotides. Because it is deposited in the liver, inotersen has the potential for hepatotoxicity.

In Study CS2, 14 of 112 (12.5% inotersen subjects had an abnormal liver function adverse event, compared to 4 of 60 (6.7%) placebo subjects (see table below); these events were generally due to elevated liver enzyme values. The frequency and type of liver-related adverse events were similar in Study CS3.

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<sup>134</sup> The diagnosis of pauci-immune crescentic glomerulonephritis cannot be confirmed given the presence of crescents in fewer than 50% of the glomeruli observed.

<sup>135</sup> P. 134 applicant response to FDA information request submitted to NDA 211172 on August 8, 2018.

**Table 41. Study CS2 On-Study Abnormal Liver Function 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
Abnormal liver function	4 (6.7)	7	14 (12.5)	21
Alanine aminotransferase increased	2 (3.3)	2	3 (2.7)	4
Ascites	0	0	2 (1.8)	2
Aspartate aminotransferase increased	2 (3.3)	2	5 (4.5)	7
Blood alkaline phosphatase abnormal	0	0	1 (0.9)	1
Blood alkaline phosphatase increased	0	0	1 (0.9)	1
Hepatic enzyme increased	0	0	1 (0.9)	1
Hypoalbuminaemia	0	0	1 (0.9)	1
International normalised ratio increased	1 (1.7)	1	0	0
Liver disorder	1 (1.7)	1	0	0
Liver function test abnormal	0	0	1 (0.9)	1
Prothrombin time prolonged	1 (1.7)	1	0	0
Transaminases increased	0	0	3 (2.7)	3
Risk difference, %			5.8	
95% CI			-3.0, 14.6	

Source: Summary of Clinical Safety Table 81

In clinical studies, 8% of inotersen patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN), compared to 3% of placebo patients; 3% of inotersen patients had an ALT at least 8 times the ULN, compared to no placebo patients (see table below).

**Table 42. Study CS2 and CS3 Subjects with Hepatobiliary Laboratory Abnormalities<sup>136</sup>**

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

<sup>136</sup> Table 3 Applicant IR response submitted March 29, 2018

There were no cases of Hy's law in Study CS2 or CS3. One subject (Subject (b) (6)) with Gilbert's disease had a confirmed increase in ALT  $\geq 3$ xULN with concomitant increase in total bilirubin  $\geq 2$ xULN.<sup>137</sup>

In some cases, the transaminase elevations resolved in the setting of continued inotersen use. Selected cases are described below.

- Study CS2 Subject (b) (6) had an elevation of ALT and AST to 8.1 x ULN at Week 18. ALT was 2.98 x ULN and AST was 1.1 x ULN when retested in local laboratory 3 days later (see Figure 16). The elevations resolved during continued dosing with inotersen.
- Study CS3 Subject (b) (6) experienced an elevation of ALT to  $\geq 3$ x ULN on Study Day 5, which resolved during continued dosing with inotersen. This subject developed a further increase in ALT to 4.3 x ULN in Study CS3 after 173 weeks of dosing with inotersen (Study Week 108 in CS3). Alkaline phosphate (ALP) was elevated to 2.9 x ULN at that time (see Figure 17). Serology for hepatitis A total antibody and IgM, hepatitis B core total antibody and IgM, surface antigen of the hepatitis B virus (HBsAg), anti-mitochondria Ab, anti-smooth muscle Ab, and alpha-1-antitrypsin were negative. No alternative explanation has been found for these enzyme elevations as of the CS3 data cutoff date.

*Reviewer comment: The Applicant states that increases in liver laboratory tests are unlikely to be related to inotersen. However, similar patterns in increases of transaminase values have been reported in other antisense oligonucleotides.*<sup>138-139</sup>

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<sup>137</sup> P. 166 Summary of Clinical Safety

<sup>138</sup> P. 269-271 FDA briefing document. Peripheral and Central Nervous System Drugs Advisory Committee Meeting. November 24, 2015. Accessed on August 23, 2018 at:  
<https://www.fdanews.com/ext/resources/files/11-15/11-20-FDA-DMD-Briefing.pdf?1520841005>

<sup>139</sup> Rabinovich-Guilatt L, et al. Impact of dosing regimen of custirsen, an antisense oligonucleotide, on safety, tolerability and cardiac repolarization in healthy subjects. *Br J Clin Pharmacol*. 2015 Sep; 80(3): 436–445.

Figure 17. Subject (b) (6) Liver Laboratory Test Results<sup>140</sup>

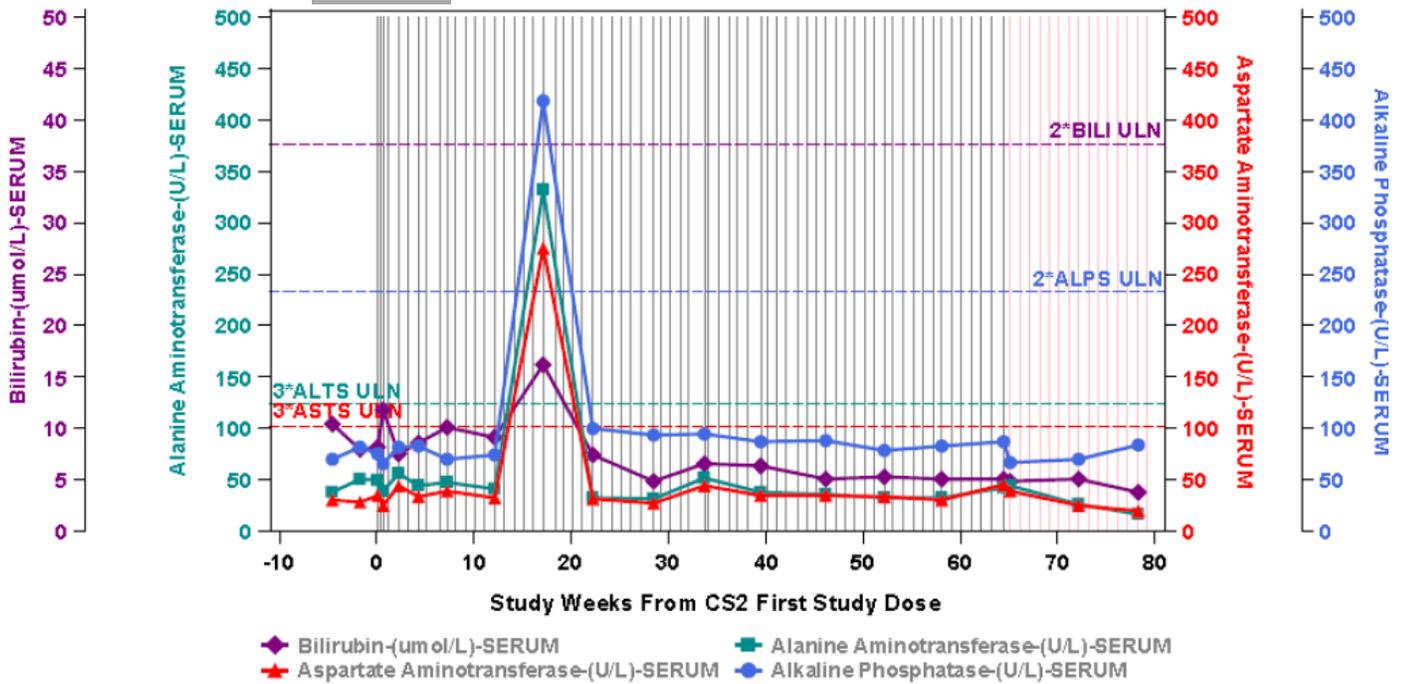
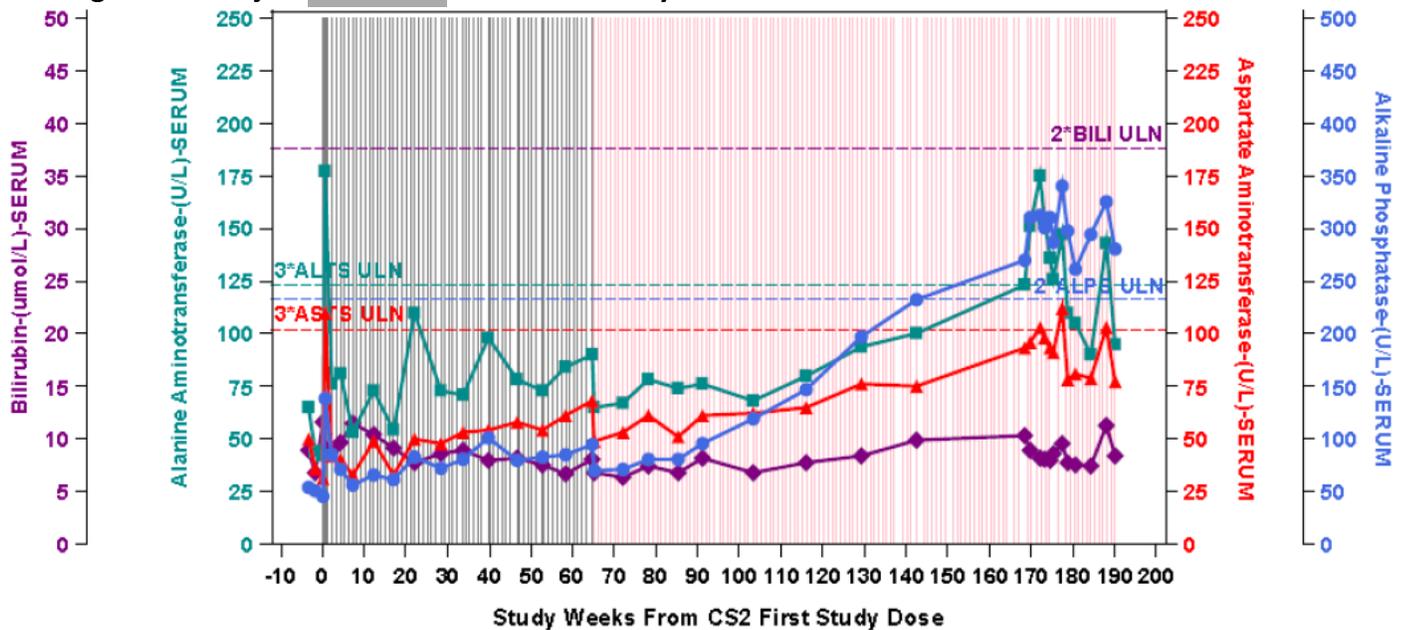


Figure 18. Subject (b) (6) Liver Laboratory Test Results<sup>141</sup>



Grey and pink lines represent the dosing records from CS2 and CS3, respectively. Horizontal lines show levels for 3 x ULN for ALT and AST and 2 x ULN for bilirubin and alkaline phosphatase.

<sup>140</sup> P. 170 Summary of Clinical Safety

<sup>141</sup> P. 173 Summary of Clinical Safety

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Two abnormal liver function serious adverse events were submitted after the original NDA submission:

Study CS3 Subject (b) (6): Primary biliary cirrhosis and autoimmune hepatitis (fatal)

This subject is a 65-year-old male from the United States, who died of autoimmune hepatitis and primary biliary cirrhosis (PBC).<sup>142</sup> He started inotersen treatment in (b) (6) (b) (6) hospitalized for vomiting with ascites and again in (b) (6) with anasarca. In (b) (6), liver biopsy results showed acute flare of autoimmune hepatitis with overlap by primary biliary cirrhosis with a significant degree of fibrosis and collapse. Congo red stains were negative for amyloid. The patient died in (b) (6). The death was attributed to autoimmune hepatitis. No known history of liver disease or PBC. His sister has PBC.

*Reviewer comment: Primary biliary cirrhosis (PBC; also called primary biliary cholangitis) is characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts. A continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance. The sustained loss of intralobular bile ducts causes the signs and symptoms of cholestasis, and eventually results in cirrhosis and liver failure. Autoimmune hepatitis can occur as an overlap syndrome or variant of primary biliary cirrhosis.*

*The prevalence differs considerably in different geographic areas, ranging from 40 to 400 per million. First-degree relatives of patients with primary biliary cirrhosis have a 1-6% prevalence of development of PBC.<sup>143</sup> There appear to be at least two distinct requirements for PBC to develop: genetic susceptibility; and a triggering event that initiates the autoimmune attack on bile duct cells. Inflammatory and immune changes are recognized as a class effect of antisense oligonucleotides, and a range of immune events have been seen with inotersen. In this reviewer's assessment, this death is possibly related to inotersen.*

Study CS3 Subject (b) (6): Biliary Obstruction<sup>144</sup>

This subject is a 64-year old male from the United Kingdom who received placebo in Study CS2 and received the first inotersen dose in Study CS3 on (b) (6) (Study Day 1). Prior to the first dose of study drug in CS3 on (b) (6) (CS3 Day 1), liver laboratory results were normal and included ALT 12 U/L, ALP 54 U/L, AST 17 U/L, direct bilirubin 3.1 µmol/L, and total bilirubin 14.4 µmol/L.

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<sup>142</sup> Submitted to IND 113968 on April 11, 2018

<sup>143</sup> Kaplan MM, Gershwin ME. Primary Biliary Cirrhosis. *N Engl J Med* 2005; 353:1261-1273

<sup>144</sup> Submitted to NDA 211172 in the Safety update report and April 19, 2018 response to FDA information request.

On (b) (6) (Study Day 464), the subject was hospitalized with cholestatic jaundice. A computed tomography (CT)/magnetic resonance cholangiopancreatography (MRCP) showed complex hilar stricture with multiple dissociated ducts.

Two sets of brushings taken during endoscopic retrograde cholangiopancreatography (ERCP) were inconclusive.<sup>145</sup> Percutaneous transhepatic cholangiogram and ultrasound-guided biopsy were performed, but results were not available.

*Reviewer comment: The hilar stricture seen on CT/MRCP was described as a probably cholangiocarcinoma. However, there was no pathologic confirmation of malignancy. Benign hilar strictures can be caused by autoimmune conditions.<sup>146</sup> No testing for autoimmune conditions was reported.*

## Conclusion

The liver is a site of accumulation of antisense oligonucleotides. In clinical studies, 8% of inotersen patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN), compared to 3% of placebo patients; 3% of inotersen patients had an ALT at least 8 times the ULN, compared to no placebo patients. There was a single clinical study case of autoimmune hepatitis with primary biliary cirrhosis in a patient with a family history of primary biliary cirrhosis, as well as a single case of biliary obstruction of unclear etiology. These cases may reflect a role of inotersen in the development of immune-mediated hepatobiliary disease.

*Reviewer comment: The hepatobiliary effects of inotersen with exposure among larger numbers of patients and over longer treatment durations are unclear. This reviewer recommends monitoring of AST, ALT, and total bilirubin at baseline and during inotersen treatment.*

### 8.5.5. Ocular Toxicity

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 clinical studies, all subjects received vitamin A supplementation. The Applicant analyzed ocular treatment-emergent adverse events potentially related to Vitamin A deficiency using a prespecified set of terms.<sup>147</sup>

*Reviewer comment: Eye disease is a manifestation of hATTR-PN.*

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<sup>145</sup> March 7 and 14, 2017.

<sup>146</sup> Baron TH, et al. Benign biliary strictures: current endoscopic management. *Nature reviews. Gastroenterology & Hepatology*. 2011, Vol.8(10), p.573-581.

<sup>147</sup> Defined as any adverse event within the MedDRA higher level terms (HLTs) of fat soluble vitamin deficiencies and disorders, with a preferred term of vitamin A decreased or vitamin A abnormal, or within the structured MedDRA queries (SMQs) of optic nerve disorders, corneal disorders, or retinal disorders (P. 119 Summary of Clinical Safety).

In CS2, on-study ocular TEAEs potentially related to vitamin A deficiency were reported in a similar proportion of subjects in both treatment groups (see table below).

**Table 43. CS2 On-Study Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency**

	Placebo (N=60)		Inotersen 300 mg (N=112)	
	Subjects, n (%)	Number of Events	Subjects, n (%)	Number of Events
Ocular TEAEs potentially related to vitamin A deficiency	12 (20.0)	13	23 (20.5)	25
Corneal disorder	1 (1.7)	1	0	0
Deposit eye	1 (1.7)	1	2 (1.8)	2
Detachment of retinal pigment epithelium	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 abnormal	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

Source: Summary of Clinical Safety Table 59

On-study ocular TEAEs potentially related to vitamin A deficiency reported in Study CS3 are listed in the table below.

**Table 44. Study CS3 On-Study Ocular Treatment-Emergent Adverse Events Potentially Related to Vitamin A Deficiency**

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 related to vitamin A deficiency	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: Summary of Clinical Safety Table 60

### FDA Ophthalmology Consult Review (September 5, 2018)

In a consult review dated September 5, 2018, the Dr. Wiley Chambers concluded the following:

- No specific pattern of ocular adverse events was identified. ERG data did not demonstrate a pattern of vitamin A deficiencies.
- The applicant adequately evaluated the potential of ocular vitamin A deficiency.

*Reviewer comment: Dr. Chambers agreed with the Applicant's proposal to recommend that patients take oral supplementation of the recommended daily allowance (RDA) of vitamin A (approximately 3000 IU vitamin A per day) throughout the time of inotersen treatment. Dr. Chambers also agreed with the Applicant's proposal (b) (4) to correct vitamin A levels that are below the lower limit of normal (LLN). This reviewer concurs with Dr. Chambers' assessments.*

### 8.5.6. Hemorrhages

In Study CS2, 40 of 112 (35.7%) inotersen subjects had an adverse event in the MedDRA SMQ Haemorrhages, compared to 20 of 60 (33.3%) placebo subjects (see table below). There was 1 severe event of fatal intracranial hemorrhage in the setting of severe thrombocytopenia (Subject (b) (6)). Other hemorrhage events were mild or moderate.

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In Study CS3, hemorrhage adverse events were generally similar to those seen in Study CS2 and occurred in 22.8% of Study CS3 subjects.<sup>148</sup>

*Reviewer comment: Hemorrhage adverse events are discussed in sections describing thrombocytopenia (Section 8.5.1) and injection site reactions (Section 8.4.5).*

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<sup>148</sup> Summary of Clinical Safety Table 99

**Table 45. Study CS2 Hemorrhage Treatment-Emergent Adverse Events**

	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

Source: Summary of Clinical Safety Table 98

## 8.6. Safety Analyses by Demographic Subgroups

For analyses of thrombocytopenia by demographic subgroups, see Section 8.5.1.

### Age

In Study CS2, the risk difference between inotersen and placebo subjects  $\geq 65$  years old for adverse events seen frequently within one day of administration (i.e., headache, myalgia, pain in extremity, nausea, chills), as well as for congestive cardiac failure, was larger than the risk difference for those adverse events between inotersen and placebo subjects  $<65$  years old (see table below).

*Reviewer comment: This reviewer recommends including this increased risk of specific AEs in patients  $\geq 65$  years old in the Geriatric use section of the label.*

**Table 46. Study CS2 On-Study Treatment-Emergent Adverse Events with At Least a 10% Difference Between Subgroups (in Either Treatment Group) by System Organ Class and Preferred Term and by Age**

System Organ Class Preferred Term	Placebo				Inotersen 300 mg			
	<65 years (N=34)		≥65 years (N=26)		<65 years (N=64)		≥65 years (N=48)	
	Subjects, n (%)	Number of Events						
Cardiac Disorders	7 (20.6)	9	6 (23.1)	6	11 (17.2)	20	16 (33.3)	31
Cardiac failure congestive	1 (2.9)	1	1 (3.8)	1	0	0	6 (12.5)	11
Gastrointestinal Disorders	22 (64.7)	41	14 (53.8)	27	41 (64.1)	108	31 (64.6)	65
Dysphagia	0	0	3 (11.5)	3	1 (1.6)	1	1 (2.1)	1
Nausea	6 (17.6)	8	1 (3.8)	1	20 (31.3)	25	15 (31.3)	19
Vomiting	1 (2.9)	1	2 (7.7)	2	14 (21.9)	19	3 (6.3)	3
General Disorders and Administration Site Conditions*								
Chills	1 (2.9)	1	1 (3.8)	2	7 (10.9)	17	13 (27.1)	23
Fatigue	4 (11.8)	4	8 (30.8)	10	13 (20.3)	19	15 (31.3)	24
Oedema	0	0	3 (11.5)	4	1 (1.6)	1	0	0
Oedema peripheral	2 (5.9)	2	4 (15.4)	4	9 (14.1)	10	12 (25.0)	13
Infections and Infestations	19 (55.9)	32	18 (69.2)	32	39 (60.9)	90	29 (60.4)	49
Urinary tract infection	5 (14.7)	6	7 (26.9)	8	14 (21.9)	26	7 (14.6)	21
Injury, Poisoning and Procedural Complications*								
Fall	3 (8.8)	3	10 (38.5)	13	7 (10.9)	11	12 (25.0)	15
Thermal burn	5 (14.7)	5	1 (3.8)	1	6 (9.4)	6	0	0
Investigations*								
Platelet count decreased	0	0	0	0	4 (6.3)	5	8 (16.7)	9
Metabolism and Nutrition Disorders	3 (8.8)	4	5 (19.2)	5	12 (18.8)	21	15 (31.3)	21
Musculoskeletal and Connective Tissue Disorders	17 (50.0)	27	12 (46.2)	30	28 (43.8)	66	29 (60.4)	59
Myalgia	5 (14.7)	5	1 (3.8)	2	6 (9.4)	10	11 (22.9)	15
Pain in extremity	7 (20.6)	9	1 (3.8)	2	3 (4.7)	3	7 (14.6)	9
Nervous System Disorders*								
Headache	6 (17.6)	7	1 (3.8)	3	16 (25.0)	21	10 (20.8)	13
Respiratory, Thoracic and Mediastinal Disorders	11 (32.4)	16	9 (34.6)	12	16 (25.0)	28	17 (35.4)	28
Skin and Subcutaneous Tissue Disorders	7 (20.6)	11	8 (30.8)	8	21 (32.8)	33	17 (35.4)	31

Source: Summary of Clinical Safety Table 131

**Sex**

In Study CS2, the risk difference between female inotersen and placebo subjects for adverse events in the MedDRA System Organ Classes (SOCs) Cardiac disorders, Infections and infestations, and Skin and subcutaneous disorders, as well as Preferred Terms Diarrhea, Vomiting, Fatigue and Myalgia (see table below).

*Reviewer comment: Female subjects may have an increase in these AE categories because dosing does not vary by weight, and some females may be receiving a higher dose by weight.*

**Table 47. CS2 On-Study Treatment-Emergent Adverse Events with At Least a 10% Difference Between Subgroups (in Either Treatment Group) by System Organ Class and Preferred Term and by Sex**

System Organ Class Preferred Term	Placebo				Inotersen 300 mg			
	Female (N=19)		Male (N=41)		Female (N=35)		Male (N=77)	
	Subjects, n (%)	Number of Events						
Cardiac Disorders	2 (10.5)	2	11 (26.8)	13	11 (31.4)	13	16 (20.8)	38
Eye Disorders	5 (26.3)	5	18 (43.9)	22	8 (22.9)	17	23 (29.9)	29
Gastrointestinal Disorders	9 (47.4)	17	27 (65.9)	51	24 (68.6)	50	48 (62.3)	123
Constipation	1 (5.3)	1	5 (12.2)	6	2 (5.7)	2	13 (16.9)	15
Diarrhoea	2 (10.5)	4	10 (24.4)	12	9 (25.7)	10	18 (23.4)	19
Nausea	4 (21.1)	5	3 (7.3)	4	15 (42.9)	18	20 (26.0)	26
Vomiting	0	0	3 (7.3)	3	8 (22.9)	8	9 (11.7)	14
General Disorders and Administration Site Conditions	9 (47.4)	23	24 (58.5)	55	30 (85.7)	173	66 (85.7)	293
Asthenia	0	0	8 (19.5)	11	2 (5.7)	3	12 (15.6)	14
Fatigue	2 (10.5)	2	10 (24.4)	12	11 (31.4)	16	17 (22.1)	27
Injection site bruising	2 (10.5)	2	0	0	1 (2.9)	1	7 (9.1)	7
Injection site pain	4 (21.1)	7	0	0	6 (17.1)	13	17 (22.1)	34
Injection site pruritus	0	0	0	0	1 (2.9)	1	12 (15.6)	15
Oedema peripheral	0	0	6 (14.6)	6	7 (20.0)	8	14 (18.2)	15
Pyrexia	0	0	5 (12.2)	6	7 (20.0)	8	15 (19.5)	24
Infections and Infestations	12 (63.2)	21	25 (61.0)	43	27 (77.1)	75	41 (53.2)	64
Nasopharyngitis	0	0	6 (14.6)	7	2 (5.7)	2	7 (9.1)	7
Urinary tract infection	7 (36.8)	9	5 (12.2)	5	12 (34.3)	36	9 (11.7)	11
Injury, Poisoning and Procedural Complications	9 (47.4)	19	23 (56.1)	35	18 (51.4)	28	31 (40.3)	49
Investigations	5 (26.3)	8	13 (31.7)	25	14 (40.0)	30	45 (58.4)	81
Alanine aminotransferase increased	2 (10.5)	2	0	0	1 (2.9)	1	2 (2.6)	3
Aspartate aminotransferase increased	2 (10.5)	2	0	0	2 (5.7)	2	3 (3.9)	5
Musculoskeletal and Connective Tissue Disorders <sup>a</sup>								
Myalgia	1 (5.3)	1	5 (12.2)	6	8 (22.9)	10	9 (11.7)	15
Psychiatric Disorders <sup>a</sup>								
Insomnia	3 (15.8)	3	0	0	1 (2.9)	1	5 (6.5)	5
Respiratory, Thoracic and Mediastinal Disorders	5 (26.3)	6	15 (36.6)	22	10 (28.6)	17	23 (29.9)	39
Cough	1 (5.3)	1	7 (17.1)	7	4 (11.4)	5	6 (7.8)	6
Nasal congestion	2 (10.5)	3	0	0	0	0	2 (2.6)	2
Skin and Subcutaneous Tissue Disorders	3 (15.8)	5	12 (29.3)	14	12 (34.3)	20	26 (33.8)	44

Source: Summary of Clinical Safety Table 128

## 8.7. Specific Safety Studies/Clinical Trials

No specific safety studies were performed in the inotersen development program.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

In clinical studies, neoplasm adverse events included:

- Study CS3 Subject (b) (6) Meningioma
- Basal cell carcinoma adverse events
  - 1 inotersen subjects in Study CS2
  - 3 subjects in Study CS3

*Reviewer comment: The limited data available in clinical studies does not indicate and increased risk of malignancy with inotersen.*

### 8.8.2. Human Reproduction and Pregnancy

There were no pregnancies in the inotersen clinical development program.

*Reviewer comment: A pregnancy registry postmarketing requirement will be necessary to evaluate the effects of inotersen during pregnancy.*

### 8.8.3. Pediatrics and Assessment of Effects on Growth

Data in the pediatric population was not obtained in the inotersen clinical development program.

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

#### Overdose

There were no adverse events of overdose in the clinical development program.

#### Drug Abuse

This reviewer performed a search using the MedDRA Drug abuse and dependence SMQ, and no events were found in inotersen clinical studies.

#### Withdrawal and Rebound

This reviewer performed a search using the MedDRA Drug withdrawal SMQ, and no adverse events of withdrawal or rebound were found in inotersen clinical studies.

## 8.9. Safety in the Postmarket Setting

### 8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. There is no previous postmarketing experience.

### 8.9.2. Expectations on Safety in the Postmarket Setting

The clinical study findings may not fully represent inotersen clinical safety in the setting of more advanced hATTR-PN. Studies CS2 and CS3 did not include patients with Stage 3 (wheelchair bound) hATTR-PN.

Inotersen is intended to be administered subcutaneously by non-health professionals (e.g., patients, caregivers). The frequent laboratory monitoring recommendations may be difficult for some patients to maintain in the postmarketing setting, which may result in differences between the postmarketing and clinical study safety profiles. Because its mechanism of action is specific to the treatment of hATTR-PN, we do not anticipate significant off-label use of inotersen.

### 8.9.3. Additional Safety Issues from Other Disciplines

The reader is referred to Section 4 of this review.

## 8.10. Integrated Assessment of Safety

Inotersen is associated with severe, potentially fatal adverse effects. Platelet counts less than  $100 \times 10^9/L$  occurred in 25% of inotersen patients, compared with 2% of placebo patients. Platelet counts less than  $75 \times 10^9/L$  occurred in 14% of inotersen patients, compared to 0 placebo patients. Three inotersen patients (3%) had sudden, severe thrombocytopenia (less than  $25 \times 10^9/L$ ), 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.

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

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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 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 patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN), compared to 3% of placebo patients; 3% of inotersen patients had an ALT at least 8 times the 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.

I recommend a post-marketing requirement to further characterize the risks of thrombocytopenia, glomerulonephritis, and neurologic toxicity (e.g., CNS arterial dissection, stroke, CNS vasculitis) using the Risk Evaluation and Mitigation Strategies (REMS) program registry data. I recommend a boxed warning with recommendations for monitoring and administration to mitigate the risks of thrombocytopenia and glomerulonephritis. In the Warnings and Precautions section of the label, I recommend 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 ethylenediaminetetra-acetic acid (EDTA), and (b) (4). I recommend enhanced pharmacovigilance (e.g., expedited reporting, provision of specified summary information in periodic reports) for the safety issues described in the Warnings and Precautions section of

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the inotersen label. I recommend a medication guide to educate patients about these risks.

## **9. Advisory Committee Meeting and Other External Consultations**

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Not applicable.

## **10. Labeling Recommendations**

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### **10.1. Prescription Drug Labeling**

This reviewer recommends a boxed warning with recommendations for monitoring and administration to mitigate the risks of thrombocytopenia and glomerulonephritis. In the Warnings and Precautions section of the label, I recommend 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 ethylenediaminetetra-acetic acid (EDTA), and (b) (4). I recommend a medication guide to educate patients about these risks.

### **10.2. Nonprescription Drug Labeling**

Not applicable.

## **11. Risk Evaluation and Mitigation Strategies (REMS)**

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Safety issues that warrant a REMS include:

- Serious bleeding due to severe thrombocytopenia
- Glomerulonephritis

A REMS will mitigate these risks by ensuring that healthcare providers and patients are educated on these risks and the patient monitoring requirement.

## **12. Postmarketing Requirements and Commitments**

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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, CNS vasculitis) using the REMS registry data.

## **13. Appendices**

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### **13.1. References**

References are included as footnotes throughout this review document.

### **13.2. Financial Disclosure**

The reader is referred to the review of clinical efficacy by Dr. Christopher Breder.

### 13.3. Study CS2 Schedule of Procedures

	Screen	Baseline Assessments	Treatment (65 Wks)																								EOT Efficacy			
Study Week	W -6 to -1 <sup>1</sup>		W 1	W 3	W 5	W 8	W 10	W 13	W 15	W 18	W 20	W 23	W 26	W 29	W 32	W 35	W 38	W 41	W 44	W 47	W 50	W 53	W 56	W 59	W 62	W 65	W 66			
Study Day	S-42 to S-1		D 1	D 3	D 5	D 15	D 29	D 50	D 64	D 85	D 99	D 120	D 134	D 155	D 176	D 197	D 218	D 239	D 240	D 260	D 281	D 302	D 323	D 344	D 365	D 386	D 407	D 428	D 449	D 456
Visit Window (+/- Days)			0	0	0	2	2	2	2	2	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	7	
Informed Consent	X																													
Inclusion/Exclusion	X																													
Medical History	X																													
Height	X																													
HIV, Hepatitis B & C	X																													
Biopsy for Amyloid <sup>3</sup>	X																													
TTR Genotyping <sup>3</sup>	X																													
Study Drug Admin.			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X		X						X								X												X	
Vital Signs <sup>A</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BP <sup>4</sup> , HR, RR, temp)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead, triplicate)	X		X <sup>6</sup>				X <sup>6</sup>										X <sup>6</sup>											X <sup>6</sup>		
Pregnancy Test <sup>5</sup>	X		X <sup>6</sup>						X					X					X						X			X		
Chemistry Panel (Fasting) <sup>A</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Creatinine (Fasting)															X			X		X		X		X		X		X		
Hematology <sup>A</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weekly Platelet Monitoring <sup>10</sup>			← Weekly Platelet Monitoring →																											
Urinalysis <sup>A</sup>	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
24 hour Urine		X																												
Thyroid Panel <sup>A</sup>	X		X						X					X							X								X	
Inflammatory Panel <sup>A</sup>			X	X	X	X	X	X	X								X												X	
PT, aPTT, INR <sup>A</sup>			X	X	X	X	X									X													X	
Complement (C3) <sup>A</sup>			X																											
Immunogenicity <sup>A</sup>			X			X			X					X							X								X	
AE & Concoms & Concomitant Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	



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13.3. Study CS2 Schedule of Procedures  
**Post Treatment Evaluation Period**

	Post-Treatment Evaluation Period (6 Mo) <sup>2</sup>								Early Term
Study Week	W 67	W 69	W 71	W 74	W 77	W 80	W 83	W 91	
Study Day	D 463	D 477	D 491	D 512	D 533	D 554	D 575	D 631	
Visit Window (+/- Days)	7	7	7	7	7	7	7	7	
Informed Consent									
Inclusion/Exclusion									
Medical History									
Height									
HIV, Hepatitis B & C									
Biopsy for Amyloid <sup>3</sup>									
TTR Genotyping <sup>3</sup>									
Study Drug Admin.									
Physical Exam								X	X
Vital Signs <sup>A</sup> (BP <sup>4</sup> , HR, RR, temp)			X		X			X	X
ECG (12-Lead, triplicate)								X	X
Pregnancy Test <sup>5</sup>					X			X	X
Chemistry Panel (Fasting) <sup>A</sup>			X		X			X	X
Serum Creatinine (Fasting)	X	X		X		X	X		
Hematology <sup>A</sup>	X	X	X	X	X	X	X	X	X
Weekly Platelet Monitoring <sup>10</sup>	Weekly Platelet Monitoring								
Urinalysis <sup>A</sup>								X	X
24 hour Urine									
Thyroid Panel <sup>A</sup>								X	X
Inflammatory Panel <sup>A</sup>			X					X	X
PT, aPTT, INR <sup>A</sup>								X	X
Complement (C3) <sup>A</sup>									
Immunogenicity <sup>A</sup>			X					X	X
AE & Conmeds & Concomitant Procedures			X		X			X	X

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13.3. Study CS2 Schedule of Procedures

**Post Treatment Evaluation Period**

	Post-Treatment Evaluation Period (6 Mo) <sup>2</sup>								Early Term
Study Week	W 67	W 69	W 71	W 74	W 77	W 80	W 83	W 91	
Study Day	D 463	D 477	D 491	D 512	D 533	D 554	D 575	D 631	
Visit Window (+/- Days)	7	7	7	7	7	7	7	7	
NIS <sup>6</sup>									
mNIS+7 Assessment <sup>7</sup>								X	EOT
Norfolk QOL-DN <sup>7</sup>								X	EOT
SF-36 Questionnaire <sup>A</sup>								X	X
PND Score								X	X
Body Weight (Fasting)					X			X	X
PD Panel (Fasting) <sup>A</sup>			X		X			X	X
PK Trough <sup>A</sup>			X		X			X	X
Transthoracic ECHO <sup>B</sup>									X
NT-proBNP <sup>A</sup>					X			X	X
Retinol (Fasting) <sup>A</sup>			X		X			X	X
ERG Exam <sup>9</sup>									X
Ophthalmology Exam <sup>9</sup>									X
C-SSRS								X	X
<b>Additional Tests for PK Subgroup Only (n = 20)</b>									
PK AUC/Trough Blood			X		X			X	X
ECG (12-Lead, triplicate)								X	X
Complement (C5a, Bb)								X	X
PT, INR, aPTT								X	X
Inflammatory Panel			X					X	X
Hematology	X <sup>A</sup>	X <sup>A</sup>	X	X <sup>A</sup>	X	X <sup>A</sup>	X <sup>A</sup>	X	X

Note: If not specifically labeled, "X" means anytime. Shaded columns represent visits with the option to be completed in clinic, by a home healthcare service, or by a local laboratory with prior Sponsor approval.

### 13.3. Study CS2 Schedule of Procedures

- 1 A 6-week period is given to complete the screening/baseline assessments. Ideally, the baseline assessments should be conducted after patient eligibility is determined.
- 2 After completing the Week 66 efficacy assessments, patients will enter the post-treatment evaluation period. However, eligible patients may elect to enroll in an OLE study pending study approval by the IRB/IEC and the appropriate regulatory authority. In this case, patients will not participate in the post-treatment evaluation period.
- 3 For determination of patient eligibility only if appropriate documentation is not available. In this case the tests may be conducted up to ten weeks prior to Day 1. For biopsy, location per local practice.
- 4 Blood pressure should be taken after patient has been sitting for  $\geq 5$  min.
- 5 For females of child-bearing potential only, by serum  $\beta$ hCG except on Day 1 where urine hCG is tested pre-dose.
- 6 At Screening for determination of eligibility only (+7 not needed). For an individual patient, every effort should be made to use the same NIS evaluator throughout the study and the NIS evaluator must be insulated from the patient's general study procedures and knowledge of the patient's adverse events.
- 7 The Norfolk QOL-DN questionnaire must be administered prior to any other study procedures. During the baseline and EOT efficacy assessment periods, the Norfolk QOL-DN questionnaire should be administered on the same day as the first mNIS+7 assessment. The mNIS+7 assessment procedure includes the NIS, +7, NSC, and additional sensory and nerve conduction testing. If an ERG or ophthalmology examination are to be conducted on a mNIS+7 assessment day, the mNIS+7 assessment must be conducted first.
  - Two (2) independent mNIS+7 assessments will be performed at Baseline on separate days. Both assessments should be performed within 14 days prior to the first dose of Study Drug (Day 1). In addition, every effort should be made to conduct the two assessments  $< 7$  days apart.
  - mNIS+7 and Norfolk QOL-DN assessments at Week 35 (D239) must be conducted approximately  $> 24$  hours from the previous weeks dose.
  - Two independent mNIS+7 assessments will be performed at Week 66 on separate days. Both assessments must be performed within 14 days from the last dose of Study Drug. The first mNIS+7 assessment must be conducted approximately  $> 24$  hours from the last dose of Study Drug. In addition, every effort should be made to conduct the two assessments  $< 7$  days apart. The EOT efficacy assessment should also be performed on patients that terminate treatment early, ideally within 14 days of the last dose of Study Drug.
- 8 Transthoracic ECHO
  - The baseline, Week 65 and early term ECHOs are conducted on all patients.
  - The Week 41 ECHO is only conducted in patients participating in the ECHO subgroup and can be done at Week 47 if the patient elects to have a Home Healthcare visit at Week 41.
  - There is a window of  $\pm 2$  weeks for all ECHOs.
- 9 ERG and ophthalmology examinations
  - The Week 29 and Week 65 examinations have a window of  $\pm 2$  weeks. The baseline ERG and ophthalmology examinations may be done up to 1-week after Study Day 1 if needed for scheduling purposes (except for Ile84 patients that fall under exclusion criteria 3 and should have eye examinations performed to determine eligibility). Week 65 ERG and ophthalmology examinations may be done at Week 59 if needed for scheduling purposes.
  - The early termination (Early term) ERG and ophthalmology examinations are only done if the patient discontinues treatment after  $\geq 9$  mo of dosing.

### 13.3. Study CS2 Schedule of Procedures

#### Legend Continued

10 Weekly platelet monitoring is required throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full 65 week treatment period). For patients participating in the Post-Treatment Evaluation Period, frequency of testing after the Week 71 visit will be determined by the Study Medical Monitor in consultation with the Investigator. For patients participating in the ISIS 420915-CS3 study, weekly monitoring should continue between the last dose of Study Drug in CS2 and first dose of Study Drug in CS3. If this period extends beyond 6 weeks, the frequency will be determined by the Study Medical Monitor.

The following visits to collect platelet values are required in addition to the visits shown in the table. These visits do not have specified windows to allow flexibility of scheduling but with the intent that platelets are assessed each calendar week. Visits may be completed in clinic, by home healthcare service, or by a local laboratory:

Week 2, 4, 6, 7, 9, 11, 12, 14, 16, 17, 19, 21, 22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 37, 39, 40, 42, 43, 45, 46, 48, 49, 51, 52, 54, 55, 57, 58, 60, 61, 63, 64, 66, 68, and 70

#### Time (time is in reference to Study Drug administration):

- A Pre-dose (during treatment period)
- B Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24-hour
- C Pre-dose, 3-hour
- D Pre-dose, 3 and 12-hour
- E Pre-dose, 24-hour, 3-day and 7-day
- F Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24-hour, 3-day and 7-day. For both E and F: where applicable, the 7-day blood draw should be taken before the next weekly dose is given. The 12-hr blood draw is encouraged but optional.

13.4. Study CS3 Schedule of Procedures

Screen	Year 1												Year 2				Year 3					
	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
<b>Study Week</b>	≤ 4 weeks <sup>1</sup>	1	4	7	10	13	15	18	21	23	26	29	39	52	65	78	91	104	117	130	143	156
<b>Study Day</b>	S-28 to S-1	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
<b>Visit Window (+/- Days)</b>		0	7	7	7	7	7	7	7	7	7	7	7	7	10	10	10	10	10	10	10	10
Informed Consent	X																					
Inclusion/Exclusion	X																					
ISIS 420915 Admin. (weekly) <sup>2</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Safety Assessments</b>																						
Full Physical Exam	X <sup>3</sup>					X					X			X		X		X		X		X
Vital Signs <sup>A</sup> (BP <sup>4</sup> , HR, RR, temp)	X <sup>3</sup>	X		X		X					X			X		X		X		X		X
ECG <sup>A</sup> (12-Lead, triplicate)	X <sup>3</sup>										X			X		X		X		X		X
ERG Exam <sup>5</sup>																X						X
Ophthalmology Exam <sup>5</sup>											X			X		X		X		X		X
AE & Con Meds & Concomitant procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact <sup>6</sup>			X		X		X	X	X	X		X	X		X		X		X		X	

13.4. Study CS3 Schedule of Procedures

	Screen	Year 1												Year 2				Year 3				
Study Week	≤ 4 weeks <sup>1</sup>	W 1	W 4	W 7	W 10	W 13	W 15	W 18	W 21	W 23	W 26	W 29	W 39	W 52	W 65	W 78	W 91	W 104	W 117	W 130	W 143	W 156
Study Day	S-28 to S-1	D 1	D 22	D 43	D 64	D 85	D 99	D 120	D 141	D 155	D 176	D 197	D 267	D 358	D 449	D 540	D 631	D 722	D 813	D 904	D 995	D 1086
Visit Window (+/- Days)		0	7	7	7	7	7	7	7	7	7	7	7	7	10	10	10	10	10	10	10	10
Labs																						
Pregnancy Test <sup>7, A</sup>	X <sup>3</sup>	X		X		X					X			X		X	X <sup>8</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X
Chemistry Panel <sup>A</sup> (fasting)	X <sup>3</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X								
Additional Platelet and Serum Creatinine <sup>13</sup>	See visit schedule Appendix C																					
Hematology <sup>A</sup>	X <sup>3</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X								
Urinalysis <sup>A</sup>	X <sup>3</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X								
24 hour Urine (serum creatinine required) <sup>9</sup>	X																					
Thyroid Panel <sup>A</sup>	X <sup>3</sup>			X		X					X			X		X		X				X
PT, aPTT, INR <sup>A</sup>	X <sup>3</sup>			X		X					X			X		X		X				X
Retinol <sup>A</sup> (fasting)		X		X		X					X			X		X		X		X		X
hs-CRP <sup>A</sup>		X		X		X					X			X		X	X <sup>8</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X
PD Panel <sup>A</sup> (fasting)		X		X		X		X <sup>8</sup>	X <sup>8</sup>		X		X <sup>8</sup>	X								
NT-proBNP <sup>A</sup>		X		X		X		X <sup>8</sup>			X		X <sup>8</sup>	X								
Immunogenicity <sup>A</sup>				X		X		X <sup>8</sup>			X		X <sup>8</sup>	X								
PK Trough <sup>A</sup>		X		X		X		X <sup>8</sup>			X		X <sup>8</sup>	X								

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13.4. Study CS3 Schedule of Procedures

	Screen	Year 1												Year 2				Year 3				
Study Week	≤ 4 weeks <sup>1</sup>	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W
		1	4	7	10	13	15	18	21	23	26	29	39	52	65	78	91	104	117	130	143	156
Study Day	S-28 to S-1	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
		1	22	43	64	85	99	120	141	155	176	197	267	358	449	540	631	722	813	904	995	1086
Visit Window (+/- Days)		0	7	7	7	7	7	7	7	7	7	7	7	7	10	10	10	10	10	10	10	10
Efficacy Assessments																						
mNIS+7 Assessment <sup>10</sup>											X			X		2X		X		X		2X
Norfolk QOL-DN <sup>11</sup>											X			X		X		X		X		X
SF-36 Questionnaire											X			X		X		X		X		X
PND Score		X									X			X		X		X		X		X
Body Weight (fasting)		X				X					X			X		X		X		X		X
Transthoracic ECHO <sup>12</sup>		X												X		X		X				X

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13.4. Study CS3 Schedule of Procedures

	Year 4				Year 5				Early Term <sup>14</sup>	Post-Treatment Evaluation
Study Week	Y4-W13	Y4-W26	Y4-W39	Y4-W52	Y5-W13	Y5-W26	Y5-W39	Y5-W52		Last Dose + 13 weeks
Study Day										
Visit Window (+/- Days)	14	14	14	14	14	14	14	14	7	14
Informed Consent										
Inclusion/Exclusion										
ISIS 420915 Admin. (weekly) <sup>2</sup>	X	X	X	X	X	X	X	X		
Safety Assessments										
Full Physical Exam		X		X		X		X	X	X
Vital Signs <sup>A</sup> (BP <sup>4</sup> , HR, RR, temp)		X		X		X		X	X	X
ECG <sup>A</sup> (12-Lead, triplicate)		X		X		X		X	X	X
ERG Exam <sup>5</sup>										
Ophthalmology Exam <sup>5</sup>		X		X		X		X	X	
AE & Con Meds & Concomitant procedures	X	X	X	X	X	X	X	X	X	X
Phone Contact <sup>6</sup>	X		X		X		X			

13.4. Study CS3 Schedule of Procedures

	Year 4				Year 5				Early Term <sup>14</sup>	Post-Treatment Evaluation
Study Week	Y4-W13	Y4-W26	Y4-W39	Y4-W52	Y5-W13	Y5-W26	Y5-W39	Y5-W52		Last Dose + 13 weeks
Study Day										
Visit Window (+/- Days)	14	14	14	14	14	14	14	14	7	14
Labs										
Pregnancy Test <sup>7.A</sup>		X	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X	X
Chemistry Panel <sup>A</sup> (fasting)	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X	X
Additional Platelet and Serum Creatinine <sup>13</sup>	See visit schedule Appendix C									
Hematology <sup>A</sup>	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X	X
Urinalysis <sup>A</sup>	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X	X
24 hour Urine (serum creatinine required) <sup>B</sup>										
Thyroid Panel <sup>A</sup>		X		X				X	X	X
PT, aPTT, INR <sup>A</sup>		X		X				X	X	X
Retinol <sup>A</sup> (fasting)		X		X		X		X	X	X
hs-CRP <sup>A</sup>		X	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X	X
PD Panel <sup>A</sup> (fasting)	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X	X
NT-proBNP <sup>A</sup>	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X	X
Immunogenicity <sup>A</sup>				X				X	X	X
PK Trough <sup>A</sup>		X	X <sup>B</sup>	X		X	X <sup>B</sup>	X	X	X

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13.4. Study CS3 Schedule of Procedures

	Year 4				Year 5				Early Term <sup>14</sup>	Post-Treatment Evaluation
Study Week	Y4-W13	Y4-W26	Y4-W39	Y4-W52	Y5-W13	Y5-W26	Y5-W39	Y5-W52		Last Dose + 13 weeks
Study Day										
Visit Window (+/- Days)	14	14	14	14	14	14	14	14	7	14
Efficacy Assessments										
mNIS+7 Assessment <sup>10</sup>									2X <sup>16</sup>	
NIS				X				X	X <sup>17</sup>	
Norfolk QOL-DN <sup>11</sup>				X				X	X	
SF-36 Questionnaire				X				X	X	
PND Score				X				X	X	
Body Weight (fasting)									X	X <sup>15</sup>
Transthoracic ECHO <sup>12</sup>									X <sup>15</sup>	

#### 13.4. Study CS3 Schedule of Procedures

Shaded columns represent non-clinic visits. Labs as indicated may be collected by the Sponsor's home healthcare service or by a local laboratory (with prior Sponsor approval). Patients also have the option to go to clinic for these visits.

Note: If not specifically labeled, "X" means anytime

- 1 For an individual patient, a maximum period of 4 weeks is allowed between a patient's last dose in ISIS 420915-CS2 (CS2 Week 65 visit) and initiation of dosing in this study (CS3 Day 1 visit). All screening assessments must be completed during this period. Longer periods may be considered after discussion and approval from the Study Medical Monitor
- 2 ISIS 420915 can be administered in the clinic or at home by the patient/caregiver. It is not necessary for ISIS 420915 to be administered on site during clinic visits. Clinic visits should occur on a dosing day, 7 days after the previous dose
- 3 Assessments from ISIS 420915-CS2 may be used for screening evaluation if they were obtained within 4 weeks of Study Day 1. A longer period may be considered after discussion and approval from the Study Medical Monitor
- 4 Blood pressure should be taken after the patient has been sitting for  $\geq 5$  min
- 5 A +/- 2-week window is given for ERG and ophthalmology examinations. The early termination ERG and ophthalmology examinations are only done if the patient discontinues treatment after  $\geq 9$  mo of dosing or unless deemed necessary by Investigator or Study Medical Monitor
- 6 To collect AEs, conmeds, and the general wellbeing of the patient
- 7 For females of childbearing potential only, by serum  $\beta$ hCG except on Day 1 by urine hCG (pre-dose)
- 8 To be collected by either a local laboratory (if approved by Sponsor), Sponsor appointed home healthcare service, or Study Center as arranged by the Study Center personnel
- 9 The 24-hour urine collection can be done any time during the screening period or during Week 1 on treatment. Serum creatinine blood draw required
- 10 If ISIS 420915 administration, ERG, or ophthalmology examinations are to be performed on the same day as a mNIS+7 assessment, they should be performed after the mNIS+7 assessment is complete. For the Week 78 and Week 156 visits, 2 mNIS+7 assessments will be performed on separate days. A maximum of 2 weeks from the visit (Week 78 or Week 156) will be allowed to complete both assessments
- 11 Norfolk QOL-DN should be the first assessment performed at the visit
- 12 Study Day 1 ECHO can be done any time in the screening period or up to 2 weeks after Day 1. The Day 1 ECHO is not done if the Week 65 ECHO was conducted in ISIS 420915-CS2. A +/- 2-week window is given for all other ECHOs
- 13 Weekly platelet and every 2-3 week serum creatinine monitoring is required throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full treatment period). The frequency of monitoring after 6 weeks from the last dose of Study Drug will be determined by the Study Medical Monitor. The visits required to collect platelets and serum creatinine not included in this table are shown in Appendix C. These visits may be completed in clinic, by home healthcare service, or by a local laboratory
- 14 Early termination should be performed at the time of withdrawal, ideally within 14 days from the last dose of Study Drug
- 15 Omit if following Year 4 or Year 5 treatment
- 16 Perform mNIS+7 only if early termination is from Year 1-3 treatment
- 17 Perform NIS only if early termination is from Year 4-5 treatment

Time (time is in reference to ISIS 420915 administration):

A Pre-dose

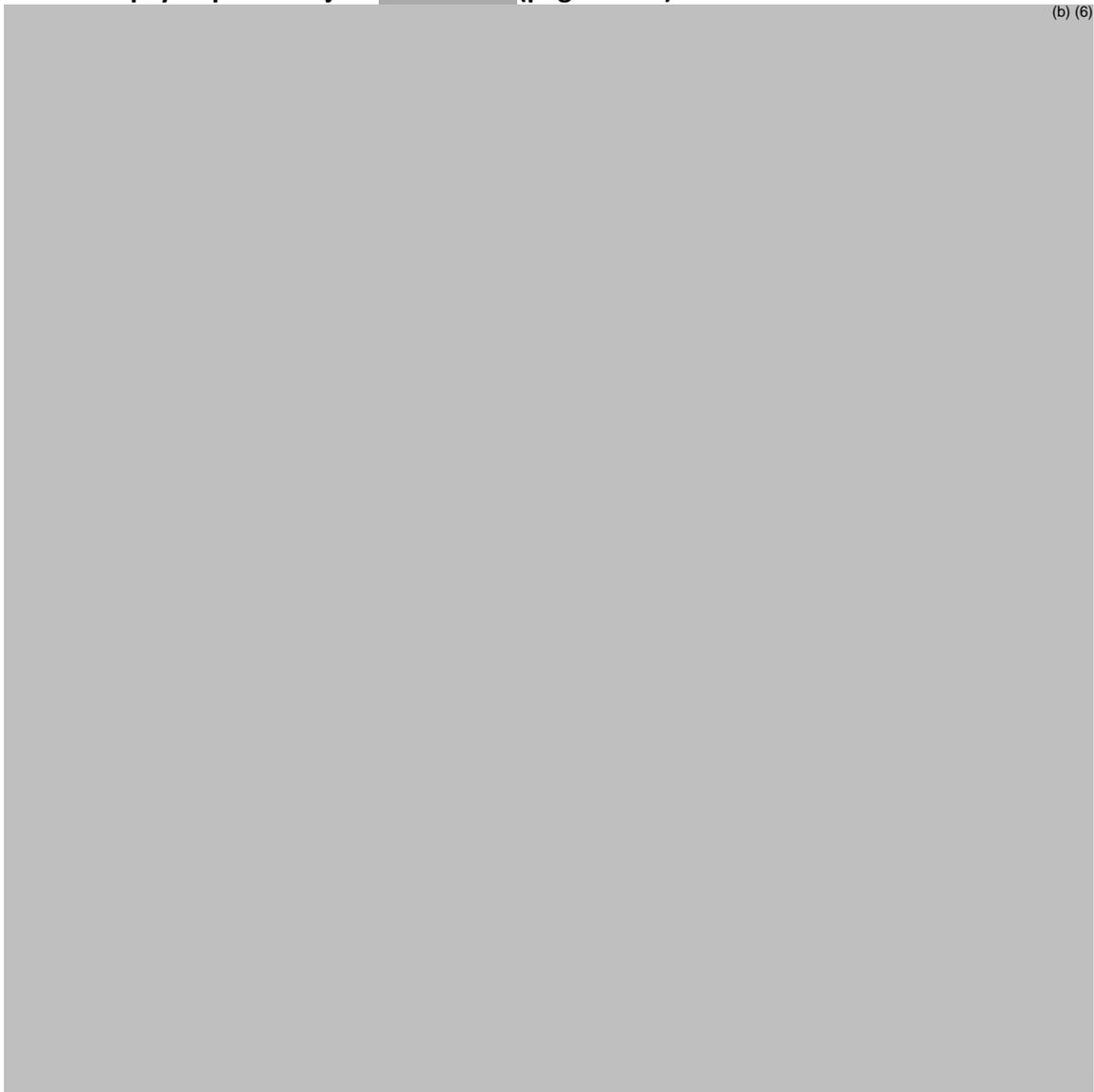
13.5. **Renal Biopsy Report. Subject** (b) (6)

(b) (6)



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**Renal Biopsy Report. Subject** <sup>(b) (6)</sup> **(page 2 of 3).**



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**Renal Biopsy Report. Subject** (b) (6) **(page 3 of 3).**



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13.6. **Renal Biopsy report. Subject** (b) (6)



(b) (6)

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13.7. **Renal Biopsy Report. Subject** (b) (6).



(b) (6)

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**Renal Biopsy Report. Subject** (b) (6) **(page 3 of 3).**



(b) (6)

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/s/  
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EVELYN K MENTARI  
10/04/2018

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10/04/2018