CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213026Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NME, original NDA
Application Number(s)	NDA 213,026 (IND 118,086)
Priority or Standard	Priority
Submit Date(s)	1/10/20 (submission 1 [clinical, nonclinical]) 6/25/20 (submission 2 [quality, complete NDA])
Received Date(s)	1/10/20; 6/25/20
PDUFA Goal Date	2/25/21
Division/Office	DN1 / ON / OND / CDER
Reviewer Name(s)	David Hosford, ; Xiang Ling (Biometrics); Thomas Biel, Ashutosh Rao (Office of Biotechnology Products [OBP])
Review Completion Date	2/15/21
Established/Proper Name	Casimersen
(Proposed) Trade Name	Amondys 45
Applicant	Sarepta Therapeutics, Inc. (Cambridge, MA)
Dosage Form(s)	concentrated solution in a single use-vial for IV infusion
Applicant Proposed Dosing Regimen(s)	30mg/kg weekly
Applicant Proposed Indication(s)/Population(s)	For the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping

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Glossary

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AC	advisory committee
ACE	angiotensin converting enzyme
AE	adverse event
APTT	activated partial thromboplastin time
AR	adverse reaction
ARB	angiotensin II receptor blocker
ASO	antisense oligonucleotide
AUC	Area Under the Curve
BIMO	Bioresearch Monitoring Conference
BRF	Benefit Risk Framework
CAS	casimersen
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CFB	change from baseline
Cmax	maximum concentration
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRP	C reactive protein
CSR	clinical study report
CSS	Controlled Substance Staff
CST	corticosteroid
CYP450	cytochrome P450
DDI	Drug-drug interference
ddRT-PCR	digital droplet reverse transcriptase polymerase chain reaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DMD	Duchenne muscular dystrophy
EAIR	Exposure-Adjusted Incidence Rate
ECG	electrocardiogram
ECHO	echocardiogram
eCTD	electronic common technical document

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EMG	electromyogram
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FS	fractional shortening of left ventricle
FVC	forced vital capacity
GCP	good clinical practice
HMAS	Hammersmith Motor Activity Scale
hpf	high-powered field
IA	interim analysis
ICH	International Council on Harmonization
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug Application
INN	International Nonproprietary Name
INR	international normalized ratio
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KIM-1	Kidney Injury Molecule-1
LOA	loss of ambulation
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRC	Medical Research Council (UK)
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAA	North Star Ambulatory Assessment
OCS	Office of Computational Science
OCT	optimal cutting temperature
OLDP	Office of Lifecycle Products
OND	Office of New Drugs
ONDP	OND Policy
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PCSA	potentially clinically significant abnormality
PD	pharmacodynamics
PDUFA	Prescription Drug User Fee

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P-gp	Permeability-glycoprotein
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	post-marketing commitment
PMO	phosphorodiamidate class of ASOs
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QTcF	QT interval corrected by the Fridericia method
PT	prothrombin time
PTT	partial thromboplastin time
REMS	risk evaluation and mitigation strategy
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
TEAE	treatment emergent adverse event
TFT	timed function test
(b) (4)	(b) (4)
USAN	US Adopted Name
USP	US Pharmacopeia
WP	Warnings and Precautions in Prescribing Information

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1. Executive Summary

1.1. Product Introduction

The product is a 22-mer RNA-targeted antisense oligonucleotide (ASO) of the phosphorodiamidate morpholino oligomer (PMO) class. Its International Nonproprietary Name (INN) and US Adopted Name (USAN) are casimersen, and its granted trade name is Amondys 45. Casimersen is an NME. The applicant's proposed indication is "for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping." The proposed dose of casimersen is 30mg/kg, to be administered weekly as an IV infusion.

The Duchenne muscular dystrophy gene (*DMD*) encodes a muscle protein, dystrophin. Mutations in *DMD* are not uncommon due to its large size (79 exons), and most mutations are deletions (65-70%). In patients with DMD, deletion mutations are typically out-of-frame (i.e., they completely change the downstream coding sequence), leading to expression of premature stop codons and a truncated dystrophin protein that is functionally inactive. Casimersen was designed to bind to pre-mRNA that is transcribed from the *DMD* gene. By binding to post-transcription pre-mRNA, casimersen can in principle cause cellular spliceosomes to skip out-of-frame exon mutations that would otherwise result in aberrant mRNA and ultimately a dysfunctional or absent dystrophin protein. The hypothesized effect of exon-skipping by this type of ASO is the production of truncated but partially functional dystrophin protein. Casimersen targets pre-mRNA from *DMD* mutations that are amenable to exon 45 skipping. Approximately 8% of patients with DMD are thought to be amenable to exon 45 skipping. The following figure depicts this mechanism of action.

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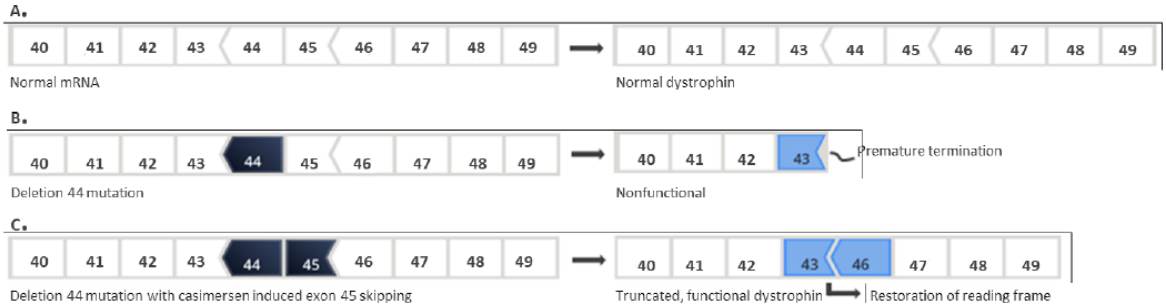
Figure 1. Hypothesized Mechanism of Action of Casimersen



mRNA=messenger ribonucleic acid
Mutational disruption of the dystrophin reading frame in Duchenne muscular dystrophy can be restored by skipping additional exons. (A) Translation of wild type dystrophin mRNA generates complete dystrophin protein that contains all essential domains and is fully functional. (B) Deletion of exon 44 or selected larger deletions ending in exon 44 (i.e. 7-44, 12-44, 18-44) or exon 46 or selected larger deletions beginning with exon 46 (ie. 46-47, 46-48, 46-49, 46-51, 46-53, 46-55, 46-57, 46-59, 46-60, 46-67, 46-69, 46-75, 46-78) disrupts the downstream reading frame, preventing translation of dystrophin and causing DMD. An example is shown of exon 44 deletion, a type of mutation amenable to exon 45 skipping. (C) Skipping exon 45 results in a newly formed exon junction 43-46, which restores the downstream reading frame and allows translation of internally truncated but functional dystrophin

[Source: Clinical Overview]

The applicant has developed and marketed two other PMO ASOs for the treatment of DMD. The first ASO was eteplirsen (Exondys 51; approved 2016) "for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping." The second ASO was golodirsen (Vyondys 53; approved 2019) "for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping."

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has reported a small but statistically significant increase in dystrophin expression in skeletal muscle fibers in casimersen-treated subjects vs. placebo-treated subjects. This finding was verified in numerous ways by FDA's clinical, biometrics, and biologic products reviewers. The applicant's corresponding finding that casimersen-treated subjects had a small but significantly higher percentage of exon-skipping compared to placebo-treated subjects was also verified. This pharmacodynamic result supports the premise that casimersen increased dystrophin expression in skeletal muscle fibers through its mechanism of exon 45 skipping. The applicant used immunohistochemical techniques to demonstrate that dystrophin was localized to the sarcolemma of muscle fibers in casimersen-treated subjects. The localization of casimersen-induced dystrophin to a cellular site is relevant to dystrophin's role in helping to protect muscle fibers from degeneration due to the stress of muscle contraction. The finding that casimersen increased skeletal muscle dystrophin meets the statutory evidentiary standards to grant accelerated approval for casimersen in the treatment of DMD that is amenable to exon

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45 skipping.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive, progressive neuromuscular disease that is usually diagnosed in young boys and that is ultimately fatal at a young age. The disease is caused by mutations in the *DMD* gene that cause inadequate production of dystrophin protein, which normally helps muscle fibers to avoid degeneration due to the stress of muscle contractions. There is an approved corticosteroid that helps to manage muscle inflammation and pain in patients with DMD, but it and other corticosteroids do not affect the course of the disease, and these drugs produce numerous unwanted effects.

For patients with particular mutations in the *DMD* gene, three genetically targeted treatments have been granted accelerated approval based on their ability to bypass the gene-coding regions (exons) that harbor the mutations, and to thereby facilitate the production of shortened (truncated) dystrophin protein that may be able to reduce or prevent muscle degeneration. Casimersen is a targeted treatment designed for patients with DMD, if they harbor mutations that are amenable skipping of exon 45 in the *DMD* gene.

The applicant submitted an NDA that includes efficacy and safety studies of casimersen in patients with DMD amenable to exon 45 skipping. In these studies, 35 unique subjects were treated with weekly intravenous (IV) infusions of placebo, and 65 unique subjects were treated with weekly IV infusions of casimersen at a dose of 30 milligrams per kilogram of body weight (30mg/kg). An interim analysis after 48 weeks in one of the studies showed that casimersen increased dystrophin protein in muscle biopsy tissue in a small (0.59% of normal levels) but statistically significant manner compared to placebo. Casimersen also increased skipping of exon 45 in a small (1.6%) but statistically significant way, as designed. The resulting dystrophin protein was localized to muscle cell membranes, where normal dystrophin exerts its protective effect. Whether increased dystrophin protein in these subjects translates into a clinically meaningful benefit is unknown until the applicant's ongoing clinical studies have been completed, and clinically meaningful endpoints can be evaluated.

Evaluation of safety and tolerability showed that casimersen increased urine protein to abnormally high levels in a proportion of subjects. In nonclinical toxicology studies, casimersen showed signs of renal injury. This nonclinical finding gives credence to the clinical finding. Moreover, a potential risk of renal injury has been identified for other approved ASOs used to treat DMD. If casimersen is granted accelerated approval, then this potential risk should be monitorable and manageable in the post-marketing clinical setting where weekly IV infusions would be administered in a home setting by IV infusion specialists. Nevertheless, this clinical reviewer recommends that a potential risk of renal injury should be included in the Warning and Precautions setting of the Prescribing Information for casimersen, if it is granted accelerated approval.

Other adverse events that appeared to be present in a higher proportion of subjects during casimersen treatment include various infections,

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fever, cough, dizziness, and headache. If marketing approval is granted, then these events will be further evaluated when the currently ongoing studies 4045-301 and 4045-302 have completed.

Considering the potential benefit of increased dystrophin production in casimersen-treated subjects, and the monitorable and manageable potential risks of renal injury or other adverse events that are cited above, this clinical reviewer recommends that casimersen should be granted accelerated approval for the treatment of the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. It is further recommended that the applicant should fulfill a post-marketing requirement (PMR) to submit all data from the currently ongoing studies after they have completed, so that FDA can evaluate whether casimersen confers substantive evidence of benefit, as assessed via clinically meaningful study endpoints.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Duchenne muscular dystrophy (DMD) is an X-linked recessive disease that affects about 1 in 5000 boys. The condition is characterized by progressive skeletal muscle weakness, and it is usually diagnosed by the age of five years. The first signs of the disease are typically weakness in the legs, with progressive weakness in other muscles including those needed for respiration. It can also affect cardiac muscle. In later stages the condition results in wheelchair and respirator dependency, and eventually in death that often occurs before the end of the third decade. • The cause of the disease is a wide variety of mutations in the *DMD* gene. This gene, when unmutated, encodes a fully functional muscle protein called dystrophin. In normal muscle cells, dystrophin helps to prevent myofiber injury and degeneration that can occur due to the stress of muscle contractions. In patients with DMD, however, the mutations lead to insufficient or a complete	Because DMD is a chronic, progressive neuromuscular disease that begins in boys and that is ultimately fatal, treatments are needed to provide affected individuals with normal muscle function and a normal lifespan. This need is currently unmet.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	absence of functional dystrophin protein. Loss of dystrophin causes the gradual loss of myofibers, the infiltration of fat into muscle, and muscle inflammation. • It is uncertain whether potential treatments that are designed to help myofibers produce greater quantities of dystrophin will help to stop or perhaps even reverse the muscle deterioration that otherwise occurs.	
Current Treatment Options	• The standard of care for any patient with DMD is the use of medicines that reduce inflammation. The most commonly used medicines are corticosteroids (CSTs), and the only FDA-approved corticosteroid for DMD is Emflaza (deflazacort). Although CSTs help to manage muscle inflammation and pain, they do not prevent the eventual onset of disability and then death. Moreover, CSTs cause a number of unpleasant side effects. • Other standards of care include physical rehabilitation, the use of mechanical braces, and surgical correction of muscle tendon contractures. • The *DMD* gene has 79 coding regions (exons), that are used to make the mRNA copy (transcript) of dystrophin. Some patients with DMD have exon mutations that prematurely stop the translation of dystrophin's mRNA transcript into the final dystrophin protein. This results in a dystrophin protein that is both truncated and nearly or completely functionless. • If the mutations in the *DMD* gene are harbored in particular exons, these exons can theoretically be bypassed, or skipped, by genetically targeted treatments during the course of dystrophin transcription. In principle, exon-skipping treatments that target these exons can help	Most patients with DMD may benefit somewhat from treatment with CSTs and from the use of other management modalities. However, the use of these management options does not lead to a satisfactory outcome in any patient. The first medicines that may selectively target the cause of DMD are the three FDA-approved exon-skipping treatments. Together, these three medicines may help about 20% to 25% of all patients with DMD, because the majority of patients do not have the particular exon-skipping mutations that are targeted by the currently approved treatments. Casimersen targets a different subset of patients who are amenable to exon 45 skipping, and as such it may hold promise in the treatment of additional patients with DMD. However, the clinical trials of

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	myofibers to make dystrophin proteins that are may be truncated but are nevertheless at least partially functional. • There are several FDA-approved exon-skipping treatments for patients with DMD, if they have exon mutations that are suitable for this type of treatment. Each of these treatments is in a class of compounds termed antisense oligonucleotides (ASOs), and each is delivered by intravenous (IV) infusion. Two of these ASOs, Exondys 51 and Viltepso, can be used to treat patients with DMD if they have mutations amenable to exon 51 skipping. The other ASO, Vyondys 53, can be used for patients with DMD if they have mutations amenable to exon 53 skipping. Together, these medicines can be used to treat approximately 20 to 25% of patients with DMD. • Each of these approved ASOs increases the amount of muscle dystrophin by a relatively small percentage of the normal level that is present in people who do not have DMD. When these ASOs were approved using the accelerated approval pathway, it was not yet known if this small increase of dystrophin in patients with DMD would help their muscles to become more functional. The clinical trials that will test whether each of these genetic treatments will improve muscle function are still ongoing as a post-marketing requirement (PMR) following accelerated approval.	casimersen, like those of the three FDA-approved exon-skipping treatments, are still ongoing. It is not yet known if the ability of casimersen to increase the amount of dystrophin protein in these subjects will result in clinical improvements.
Benefit	• The applicant has two studies that were ongoing at the end of May 2019, which was the stopping point for collecting data submitted in this NDA (i.e., the data cut-off). The first study is called 4045-301, and the second study is called 4045-302. • Ongoing study 4045-301 had enrolled 88 subjects with DMD amenable to exon 45 skipping by the data cut-off. The first 96-week	The premise of using casimersen to treat patients with DMD amenable to exon 45 skipping is as follows. Casimersen enters the nucleus of myofibers (muscle cells) and promotes the skipping of exon 45 of the *DMD* gene when the mRNA transcript of dystrophin

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	period of this study was randomized and double-blinded. Subjects received either placebo (n = 31 subjects) or casimersen (n = 57 subjects) by intravenous (IV) infusion once weekly. The casimersen dose was 30 milligrams for every kilogram of body weight (30mg/kg). After this 96-week double-blind period of the study, all subjects received 30mg/kg of casimersen for another 48 weeks of open-label evaluation. • In ongoing study 4045-302, all subjects who completed a small prior safety study, 4045-101 (described below), and all subjects who completed 4045-301 were eligible to enroll and to receive 30mg/kg of casimersen in an open-label fashion. • In study 4045-301, clinical endpoints include the 6-Minute Walk Test, which is a clinically meaningful assessment often used in studies of DMD. However, because this study is still ongoing, the data from clinical endpoints were not included in this NDA. The endpoints that were included are measurements that were taken using muscle biopsies from the first 43 subjects in the study to reach an interim analysis timepoint after 48 weeks of double-blinded treatment. Twenty-seven of these 43 subjects received casimersen, and 16 received placebo. Muscle biopsy tissue obtained at the 48-week time point were analyzed and compared to muscle biopsy tissue that was obtained immediately before these subjects started to receive double-blinded casimersen or placebo. • Muscle biopsy tissue showed that subjects who received casimersen had a small but statistically significant increase in dystrophin protein compared to subjects who received placebo. The mean difference in dystrophin between casimersen and placebo was 0.6% of the normal	is made. This leads, in principle, to translation of a dystrophin protein that is truncated but nevertheless at least partially functional when this protein is localized at the muscle cell membrane. In this manner, the dystrophin protein can help prevent degeneration of myofibers. Study 4045-301 tested this premise by using muscle biopsy tissue to answer three questions. Did casimersen produce more dystrophin protein? Did casimersen skip exon 45? And did dystrophin protein localize to the muscle cell membrane, where it is needed to help prevent myofiber degeneration? The results obtained in the interim analysis of muscle biopsy tissue suggest that the answers to each of these questions was “Yes.” Even though the mean amount of increased dystrophin was only 0.6% higher in the casimersen group compared to the placebo group, this increase was statistically significant. Moreover, casimersen also increased the skipping of exon 45 in a statistically significant manner; and dystrophin protein was localized to the muscle cell membrane.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	level in people who do not have DMD. The biopsy tissue also showed that casimersen increased skipping of exon 45 by approximately 1.6% when compared to placebo; this increase was statistically significant. This result suggests that casimersen produced the exon-skipping that was intended, in order to increase the production of dystrophin. Finally, when microscopic sections of muscle tissue were examined, dystrophin protein was located near myofiber (muscle cell) membranes, which is the site at which dystrophin can mitigate the stress of muscle contractions.	It is still uncertain if this small increase in dystrophin protein will lead to increased muscle function in the casimersen group as compared to the placebo group. The answer to this most important question will not be known until the final data are submitted from the ongoing studies. In the meantime, casimersen can be considered for accelerated approval based upon its ability to increase dystrophin protein. Exondys 51, Vyondys 53, and Viltepso were granted accelerated approval after they showed an ability to increase dystrophin protein in patients with DMD. If it is granted accelerated approval, then casimersen, like the other three ASO that were granted accelerated approval on this basis, will have a post-marketing requirement (PMR) to submit clinical data that can be used to evaluate whether casimersen-treated patients show a substantive, clinically meaningful benefit in function.
Risk and Risk Management	• The safety database of casimersen-treated subjects with DMD is derived from three studies, one completed and two ongoing. • The applicant has completed a small study in 12 subjects with DMD amenable to exon 45 skipping, in order to study the safety of	If casimersen is granted accelerated approval, then in a post-marketing setting it is anticipated there may be a potential risk of renal injury, which is monitorable by

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	casimersen as compared to placebo. The study was called 4045-101. For approximately 12 weeks, casimersen (n = 8 subjects) or placebo (n = 4 subjects) were administered once weekly by IV infusion. This period of the trial was randomized and double-blinded. After this period, all subjects received open-label casimersen once weekly at a dose of 30mg/kg for another 132 weeks. These data were submitted in the NDA. • The ongoing studies, 4045-301 and 4045-302, were described in the section above. As of the data cut-off, the NDA submission included safety data from 31 placebo-treated subjects and 57 casimersen-treated subjects in study 4045-301. Another 11 non-unique subjects who had completed study 4045-101 were in study 4045-302 at data cutoff, and these data were also submitted. The total size of the safety database in this NDA is therefore 35 placebo-treated subjects and 76 casimersen-treated subjects, 65 of whom are unique. The size of this safety database is in keeping with that of other ASOs that have been granted accelerated approval for DMD. During a pre-NDA meeting with the applicant in June 2019, FDA commented that a safety database of this size would be sufficient for review, and that the adequacy of this database would be a matter of review at the time of NDA submission. The FDA review team deemed that the safety database was adequate at the time of submission. • In this safety database, treatment-emergent SAEs and/or severe treatment-emergent adverse events (TEAEs) in casimersen-treated subjects did not congregate in a clinically noteworthy manner into a particular system organ class or into similar types of TEAEs, with the possible exception of infections. There was a small increase in the	measuring dipstick urine protein. Because patients with DMD amenable to exon 45 skipping will have periodic clinical office visits in the post-market setting, then it should be possible to identify and manage this potential risk in that setting. Nevertheless, the potential risk for renal injury should be included in the Warnings and Precautions section of the Prescribing Information if casimersen is granted accelerated approval. Other adverse events that may arise in a clinical setting include cough, headache, dizziness, infections, and fever. Due to weekly observation of casimersen-treated patients by infusion specialists, these events should be detectable, whereupon patients can be seen in a clinical office setting for appropriate evaluation and management. There were no overt clinical signs of immunogenicity in the submitted safety data, and laboratory measurements of serum antibodies directed against dystrophin in the immunoglobulin (Ig) classes IgE, IgG, and IgM did not demonstrate any anti-dystrophin responses. However, should casimersen be approved, a PMR will likely be issued for the

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	proportion of casimersen-treated subjects with both serious and nonserious TEAEs of a variety of infections. The rate of severe infections during post-marketing treatment with casimersen should be manageable in a clinical setting on an as-needed basis, and a focused analysis of all infections should be a required element of Periodic Safety Update Reports (PSURs) if this agent is granted accelerated approval. • Other non-serious and non-severe TEAEs that were proportionally higher in the casimersen group included cough, dizziness, headache, and pyrexia (fever). These events will be further evaluated when the currently ongoing studies 4045-301 and 4045-302 have completed.. • Laboratory assessments of dipstick urine protein showed a higher proportion of casimersen-treated subjects had potentially clinically significant abnormalities. This observation may be in keeping with nonclinical toxicology studies that showed signs of renal injury in casimersen-treated rodents and non-human primates. Other approved ASOs used to treat DMD have also shown elevated levels of dipstick urine protein in some patients. • Potential safety risks that have been observed during treatment with other approved ASOs (whether used to treat DMD or other conditions) include: hypersensitivity; hepatotoxicity; events related to IV drug infusions or to the central venous ports through which IV infusions are made; and coagulopathy/decreased platelet counts. Evaluations of each of these potential risks identified no noteworthy evidence of their presence in the casimersen group compared to the placebo group.	applicant to conduct an *in silico* analysis for the possible presence of new dystrophin epitopes (neoepitopes) due to exon-skipping.

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1.4. Patient Experience Data

Table 1. Subject Experience Data Relevant to this Application

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

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2.1. Analysis of Condition

Named after French neurologist Guillaume-Benjamin-Amand Duchenne de Boulogne, who described the condition in 1861, Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that affects approximately 1 in 5000 male births (Bushby et al., 2010; Mendell et al., 2012; Guiraud et al., 2015). The *DMD* gene, with a locus on chromosome Xp21, was cloned in 1987 (Koenig et al., 1987), and its protein product, dystrophin, was also identified in 1987 (Hoffmann et al., 1987). The largest mammalian gene with more than 2 million base-pairs, *DMD* is comprised of 79 exons. Mutations in *DMD* are not uncommon due to its large size. Most mutations are deletions (65-70%), with the remainder either duplications (20%) or nonsense mutations (10%). In patients with DMD, deletion mutations are typically out-of-frame (i.e., they completely change the downstream coding sequence), leading to expression of premature stop codons and a truncated dystrophin protein that is functionally inactive. Nonsense mutations are single-base deletions that can also cause a premature stop codon (Aartsma-Rus et al., 2016). In the less severe phenotype of Becker muscular dystrophy (BMD), mutations affecting the *DMD* gene are in-frame. The resulting dystrophin proteins are truncated but somewhat functional (Guiraud et al., 2015). Although in principle, deletions may occur anywhere within the *DMD* gene, they tend to cluster from exons 45 to 55 (Aartsma-Rus et al., 2016).

The pathologic consequence of compromised dystrophin function relates to the protein's role in muscle. In muscle fibers, the N-terminal of the dystrophin protein binds to cytoskeletal actin, and the C-terminal is tightly attached to the sarcolemma through a protein complex, and also indirectly attached to the extracellular matrix via a separate dystroglycan complex. Dystrophin's action during muscle contraction helps to reduce sarcolemmal stress (Aartsma-Rus and Van Ommen, 2007). As a consequence of reduced or absent dystrophin function, muscle fibers undergo deterioration and degeneration, resulting in a host of changes that include the replacement of muscle fibers by connective tissue and fat, progressive muscle weakness, and the onset of inflammation that further compromises remaining muscle fibers (Bushby et al., 2010; Guiraud et al., 2015).

In principle, antisense oligonucleotides (ASOs) that promote the skipping of mutated exons during the transcription of dystrophin pre-mRNA can yield in-frame mRNA without the presence of premature stop codons. The result is translation of the dystrophin mRNA to a truncated but potentially functional dystrophin protein. Some have likened this exon-skipping effect of ASOs as a conversion of the more severe DMD phenotype to a less severe phenotype more akin to BMD. It may seem paradoxical that skipping exons of dystrophin pre-mRNA should result in any functionality in the truncated proteins. However, the critical features of dystrophin are the N-terminal actin-binding motif and the C-terminal sarcolemma-binding motif. Truncated central parts of the protein appear to be less important to dystrophin function (Aartsma-Rus and Van Ommen, 2007).

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Clinically, DMD is characterized by progressive skeletal muscle weakness that is typically diagnosed by the age of five years. Although the condition may occur in the rare girls who carry *DMD* mutations in both alleles, it is essentially confined to boys. At onset, weakness affects primarily the proximal muscles in the legs, and eventually it affects other skeletal muscles including those necessary for respiration. It also affects cardiac muscle, typically resulting in a dilated cardiomyopathy. The progressive course of the disorder results in wheelchair dependency, with approximately 80% of patients losing ambulatory capacity by the age of 14 years (Haber et al., 2020). Ultimately patients are dependent on mechanical ventilation, and death typically ensues by the end of the third decade. Greater longevity is highly dependent on intensive support (Bushby et al., 2010).

Patients with BMD may have a later onset of weakness, which is often milder than in DMD. The longevity of patients with BMD is greater than in DMD, and in some cases it is normal.

The most direct method of diagnosing DMD in affected boys is by genotype confirmation of a *DMD* mutation via a blood sample. Other data that support this diagnosis include a positive family history and a characteristic physical and electromyographic (EMG) exam. Muscle biopsies are no longer viewed as necessary to establish the diagnosis (Bushby et al., 2010).

2.2. Analysis of Current Treatment Options

Global Note for this Review

The word "*patients*" will be used when referring to people who have the condition of DMD, unless these patients are participants in a clinical trial. The word "*subjects*" will be used when referring to any person who is a participant in a clinical trial. This convention is per FDA standards, as codified in a Glossary of Terms that can be downloaded at: https://www.fda.gov/media/108378/download .

Safety and efficacy for the four approved products for DMD are described below. Regarding findings of ASO-induced increases in dystrophin protein levels as measured by western blot assays, it is important to note that differences in the western blot assay methodology across studies may prevent comparisons between drugs. Specifically, the western blot methodology used to measure dystrophin expression in the studies that supported accelerated approval of Exondys 51 and Vyondys 53 was different than that used for the accelerated approval of Viltepso.

Exondys 51

The first approved treatment for DMD was eteplirsen (Exondys 51; approved 2016), a phosphorodiamidate morpholino (PMO) antisense oligonucleotide "indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping" (Exondys 51 Prescribing Information, July

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2020 version). Eteplirsen produces skipping of exon 51 in pre-mRNA, leading to production of a truncated dystrophin protein that may be functional. Approximately 13% of patients with DMD are amenable to exon 51 skipping.

Eteplirsen was granted accelerated approval based on the demonstration of a small increase in dystrophin in skeletal muscle in patients with DMD amenable to exon 51 skipping. In one of the studies described in the Prescribing Information, "13 subjects were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment…Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 subjects with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1% (Exondys Prescribing Information)." Clinical efficacy with eteplirsen has not been established. "Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials (Exondys 51 Prescribing Information)."

<u>Emflaza</u>
The second approved treatment was deflazacort (Emflaza; approved 2017), "a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older" (Emflaza Prescribing Information, July 2020 version)." In clinical practice, corticosteroids have been generally recommended from the time of initial diagnosis until the non-ambulatory phase of DMD, but their use is complicated by a wide variety of common side effects (Bushby et al., 2010).

A traditional approval pathway was used for Emflaza, based upon a clinically meaningful increase in skeletal muscle strength. "The effectiveness of EMFLAZA for the treatment of DMD was established in…a randomized, double-blind, placebo-controlled, 52-week study conducted in the US and Canada. The study population consisted of 196 male pediatric subjects 5 to 15 years of age with documented mutation of the dystrophin gene…Individual muscle strength was graded using a modified Medical Research Council (MRC) 11-point scale…The change in average muscle strength score between Baseline and Week 12 was significantly greater for the deflazacort 0.9 mg/kg/day dose group than for the placebo group…(EMFLAZA Prescribing Information, July 2020 version)."

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Table 2. Analysis of Change from Baseline in Muscle Strength with Emflaza

Analysis of Change from Baseline at Week 12 in Average Muscle Strength Score	N	Change from Baseline LS Mean (95% CI)	P-value
Deflazacort 0.9 mg/kg/day	51	0.15 (0.01, 0.28)	0.017
Placebo	50	-0.10 (-0.23, 0.03)	

[Source: Emflaza Prescribing Information, Table 2]

Vyondys 53

The third approved treatment was golodirsen (Vyondys 53; approved 2019), a PMO antisense oligonucleotide "indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials (Vyondys 53 Prescribing Information, December 2019 version).

In one of the studies described in the Prescribing Information, "Efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48…Muscle biopsies were obtained at baseline prior to treatment and at Week 48…in all VYONDYS 53 treated subjects (n = 25) and were analyzed for dystrophin protein level by Western blot. Mean dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48…, with a mean change in dystrophin of 0.92% (SD 1.01) of normal levels ($p < 0.001$); the median change from baseline was 0.88% (Vyondys 53 Prescribing Information)."

Viltepso

The most recent approved treatment for DMD is viltolarsen (Viltepso; approved 2020). Viltepso is "an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping (Viltepso Prescribing Information, August 2020 version)."

One of the studies described in the Prescribing Information, "enrolled ambulatory male patients…Efficacy was assessed based on change from baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 25… by Western blot normalized to myosin heavy chain (primary endpoint)…In patients who received VILTEPSO 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by Week 25, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels ($p=0.01$) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%. All patients demonstrated an

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increase in dystrophin levels over their baseline values (Viltepso Prescribing Information, August 2020 version). "

Medical Management

In addition to the treatments described above, the mainstay of management in DMD consists of supportive measures (e.g., the use of orthoses; rehabilitative, respiratory, or cardiac support; and surgical amelioration of soft tissue or bony deformities; Bushby et al., 2010). At best these treatments delay but do not prevent mortality.

Comparison of Approved Treatments for DMD

A consideration for comparison of the magnitude of increase in dystrophin expression as a function of ASO treatment is that two of the three ASOs listed below (i.e., Exondys 51 and Vyondys 53) used a different western blot methodology than was used for the other ASO (i.e., Viltepso).

Table 3. Features of Approved Treatments for DMD

Product Name	Indication	Year Approved [Approval Basis]	Route and Frequency of Administration	Efficacy Information	Warnings and Precautions (WP) Most common adverse reactions (AR)
Exondys 51 NDA 206,488	the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping	2016 [Accelerated approval based on dystrophin protein level as a % of normal, measured by western blot]	30mg/kg by IV infusion, once weekly	13 subjects in open label trial In the 12 subjects with evaluable results, the pre-treatment dystrophin level was 0.16% normal, and it was 0.44% after 48 weeks of treatment ($p < 0.05$). The median increase after 48 weeks was 0.1% normal.	WP: Hypersensitivity Reactions AR: balance disorder and vomiting
Emflaza	the treatment of Duchenne	2017	0.9mg/kg/day orally, once daily	196 subjects in a	WP: Alterations in

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NDAs 208,684 and 208,685	muscular dystrophy (DMD) in patients 2 years of age and older	[Standard approval based on change in skeletal muscle strength]		randomized, double-blind, placebo-controlled, 52-week study. The change in average muscle strength score between Baseline and Week 12 on the MRC score was significantly greater for the deflazacort 0.9 mg/kg/day dose (0.15 points) group than for the placebo group (- 0.10 points; p = 0.017).	Endocrine Function; Immunosuppression and risk of infection; Alterations in Cardiovascular/Renal Function; GI perforation; Behavioral and Mood Disturbances; Effects on Bones; Ophthalmic Effects; Vaccinations; Serious Skin Rashes AR: Cushingoid appearance, weight increased, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis
Vyondys 53 NDA 211, 970	the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping	2019 [Accelerated approval based on dystrophin protein level as a % of normal, measured by western blot]	30mg/kg by IV infusion, once weekly	25 subjects in an open-label study. Mean dystrophin levels (western blot) increased from 0.10% of normal at baseline to 1.02% of normal by Week 48, with a mean change in dystrophin of 0.92% of normal levels (p < 0.001). The median change from baseline was 0.88%.	WP: Hypersensitivity Reactions; Hypersensitivity AR: headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea

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Viltepso NDA 212,154	the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.	2020 [Accelerated approval based on dystrophin protein level as a % of normal, measured by western blot]	80mg/kg by IV infusion, once weekly	8 subjects who received the 80mg/kg dose in a randomized double-blind, placebo-controlled study. Mean dystrophin levels increased from 0.6% of normal at baseline to 5.9% of normal by Week 25, with a mean change in dystrophin of 5.3% of normal levels (p = 0.01) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%.	WR: Kidney Toxicity AR: upper respiratory tract infection, injection site reaction, cough, and pyrexia

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Casimersen is a New Molecular Entity (NME). It is not being reviewed by other FDA Divisions.

3.2. Summary of Pre-submission/Submission Regulatory Activity

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The following US regulatory listing for casimersen is in chronological order.

3.2.1. PIND Meeting (minutes issued 6/11/13)

Key clinical FDA responses were:

1. An IND-opening study (4045-101) would treat 12 subjects with advanced DMD, using 12 weekly doses of casimersen in 8 subjects (at least 2 weeks on each of 4mg/kg, 10mg/kg, and 30mg/kg), and weekly dosing of placebo in the other 4 subjects.

2. A number of CMC, nonclinical, and clinical pharmacology topics were also addressed.

3.2.2. Fast Track Designation Granted

Fast Track Designation was granted on 7/24/14 based on a positive determination on the four key requirements for this designation:

1. The condition of DMD is serious or life-threatening;
2. The development program is designed to demonstrate an effect on a serious aspect of DMD;
3. There is an unmet medical need because no available therapy exists;
4. The product shows potential to address an unmet medical need.

3.2.3. Type A Meeting (minutes issued 11/18/14)

Key clinical responses were:

1. The proposed efficacy and safety study 4045-301 (for both casimersen and golodirsen) for a then-proposed treatment duration of 48 weeks should add 5- and 6-year old boys.
2. Use the 6-minute walk test (6MWT) as the primary endpoint, and add dystrophin protein quantitation as a secondary endpoint. The 6MWT analysis should be stratified into 2 subgroups: 300-375m 6MWT at baseline (BL); and 375-450m 6MWT at BL.
3. North Star Ambulatory Assessment (NSAA) and Timed-Function Tests (TFTs) can be secondary endpoints.
4. The placebo group may be used for comparison with pooled golodirsen and casimersen groups.

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3.2.4. Partial Clinical Hold Letter (letter issued 11/9/15)

Regarding the initiation of study 4045-301, a Partial Clinical Hold was issued on 11/9/15 to require the following protocol revision:

> "The provision in the clinical protocol that allows for investigator discretion to place central venous catheters presents more than a minor increase over minimal risk (21 CFR 50.53) without the prospect of direct benefit if being used to infuse placebo as planned. You must revise the protocol to preclude the use of implantable central venous catheters."

The sponsor agreed to the protocol revision, and the partial clinical hold was lifted on 12/17/15. Note, however, that implantable central venous catheters was again allowed in June 2017, following a public meeting of the Office of Pediatric Therapeutics (OPT) that recommended the allowance of procedures such as these during pediatric clinical trials. This renewed allowance of central venous catheter placement was included in study 4045-301's Protocol Amendment 5, as described further below.

3.2.5. Type C Meeting (minutes issued 2/15/18)

Much of the discussion regarded subjects who would be treated with golodirsen in the ongoing and revised 144-week efficacy and safety study 4045-301. However, the following key clinical responses were implicitly relevant to casimersen-treated subjects in that study:

1. Consider a 48-week interim analysis of dystrophin protein levels for accelerated approval, and also to verify that the planned sample size will be sufficient for a final analysis at 96 weeks, based upon the testing of key assumptions.
2. Submit any revisions for an interim analysis in a Statistical Analysis Plan to FDA prior to implementation.
3. Ensure that data integrity is maintained with the interim analysis.

3.2.6. Type C Meeting (minutes issued 8/23/18)

Key clinical points were:

1. Study 4045-301 may be increased in size to a proposed 222 enrolled subjects.
2. The primary endpoint analysis of 6MWT may be removed from the interim analysis at 48 weeks for both casimersen and golodirsen.
3. The interim analysis for casimersen at 48 weeks may include only dystrophin analyses from an efficacy standpoint (i.e., analyses of secondary endpoints and exploratory endpoint are not required).

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3.2.7. Orphan Drug Designation

This designation was issued on 9/4/19.

3.2.8. Pre-NDA Meeting (minutes issued 6/27/19)

Key agreements with multiple disciplines were:

1. Acceptance that the casimersen NDA could include *de novo* dystrophin protein data from only the first 43 subjects in the Week 48 interim analysis of study 4045-301, without any functional data (e.g., 6MWT), provided that point 2 is also met;
2. Acceptance in principle of the western blot and exon-skipping bioassays, pending a review of many requested validation and technical reports for the bioassays;
3. Acceptance of blinded western blot dystrophin protein data from subjects that have been de-identified by using sham IDs, because of the ease of unblinding otherwise (i.e., many of the 45 study sites have only 1 or 2 subjects);
4. Acceptance in principle of a safety database of approximately 69 subjects (studies 4045-101, 4045-301, and 4045-302 (an open-label extension study);
5. No need for a special population study in subjects with hepatic impairment;
6. Possible absence of a requirement for a TQT study if the hERG IC50 is acceptably high when the assay is conducted at 36^0C; with a note that analysis of the clinical ECGs from study 4045-301 should support that there is not a large (i.e., 20msec) mean increase in QTc.
7. Submission of anti-dystrophin antibody data from study 4045-101 within 90 days of NDA acceptance date;
8. Submission of all other requested CMC and BIMO (Bioresearch Monitoring Conformance) data.

3.2.9. Rolling Review Granted

A rolling review for the submission of the NDA was granted on 1/2/20. The final round of the rolling NDA submission (based on a data lock-point of 5/31/19) was completed on 6/25/20.

3.2.10. Proprietary Name Granted

The proprietary name that was requested by the applicant, Amondys 45, was granted on 3/26/20.

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3.2.11. Priority Review Granted

When the Filing acceptance letter was issued on 8/24/20, Priority Review was granted with a PDUFA date of 2/25/21.

3.3. Foreign Regulatory Actions and Marketing History

There have been no foreign regulatory interactions for casimersen, which is not marketed in any region.

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

4.1. Office of Scientific Investigations (OSI)

The OSI review team summarized as follows their investigations regarding the key efficacy clinical trial, 4045-301. "The clinical sites of Drs. Iannaccone, Mathews, and Mendell were inspected in support of this NDA and covered Protocol 4045-301. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. For Protocol 4045-301, the primary efficacy endpoint supporting accelerated approval was dystrophin expression (a biological endpoint) at baseline and Week 48. With regard to this endpoint, the inspections focused on verifying whether the protocol was followed with respect to obtaining muscle biopsy samples. No significant issues were identified with regard to muscle biopsy collection, preparation, and processing."

4.2. Office of Product Quality (OPQ)

The OPQ review team "identified one outstanding product quality concern, which is the formation of visible particles in the product under long-term storage conditions. These conditions are characterized by the applicant as inherent to the chemical and physical properties of casimersen. The presence of visible particles in a product intended for intravenous (IV) administration would normally preclude an approval recommendation for the application. However, the clinical team within the Division of Neurology 1 (DN1) has previously determined that: a) the clinical benefits of casimersen in the proposed patient population outweigh the risks associated with particulate matter; and b) use of a 0.2 µm in-line filter mitigates the risk. Therefore, OPQ recommends approval of the application. The approval

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recommendation is subject to post-marketing requirements (PMRs) to characterize and reduce particulate matter in the rug product."

4.3. Clinical Microbiology

This section is not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Casimersen repeat-dose toxicology studies of 12 to 39 weeks in duration in two strains of adult mice, in juvenile rats, and in adult nonhuman primates (NHPs) revealed the target organ to be the kidney. In these studies, renal tubule basophilia and micro-vacuolation were observed, along with renal tubule degeneration and regeneration. After 4-week recovery periods, the findings were partially reversible. After an 8-week recovery period in the longest repeat dose toxicology study (39 weeks in NHPs), the findings were fully reversible.

The Pharmacology / Toxicology review team assessed the approvability of this NDA from the standpoint of nonclinical studies, as follows.

> "The pivotal nonclinical studies indicate that renal impairment can result from chronic exposure to casimersen. However, because kidney function is monitorable, the nonclinical data are considered adequate to support approval of casimersen for the treatment of DMD in patients with mutations amenable to exon 45 skipping therapies."

Please refer to the separate review by the Pharmacology / Toxicology team for further details, analyses, and conclusions.

4.5. Clinical Pharmacology

In principle, antisense oligonucleotides (ASOs) that promote the skipping of out-of-frame *DMD* exon mutations can yield dystrophin mRNA that is translated to a truncated but potentially functional dystrophin protein. Casimersen was designed to target *DMD* mutations that are amenable to exon 45 skipping. Dystrophin protein is largely expressed in skeletal muscle, and hence skeletal muscle is a target organ for both potential benefits of the product, and also for potential adverse reactions. Based on the results identified in nonclinical toxicology studies (described above), kidney is an additional target organ.

The effects of casimersen on levels of dystrophin in skeletal muscle tissue is the primary pharmacodynamic biomarker that the applicant has submitted in this application for accelerated approval. Effects of casimersen on the skipping of exon 45 in muscle tissue and on

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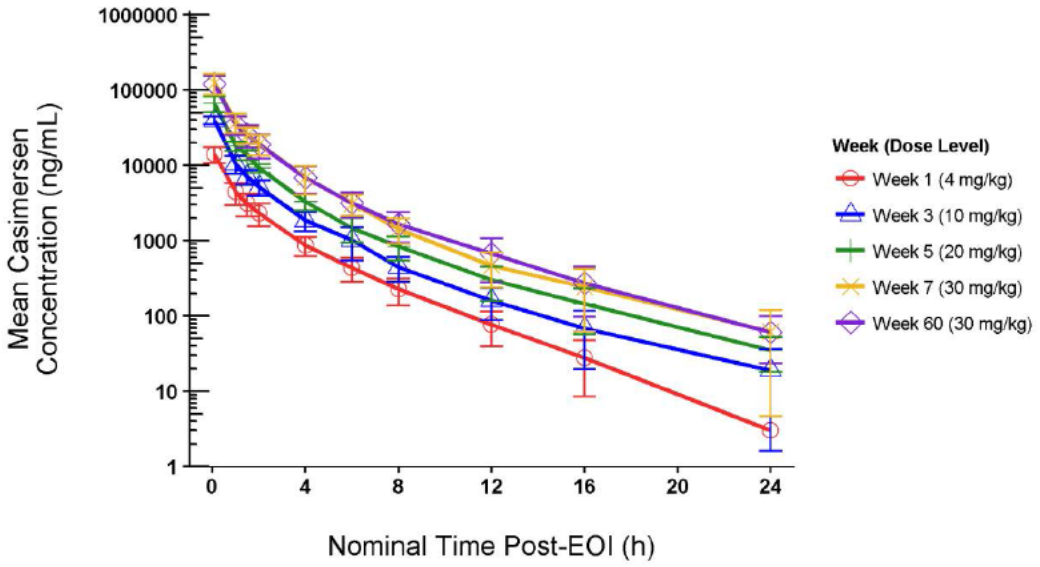
the cellular localization of truncated dystrophin were also submitted. These data will be discussed in later sections that deal with the potential efficacy of casimersen.

The pharmacokinetic (PK) profile of casimersen in subjects with DMD was assessed in study 4045-101. As described in more detail in later sections, this was a small study in which 12 subjects were randomized to four escalating doses of casimersen (n = 8) or to placebo (n = 4) during a 12-week randomized, double-blind period. A subsequent 132-week open label period followed. The figure below illustrates the dose-dependent profile of casimersen over a dose range from 4mg/kg IV weekly through 30mg/kg IV weekly. The PK profile of the 30mg/kg dose was measured both during the first 12-week period, and then again after 60 weeks of treatment.

Figure 2. Log-concentration of Plasma Casimersen over Time.



EOI=end of infusion; h=hour; SD=standard deviation
Negative error bars have been removed from this plot.

[Source: Fig. 4 of CSR for Study 4045-101]

Absorption, metabolism, and elimination of casimersen were studied *in vitro* in human-derived tissues; and also in study 4045-102, a Phase 1 open-label study of a single 1800-mg IV dose of ^{14}C-casimersen (containing approximately 100 µCi of radiocarbon) in 8 healthy adult males. More than 90% of radioactivity was recovered in urine as unmetabolized parent. Casimersen did not significantly induce or inhibit key CYP450 isoforms. The product was not a substrate for a variety of transporters including P-glycoprotein (P-gp), nor did it inhibit these transporters. Based upon these results, the applicant does not anticipate the potential for drug-drug interactions (DDI). No DDI studies have been conducted.

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One study in a special population has been conducted. Study 4045-102 was a Phase 1, open-label study of a single IV dose of 30mg/kg IV of casimersen in adult males with stage 2 (n = 8) or stage 3 (n = 8) chronic kidney disease (CKD), compared with healthy, matched adult males with normal kidney function (n = 9). Compared to parameters in healthy subjects, the plasma maximal concentration (Cmax) of casimersen was unchanged in stage 2 CKD and it was slightly increased (approximately 1.2-fold) in stage 3 CKD. Compared to healthy adults, the exposure (AUC) of casimersen was slightly increased (approximately 1.2-fold) in stage 2 CKD and moderately increased (approximately 1.8-fold) in stage 3 CKD.

The to-be-marketed formulation of casimersen is identical to that used in all clinical studies conducted by the applicant. Consequently, there is no need for any bioavailability/ bioequivalence study.

The Office of Clinical Pharmacology (OCP) recommended approval of this product.

4.6. Devices and Companion Diagnostic Issues

This section is not applicable.

4.7. Consumer Study Reviews

This section is not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

5.1.1. Description of Three Completed Studies

The applicant has completed three studies and two are ongoing. The following tables summarize the three completed studies.

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Table 4. Completed Study 4045-101

A Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study Followed by an Open-Label Safety and Efficacy Evaluation of SRP-4045 in Advanced-Stage Patients with Duchenne Muscular Dystrophy Amenable to Exon 45 Skipping **[Study identifier on clinicaltrials.gov website: NCT02530905]**

This study was completed at three US sites.

Study Number/ (Phase)	Study Design	Number of Patients Planned	Study Objectives	Status
4045-101/ (Phase 1/2)	This was a first-in-human, multicenter, randomized, double-blind, placebo-controlled, dose-titration study designed to assess the safety, tolerability, and PK of once-weekly IV infusions of casimersen in advanced-stage patients with genotypically confirmed DMD characterized by deletions amenable to exon 45 skipping (eg, exons 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55). This study evaluated 4 ascending dose levels of casimersen (4, 10, 20, and 30 mg/kg administered weekly for a minimum of 2 weeks per level) compared to placebo over approximately 12 weeks of a double-blind dose-titration period. The double-blind dose-titration period was followed by an open-label extension period evaluating the safety and efficacy of casimersen at 30 mg/kg (or the highest tolerated dose as determined during dose titration) administered weekly through Week 144.	12 advanced-stage DMD patients (8 casimersen + 4 placebo) amenable to exon 45 skipping	Primary: Evaluate the safety and tolerability of 4 escalating IV doses (4, 10, 20, and 30 mg/kg) of casimersen administered once weekly for ≥ 2 weeks per dose level compared with placebo Secondary: Determine the PK profile of 4 escalating doses of casimersen Exploratory: Assess exploratory efficacy (pulmonary function testing, Brooke Upper Extremity Scale, PODCI), population PK and potential disease-related biomarkers, serum anti-PMO antibodies, and anti-dystrophin antibodies in patients treated with casimersen	Completed; all 12 patients completed the double-blind, placebo-controlled, dose-titration portion of the study and 11 patients completed the open-label extension period

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Table 5. Completed Study 4045-102

A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [14C]-Casimersen Following a Single Intravenous Dose Administration in Healthy Male Participants [No NCT number identified on clinicaltrials.gov website or applicant's website]

This study was completed at one US site.

Study Number/ (Phase)	Study Design	Number of Patients Planned	Study Objectives	Status
4045-102/ (Phase 1)	This was an open-label, uncontrolled, single-center, absorption, metabolism, and excretion study of a single 1800-mg IV dose of [^{14}C]-casimersen (containing approximately 100 µCi of radiocarbon).	8 subjects	Primary: Determine the mass balance and routes of elimination of [^{14}C]-casimersen following IV administration of a single 1800-mg (containing approximately 100-µCi) [^{14}C]-radiolabeled dose of casimersen in healthy male subjects; assess the PK of a single IV dose of casimersen using [^{14}C]-radiolabeled casimersen; determine the whole blood and plasma concentrations of total radioactivity following a single IV dose of [^{14}C]-casimersen; and determine the urinary and fecal recovery of total radioactivity Secondary: Characterize and identify, if possible, the major metabolites of casimersen in plasma, urine, and/or feces following a single IV dose of [^{14}C]-casimersen; determine the plasma and urine concentrations of unchanged casimersen (the parent drug); and evaluate the safety and tolerability of a single IV dose of [^{14}C]-casimersen in healthy male subjects	Completed; all 8 subjects completed the study

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Table 6. Completed Study 4045-103

A Phase 1, Open-label, Parallel Group Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single Dose of Casimersen (SRP-4045) in Adult Male Participants with Stage 2 or Stage 3 Chronic Kidney Disease and Normal Kidney Function [No NCT number identified on clinicaltrials.gov website or applicant's website]

This study was completed at four US sites.

Study Number/ (Phase)	Study Design	Number of Patients Planned	Study Objectives	Status
4045-103/ (Phase 1)	This was an open-label, multicenter, single-dose, parallel-cohort study in adult males with Stage 2 or 3 CKD compared with healthy, adult male subjects with normal kidney function matched by age (within 10 years) and body mass index (within 20%).	Up to 32 subjects (8 subjects in each of the Stage 2 and Stage 3 CKD groups and between 8 and 16 matched healthy subjects with normal kidney function)	Primary: Evaluate the safety and tolerability of a single IV dose of casimersen in adult male subjects with Stage 2 or 3 CKD Secondary: Evaluate the PK of a single IV dose of casimersen in adult male subjects with Stage 2 or 3 CKD	Completed; 25 subjects (16 subjects with Stage 2 or 3 CKD and 9 matched healthy subjects with normal kidney function) completed the study

CKD = chronic kidney disease; DMD = Duchenne muscular dystrophy; IV = intravenous; PK = pharmacokinetics; PMO = phosphorodiamidate morpholino oligomer; PODCI = Pediatric Outcomes Data Collection Instrument.

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5.1.2. Description of Two Ongoing Studies

The following tables summarize the two ongoing studies from which data were submitted with a data cut-off of 5/31/19.

Table 7. Ongoing Study 4045-301

A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy [NCT02500381]

As of data cut-off on 5/31/19, this study was ongoing at 54 sites in 11 countries:
US / CANADA / UK / FRANCE / ITALY / BELGIUM / SWEDEN / GERMANY / SPAIN / CZECH REPUBLIC / ISRAEL

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Study Number/ (Phase)	Study Design	Number of Patients Planned	Study Objectives	Status
4045-301 (ESSENCE) (Phase 3)	This is a double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate the efficacy and safety of 2 PMOs, casimersen and golodirsen, in approximately 222 patients (~111 patients per genotype) with genotypically confirmed DMD with deletion mutations amenable to skipping exon 45 or 53, respectively. Patients are randomized in a 2:1 ratio, combined active (casimersen or golodirsen) to placebo.	111 patients amenable to exon 45 skipping ~74 patients randomized to study drug, casimersen ~37 patients randomized to placebo	Primary: Evaluate the effect of casimersen and golodirsen (combined-active group) compared with placebo on ambulation, endurance and muscle function as measured by the 6MWT Secondary: Evaluate the effect of casimersen and golodirsen (combined-active group) on dystrophin protein expression in biopsied muscle tissue as measured by Western Blot (quantification) and immunohistochemistry fiber intensity; functional status as measured by the ability to rise independently from the floor (without external support), loss of ambulation, and North Star Ambulatory Assessment; respiratory muscle function as measured by forced vital capacity percent predicted; and safety and tolerability of golodirsen and casimersen Additional: Characterize exon skipping and PDPFs; evaluate endurance, muscle function, respiratory muscle function, quality of life; and evaluate psychometric characteristics of instruments to measure physical functioning	Ongoing; as of the cutoff date (21 July 2019), 88 patients[a] have received blinded study drug per protocol

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Table 8. Ongoing Study 4045-302

Long-term, Open-label Extension Study for Patients with Duchenne Muscular Dystrophy Enrolled in Clinical Trials Evaluating Casimersen or Golodirsen [NCT03532542]

This study was ongoing at three US sites as of the cut-off date (5/31/19). On the clinicaltrials.gov website, 27 study sites are currently listed.

Study Number/ (Phase)	Study Design	Number of Patients Planned	Study Objectives	Status
4045-302/ (Phase 3)	This is an open-label, multicenter, long-term (up to 144 weeks), extension study of Study 4045-101 and Study 4045-301 to evaluate the efficacy and safety of casimersen and golodirsen in patients with genotypically confirmed DMD with deletion mutations amenable to skipping exon 45 or 53, respectively.	Up to 111 patients casimersen (up to 111 additional patients golodirsen)	Primary: Evaluate the safety and tolerability of long-term treatment with casimersen 30 mg/kg or 30 mg/kg golodirsen Exploratory: Evaluate changes in physical functioning with long-term treatment with 30 mg/kg casimersen or golodirsen; evaluate changes in pulmonary function with long-term treatment with 30 mg/kg casimersen or golodirsen; and evaluate immunogenicity of long-term treatment with 30 mg/kg casimersen or golodirsen	Ongoing; as of the cutoff date (21 July 2019), 11 patients amenable to exon 45 skipping have entered the study and received study drug

6MWT = 6-Minute Walk Test; DMD = Duchenne muscular dystrophy; PDPF = percent dystrophin-positive fibers; PMO = phosphorodiamidate morpholino oligomer.
[a] Excludes 2 patients with DMD amenable to exon 53 skipping who were misrandomized and received casimersen 30 mg/kg instead of golodirsen 30 mg/kg as well as 1 patient who was dosed after the data cutoff date of 21 July 2019. These patients are excluded from the safety population.

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5.1.3. Pediatric Enrollment Data for the Five Completed or Ongoing Studies

The following table provides additional data and the number of pediatric subjects enrolled in each study. A pediatric subject is defined as a person who is less than 16 years of age at enrollment.

Table 9. Additional Data for Each Study

Study Number	Study Objectives	Study Design	Pediatric Subjects (N) with DMD	Study Sites / Locations
4045-101 Phase 1 / 2	safety, tolerability, PK	randomized, double-blind, placebo-controlled phase followed by open-label phase	N = 11 pediatric subjects with DMD plus one 20-year-old subject with DMD	3 US sites
4045-102 Phase 1	measurements of absorption, metabolism, elimination	open label	N = 0 with DMD (8 healthy adults)	1 US site
4045-103 Phase 1	safety, tolerability, PK in healthy adults vs. adults with chronic kidney disease (CKD)	open label	N = 0 with DMD (9 healthy adults, 8 adults with stage 2 CKD, 8 adults with stage 3 CKD)	4 US sites
4045-301 Phase 3	efficacy, safety	randomized, double-blind, placebo-controlled period followed by open-label period	N = 88 with DMD (as of cut-off date of 5/31/19)	54 global sites (as of cut-off date): US/CAN/UK/FRA/ITA BELG/SWE/GER/SPA CZECH/ISRAEL
4045-302 Phase 3	safety, tolerability	long-term open-label extension	N = 10 pediatric patients with DMD (plus 1 adult with DMD)	3 US sites (as of cut-off date)

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5.2. Review Strategy

5.2.1. Efficacy Review Strategy

The applicant seeks accelerated approval based upon the effect of casimersen vs. placebo on dystrophin expression in skeletal muscle tissue that was collected in study 4045-301 by biopsies at Baseline and at Week 48 (n = 16, placebo vs. n = 27, casimersen). Dystrophin expression was measured using western blot methodologies. Additional analyses of these biopsy tissues using RT-PCR and immunofluorescence methods are used to support the effect of casimersen on dystrophin expression. This primary clinical reviewer [DAH] will evaluate the applicant's submitted results, and this reviewer will conduct additional statistical evaluations to verify the applicant's results. The methodologies used by the applicant will also be reviewed by FDA staff from OBP (Office of Biotechnology Products). Verification of the applicant's statistical analyses of these data will also be provided by FDA's Biometrics staff.

The completed 144-week study, 4045-101 (n = 12), provides a limited dataset of clinical efficacy results that compare a Change from Baseline (CFB) to Week 144 in a subset of Pulmonary Function Tests, the Brooke Upper Extremity scale, and the Pediatric Outcomes Data Collection Instrument (PODCI). Only the first 12-weeks of this 144-week were randomized, double-blind, and placebo-controlled, and the remaining 132 weeks were an open-label extension in which all subjects received casimersen. For that reason, and also because of the small sample size, the CFB to Week 144 in these clinical assessments provides no real ability to compare treatment effects of casimersen vs. placebo.

Based upon the factors discussed above, the efficacy review (section 6) will focus solely on study 4045-301.

5.2.2. Safety Review Strategy

Safety information from studies 4045-101, 4045-301, and 4045-302 provide the only databases that contain information about the safety and tolerability of multiple dosing (study 4045-101) or single-dosing of the to-be-marketed dose (30mg/kg: in studies 4045-101, 4045-301 and 4045-302) in the intended treatment population of patients with DMD amenable to exon 45 skipping. The two completed phase 1 studies, 4045-102 and 4045-103, enrolled only healthy adults or adults with CKD. These subjects received single doses of casimersen. Safety data from these latter studies are limited, and they provide little bearing on the safety and tolerability of multiple casimersen doses in the younger target patient population of patients with DMD amenable to exon 45 skipping. For these reasons, only the safety data derived from

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the three studies in subjects with DMD amenable to exon 45 skipping (i.e., 4045-101, 4045-301, and 4045-302) will be evaluated in this review.

The clinical safety database that was submitted on 1/10/20 for the two ongoing studies, 4045-301 and 4045-302, had a data cut-off date of 5/31/19. These original NDA safety data will be evaluated in section 8. A 120-day safety update report was provided on 9/29/20, and it covered the additional reporting period from 6/1/19 through 2/28/20. These cumulative safety data will also be evaluated in section 8, but in a separate and later subsection (section 8.7) than the sections that describe and evaluate the original NDA safety data.

Expert assistance with this safety review was provided by the Division of Neurology's Safety staff, Dr. Sally Jo Yasuda and Dr. Rui Li.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 4045-301

6.1.1. Study Design

"*A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy.*"

As described in greater detail below, casimersen (SRP-4045) is being evaluated in this ongoing study. The study consists of a 96-week randomized, double-blind, placebo-controlled period, followed by a 48-week open-label period.

<u>Primary Objective of Double-blind Period</u>
The primary objective is to evaluate the effects of both casimersen (SRP-4045) and golodirsen (SRP-4053; accelerated approval as Vyondys 53), compared with placebo, on ambulation, endurance, and muscle function as measured by the 6 Minute Walk Test (6MWT).

<u>Secondary Objectives of Double-blind Period</u>
As regards casimersen, the secondary objectives are to evaluate:

- Dystrophin protein expression in biopsied muscle tissue as measured by:
  - Western blot (quantification)
  - Immunohistochemistry (IHC) fiber intensity
- Functional status as measured by:
  - Ability to rise independently from the floor (without external support)

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    - Loss of ambulation (LOA)
    - North Star Ambulatory Assessment (NSAA)
- Respiratory muscle function as measured by forced vital capacity (FVC) % predicted
- Safety and tolerability

Additional Efficacy Objectives of Double-blind Period
As regards casimersen, additional efficacy objectives are to:

- Characterize exon skipping determined by measurement and sequence verification of exon 45 skipped messenger RNA
- Characterize dystrophin protein expression in biopsied muscle tissue as measured by immunohistochemistry (IHC: the percent of dystrophin-positive fibers [PDPF])
- Evaluate the effect of casimersen on endurance and muscle function, as measured by:
    - Frequency of falls
    - Cardiac function, as measured by left ventricular ejection fraction (LVEF)
    - 10-meter walk/run time (seconds) assessed by NSAA
    - Timed 4-step test
    - 9-hole peg test
    - Performance of the Upper Limb (PUL)
    - Quantitative muscle testing (QMT) by hand-held myometry / dynamometry and maximum voluntary isometric contraction testing (MVICT) at a subset of sites.
- Evaluate the effect of casimersen on respiratory muscle function, as measured by percent predicted maximal inspiratory pressure (MIP %p) and percent predicted maximal expiratory pressure (MEP %p)
- Evaluate the effect of casimersen on subject quality of life (QoL), as measured by the Pediatric Outcomes Data Collection Instrument (PODCI).
- Evaluate the psychometric characteristics of 2 DMD-specific instruments evaluating physical functioning as well as the effect of casimersen on physical functioning as measured by these instruments.

Objectives of the Open-label Period
The objectives of this final 48-week period of the 144-week study are to:

- Evaluate the long-term effects of casimersen on functional status up to 144 weeks
- Evaluate the long-term safety and tolerability of casimersen
- Evaluate the psychometric characteristics of two DMD-specific instruments evaluating physical functioning as well as the effect of casimersen on physical functioning using these instruments.

Pharmacokinetic (PK) Objective of the Overall Study
The PK objective is to evaluate the PK properties of casimersen via a population PK model.

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Efficacy Data That Were Submitted in this NDA

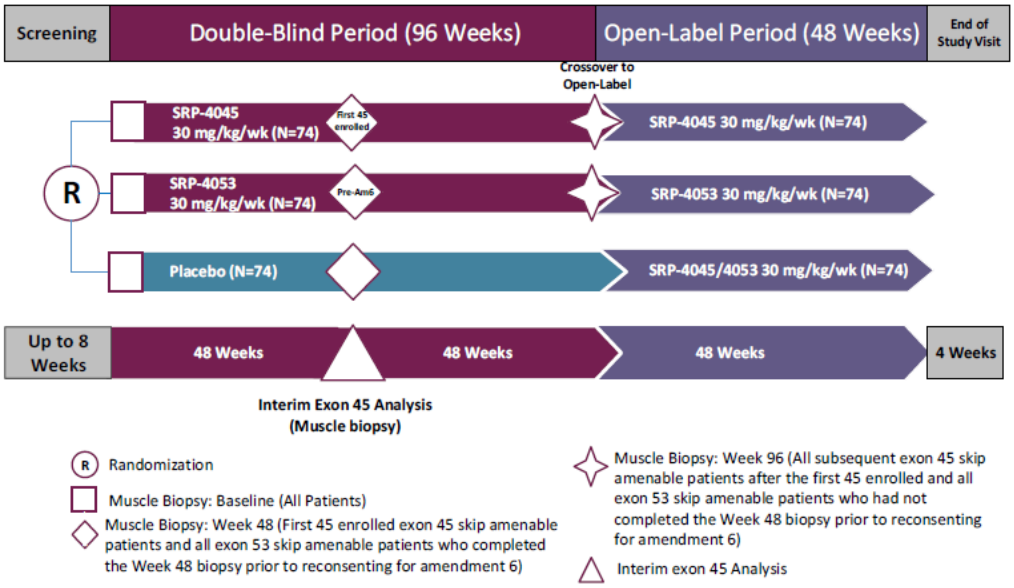
As agreed at the pre-NDA meeting of 6/5/19, the efficacy data submitted for consideration of accelerated approval include measurements of dystrophin protein by western blot assessment, measurements of exon 45 skipping using two methods of RT-PCR, and a qualitative evaluation of dystrophin localization as assessed through immunohistochemical (IHC) techniques. The source of these measurements were muscle biopsies collected at Baseline and at Week 48 from subjects treated with placebo (n = 16) or with casimersen (n = 27).

Trial Design

Overview of Design

The ongoing efficacy and safety trial (4045-301) consists of a Screening Period of up to 8 weeks, a randomized, double-blind, placebo-controlled treatment period of 96 weeks, an open-label period of 48 weeks, and an End of Study visit 4 weeks later. The trial is designed to enroll approximately 111 subjects with DMD amenable to exon 45 skipping to evaluate casimersen (SRP-4045) or placebo in a 2:1 randomization ratio, and approximately 111 subjects with DMD amenable to exon 53 skipping to evaluate golodirsen (SRP-4053; Vyondys 53) or placebo in a 2:1 randomization ratio. The figure below depicts the overall trial design for both casimersen and golodirsen. The remainder of this review will be confined to the part of the trial that evaluates the effects of casimersen.

Figure 3. Depiction of Design of Study 4045-301



[Source: Summary of Clinical Efficacy, Fig. 4]

During the 96-week double-blind portion of the trial, subjects were randomized 2:1 to receive a

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weekly IV infusion at the study site of either casimersen (30mg/kg) or placebo. All study staff, subjects, caregivers, and pharmacists who prepared solutions for infusion were blinded. Each subject's weight was measured at Baseline (Week 1) and every 4 weeks thereafter. Weights used for dosing were those obtained most recently. IV infusions were administered either peripherally or centrally, and the infusion duration was 35 – 60 minutes. The key efficacy evaluation for accelerated approval was based upon muscle biopsies that were collected at Baseline and at Week 48 for the first 45 subjects to reach that visit.

During the 48-week open-label period, all subjects who had completed the prior 96-week double-blinded period received a weekly IV infusion of 30mg/kg casimersen.

Schedule of Events for the Double-blind Placebo-Controlled Period of Study 4045-301
The schedule of events for the first 96-week period of study 4045-301 is below.

Table 10. Schedule of Events for 96-week Double-blind Period of Study 4045-301

Study Period	**Screening**		**Baseline** 3-5 weeks after Screening	**Double-Blind Treatment Period[a]**																	
Week	**Up to 8 weeks prior to Week 1**			**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12[c]**	**16**	**20**	**24[c]**	**28**	**32**	**36[c]**	**40**	**44**	**48[c]**
Safety Laboratory Assessments[i]	X		SU	X	X	X	X	X	X	X	X	X			X			X			X
Immunogenicity			SU	X			X				X	X			X			X			X
Biomarkers			SU	X			X								X						X
PK[j]				X							X		X		X		X		X		X
Whole Blood for *DMD*, *LTBP4*, and *SPP1* Genotyping[d]	X																				
Height (and ulnar length at HS visits)	X		HS									HS			HS			HS			HS
6MWT[k]		HS	HS									HS			HS			HS			HS
NSAA[k]		HS	HS									HS			HS			HS			HS
Fall Collection[l]	X		X				X				X	X			X			X			X
CWU												HS			HS			HS			HS
Timed 4-Step Test			HS									HS			HS			HS			HS
9-Hole Peg Test			HS												HS						HS
PUL			HS												HS						HS
QMT[m]			HS																		HS
PODCI			HS									HS			HS			HS			HS
PFTs[n]		HS	HS									HS			HS			HS			HS

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ECG[o]		HS	HS									HS			HS			HS			HS
Triplicate 12-Lead ECGs				X[u]																	
ECHO[o]		HS																			
Muscle Biopsy[p]			SU																		SU
Study Treatment Infusion[q]				Once Weekly																	
Physiotherapy Interventions	Continuous																				
Concomitant Medications/Therapy	Continuous																				
AE Assessment	Continuous																				

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Study Period	Double-blind Treatment Period (continued)			
Week	60[c]	72[c]	84[c]	96[c]
Full Physical Examination[f]		X		X
Brief Physical Examination[f]	X		X	
Vital Signs[g]	Weekly at Local Site (pre- and post-infusion)[g]			
Weight[h]	Every 4 weeks[h]			
Caregiver Questionnaire and Videography[r]	X	X	X	X
Clinical Global Impression of Change (CGIC)[s]	X	X	X	X
Safety Laboratory Assessments[i]	X	X	X	X
Immunogenicity		X		X
Biomarkers		X		X
PK[j]		X		X
Height (and ulnar length at HS visits)	HS	HS	HS	HS
6MWT[k]	HS	HS	HS	HS
NSAA[k]	HS	HS	HS	HS
Fall Collection[l]	X	X	X	X
CWU	HS	HS	HS	HS
Timed 4-Step Test	HS	HS	HS	HS
9-Hole Peg Test		HS		HS
PUL		HS		HS
QMT[m]				HS
PODCI	HS	HS	HS	HS
PFT[n]	HS	HS	HS	HS
ECG[o]	HS	HS	HS	HS
Triplicate 12-Lead ECGs				X[v]
ECHO[o]				HS
Muscle Biopsy[p]				SU
Study Treatment Infusion[q]	Once Weekly			
Physiotherapy Interventions	Continuous			
Concomitant Medications/Therapy	Continuous			
AE Assessment	Continuous			

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6MWT = 6-minute walk test; AE = adverse event; CWU = continuous wheelchair use; *DMD* = Duchenne muscular dystrophy; ECG = electrocardiogram; ECHO = echocardiogram; ET = early termination; HEENT = head, ears, eyes, nose, and throat; HS = hub site; *LTBP4* = latent transforming growth factor beta binding protein 4; NSAA = North Star Ambulatory Assessment; PFT = pulmonary function test; PK = pharmacokinetics; PODCI = Pediatric Outcomes Data Collection Instrument; PUL = Performance of the Upper Limb; QMT = quantitative muscle testing *SPP1* = secreted phosphoprotein 1; SU = surgical unit; X = local site.

[a] Early termination assessments are the same as Week OL48 assessments as described in Table 2. An Early Termination visit is required if the patient discontinues more than 28 days after a Functional Assessment visit (Weeks 12, 24, 36, 48, 60, 72, 84, or 96).

[b] Week 1 should occur within 4 weeks of the Baseline Functional Assessment visit. If the Week 1 visit is >4 weeks after Baseline, the patient is required to repeat the Baseline functional assessments to reconfirm eligibility. The 2-day mean of this repeated 6MWT assessment must be within 15% of the 2-day mean for the previous Baseline assessment in order to meet eligibility.

[c] Functional assessment (Hub Site) visits may occur within ±1 week of the visit date specified in the schedule of events, with the exception of Week 96, where the functional assessment (Hub Site) visit may occur within -3 weeks of the visit date specified in the schedule of events.

[d] Eligibility will be assessed during Screening and confirmed by the local site and the Sponsor after completion of the 6MWT, PFT, and ECG at the Baseline visit. Eligibility will be reconfirmed before dosing at Week 1 based on all available data including safety laboratory assessments. This confirmation must include review of results of the Screening test for *DMD* genotyping. It is not necessary for results of the Screening tests for *LTBP4* or *SPP1* genotyping to be available for confirmation of patient eligibility.

[e] Eligible patients will be randomized using a 2:1 ratio to either the combined-active group to receive SRP-4045 or SRP-4053, according to genotype and age [7 to 8.5 vs >8.5 to 13 yrs]; approximately 74 patients per genotype), or the placebo group (approximately 37 patients per genotype). Randomization will occur at Baseline after the local site has confirmed patient eligibility after completion of the 6MWT, PFT, and ECG done at the HS Baseline visit.

[f] Full physical examination: general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems (refer to Section 10.4.1 for components of the neurological systems examination). Brief physical examination: general appearance, HEENT, heart, chest, abdomen, and skin.

[g] Vital signs include blood pressure, heart rate, respiration, and temperature (oral, tympanic, or axillary). Patients will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[h] Weight is recorded at the Hub Site on Baseline Day 1 and at the Surgical Site prior to biopsy. Starting at Week 1, weight is to be recorded every 4 weeks throughout the study. The weight obtained at the local site at Week 1 will be used to calculate the initial dose of study treatment. Subsequently, the study treatment dose will be calculated based on the most recent patient weight obtained per protocol prior to the current visit.

[i] Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.

[j] At Weeks 1, 8, 16, 24, 32, 40, 48, 72, and 96, blood samples for assessing plasma drug concentrations will be obtained at select participating sites predose (prior to the start of the infusion), and immediately prior to the end of the infusion (expected approximate time of postdosing maximum plasma concentration for SRP-4045 and SRP-4053). Additionally, 1 blood sample will be taken during each of the following windows: approximately 1 to 3 hours and approximately 4 to 12 hours after the end of the infusion. The specific time of sample collection within each window is at the discretion of the site.

[k] The 6MWT and NSAA will be performed on 2 consecutive business days at Screening, Baseline (prior to Week 1), and every 24 weeks (at the Week 24, 48, 72, and 96 visits). This may require 2-night overnight stays. The 6MWT and NSAA will be performed on only 1 day at the Week 12, 36, 60, and 84 visits. Pulse will be obtained prior to and immediately after the 6MWT.

[l] The number of falls will be collected from the patient with the help of parents or guardians and recorded in the Patient Fall Diary as a patient-reported outcome. The Local Site is to distribute the Patient Fall Diary to the parents or guardians during the initial Screening visit and the first collection period will be 1 week prior to the start of travel to the Hub Site for the Baseline Hub visit.

[m] QMT using a hand-held myometer/dynamometer will be done for all patients. In addition, maximum voluntary isometric contraction testing (MVICT) will be done only at a subset of HS with MVICT capabilities.

[n] PFT measurements will consist of forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), and will be performed on 2 consecutive business days at Screening, Baseline (prior to Week 1), and every 24 weeks (at the Weeks 24, 48, 72, and 96 visits). PFTs will be performed on only one day at the Week 12, 36, 60 and 84 visits.

[o] ECG and ECHO are permitted to be conducted on either Day 1 or Day 2 of the following study visits for patient convenience: Screening, Baseline (ECG only), Week 24 (ECG only), Week 48 (ECG only), Week 72 (ECG only), and Week 96.

[p] Upon qualification for the study based on Screening and Baseline assessments and after eligibility is confirmed by both the local site and the Sponsor's Medical Monitor, all patients will undergo a muscle biopsy at Baseline. A second biopsy will be collected at either Week 48 or 96 (as detailed in Section 7.1). The first 45 patients amenable to exon 45 skipping randomized into this study will undergo muscle biopsy at Week 48 and all subsequent patients amenable to exon 45 skipping randomized into this study will undergo a muscle biopsy at Week 96. Patients amenable to exon 53 skipping who have completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 will not undergo a further muscle biopsy. Patients amenable to exon 53 skipping who have not completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 will undergo a muscle biopsy only at Week 96. The biopsies at Weeks 48 (±2 weeks) or 96 (within 3 weeks prior to this visit) must occur after the clinical evaluation for Weeks 48 or 96 and at least 48 hours after the most recent infusion. For biopsies done at Week 96, biopsies must be completed prior to the transition to open-label study drug. Study infusions must not be administered until at least 24 hours post biopsy, and the Investigator must medically clear the patient before the infusion may be given.

[q] According to randomization and genotype, treatment (active treatment or placebo) will be administered by IV infusion (approximately 35-60 minutes). Patients are to be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream or other per Investigator's discretion) be applied prior to infusions. Patients who discontinue treatment are to have an End of Study visit 28 days after their last infusion as described in Table 2. The following guidelines for the timing of dosing are to be followed throughout the study: (1) Patients should receive study treatment once every 7 days starting at the Week 1 visit. After the first infusion, a window of ±2 days around the scheduled weekly dosing date (referenced back to the first dose at Week 1) is acceptable; (2) patients may not receive 2 separate doses of study treatment within the same 60-hour period; (3) the medical monitor is to be contacted in the event of a missed dose.

[r] Patients from select sites will participate in the Caregiver Questionnaire and Videography assessments under a separate informed consent. Patients who are already enrolled in the study and who consent to participate in the caregiver assessments will have an ad hoc first collection, per the Assessment Manual schedule. The Caregiver Questionnaire and Videography will be performed in the patient's home setting, not at the investigational site.

[s] The Clinical Global Impression of Change assessment will be required only for patients who participate in the Caregiver Questionnaire and Videography assessments and who have these assessments performed at study Baseline. To obtain the most reliable and consistent data, the Sponsor strongly recommends that the Clinical Global Impression of Change be performed by the local site study physician who knows the patient best, and the patient should be rated by the same evaluator throughout the study.

[t] An optional additional Informed Consent Form may be signed prior to the initial screening visit if needed to provide patient information for biopsy scheduling to ensure that the biopsy is performed per protocol timelines.

[u] For newly enrolled patients at select participating sites, on the day of the first dose, triplicate 12-lead ECGs will be obtained immediately prior to PK sampling at predose (Baseline), at the end of infusion, and at 1 to 3 hours after the end of infusion.

[v] For patients at select participating sites, on the day of dosing, triplicate 12-lead ECGs will be obtained immediately prior to PK sampling at predose (Baseline), at the end of infusion, and at 1 to 3 hours after the end of infusion.

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Schedule of Events for the Open-label Period of Study 4045-301

The schedule of events for the 48-week open-label period of this study is shown below.

Table 11. Schedule of Events for 48-week Open Label Period of Study 4045-301

	Open-Label Treatment Period[a,b]												End of Study
Week	**OL1[a]**	**OL 2**	**OL 3**	**OL 4**	**OL 5**	**OL 6**	**OL 7**	**OL 8**	**OL12[c]**	**OL24[c]**	**OL36[c]**	**OL48[c]**	**OL52[q] (or ET +28 days)[d]**
Full Physical Examination[d]	X			X						X		X	X
Brief Physical Examination[d]								X	X		X		
Vital Signs[e]	Weekly at Local Site (pre- and post-infusion)[e]												X
Weight[f]	Every 4 weeks[f]												
Caregiver Questionnaire and Videography[o]									X	X	X	X	
Clinical Global Impression of Change (CGIC)[p]									X	X	X	X	
Safety Laboratory Assessments[g]	X[g]	X	X	X		X		X	X	X	X	X	X
Immunogenicity Assessments	X							X		X		X	X
Biomarkers	X									X		X	
PK[h]	X									X		X	
Height (and ulnar length at HS visits)									HS	HS	HS	HS	
6MWT[i]									HS	HS	HS	HS	
NSAA[i]									HS	HS	HS	HS	
Fall Collection[j]				X				X	X	X	X	X	
CWU									X	X	X	X	
Timed 4-Step Test									HS	HS	HS	HS	
9-Hole Peg Test										HS		HS	
PUL										HS		HS	
QMT[k]												HS	
PODCI									HS	HS		HS	
PFT[l]									HS	HS	HS	HS	
ECG[m]												HS	
Triplicate 12-Lead ECGs	X[s]												
Study Treatment Infusion[n, r]	Once Weekly												
Physiotherapy Interventions	Continuous												
Concomitant Medications/ Therapy	Continuous												
AE Assessment	Continuous												

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6MWT = 6-minute walk test; AE = adverse event; CWU = continuous wheelchair use; ECG = electrocardiogram; ET = early termination; HEENT = head, ears, eyes, nose, and throat; HS = hub site, MVICT = maximum voluntary isometric contraction testing; NSAA = North Star Ambulatory Assessment; OL = open-label; PFT = pulmonary function tests; PK = pharmacokinetics; PODCI = Pediatric Outcomes Data Collection Instrument; PUL = Performance of the Upper Limb; QMT = quantitative muscle testing; SU = surgical unit; X = local site.

[a] Open-label treatment will commence at Week OL1. Duplicate assessments at the same study visit should not be performed.

[b] Early termination assessments are the same as Week OL48 assessments. An ET visit is required if the patient discontinues more than 28 days after a Functional Assessment visit (Weeks OL12, OL24, OL36, or OL48).

[c] Functional assessment (Hub Site) visits may occur within ±1 week of the visit date specified in the Schedule of Events.

[d] Full physical examination: general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems (refer to Section 10.4.1 for components of the neurological systems examination). Brief physical examination: general appearance, HEENT, heart, chest, abdomen, and skin.

[e] Vital signs include blood pressure, heart rate, respiration, and temperature (oral, tympanic, or axillary). Patients will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[f] Weight will be recorded every 4 weeks throughout the study.

[g] Before patients may begin open-label treatment, safety laboratory assessments must be performed within 2 weeks prior to first dose. If safety laboratory samples were collected more than 2 weeks prior to the first open-label visit, samples must be collected again and results must be reviewed before initiation of open-label dosing. Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.

[h] At Weeks OL1, OL24, and OL48, blood samples for assessing plasma drug concentrations will be obtained at select participating sites predose (prior to the start of the infusion), and immediately prior to the end of the infusion (expected approximate time of postdosing maximum plasma concentration for SRP-4045 and SRP-4053). Additionally, 1 blood sample will be taken during each of the following windows: approximately 1 to 3 hours and approximately 4 to 12 hours after the end of the infusion. The specific time of sample collection within each window is at the discretion of the site.

[i] The 6MWT and NSAA will be performed on only 1 day in the open-label period of the study. Cardiac assessments may be done on as second day if necessary. Pulse will be obtained prior to and immediately after the 6MWT.

[j] The number of falls will be collected from the patient with the help of parents or guardians and recorded in the Patient Fall Diary as a patient-reported outcome.

[k] QMT using a hand-held myometer/dynamometer will be done for all patients. In addition, maximum voluntary isometric contraction testing (MVICT) will be done only at a subset of HS with MVICT capabilities.

[l] PFT measurements will consist of FVC, MIP, and MEP, and will be performed on only one day in the open-label period of the study.

[m] ECGs are permitted to be conducted on either Day 1 or Day 2 of the following study visits for patient convenience: Week OL48.

[n] During the Open-Label Treatment Period, active treatment (by genotype) will be administered to all patients by IV infusion (approximately 35-60 minutes). Patients are to be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream or other per Investigator's discretion) be applied prior to infusions. Patients who discontinue treatment are to have an End of Study visit 28 days after their last infusion. The following guidelines for the timing of dosing are to be followed throughout the study: (1) Patients should receive study treatment once every 7 days starting at the Week 1 visit. After the first infusion, a window of ±2 days around the scheduled weekly dosing date (referenced back to the first dose at Week 1) is acceptable; (2) patients may not receive 2 separate doses of study treatment within the same 60-hour period; (3) the medical monitor is to be contacted in the event of a missed dose.

[o] Patients from select sites will participate in the Caregiver Questionnaire and Videography assessments under a separate informed consent. Patients who are already enrolled in the study and who consent to participate in the caregiver assessments will have an ad hoc first collection, per the Assessment Manual schedule. The Caregiver Questionnaire and Videography will be performed in the patient's home setting, not at the investigational site.

[p] The Clinical Global Impression of Change assessment will be required only for patients who participate in the Caregiver Questionnaire and Videography assessments and who have these assessments performed at study Baseline. To obtain the most reliable and consistent data, the Sponsor strongly recommends that the Clinical Global Impression of Change be performed by the local site study physician who knows the patient best, and the patient should be rated by the same evaluator throughout the study.

[q] The Follow-Up End of Study visit is applicable for patients who complete Study 4045-301, but who do not choose to participate in the long-term extension (LTE) study. A safety follow-up visit will occur approximately 4 weeks after the last study infusion at the End of Study or for ET. ET is required for patients who discontinue prematurely from Study 4045-301. Patients who complete Study 4045-301 per protocol and who roll over to the LTE study will not require a Follow-Up End of Study visit (as specified in this table) for Study 4045-301.

[r] Starting at Week OL9, home infusions may take place 3 out of every 4 weeks, with the fourth week conducted at the study site. This schedule is intended to reduce study burden while maintaining ongoing in-person surveillance by the study site. Detailed instructions for in-home dosing will be provided in a separate manual to the visiting nurse.

[s] For patients at select participating sites, on the day of dosing, triplicate 12-lead ECGs will be obtained immediately prior to PK sampling at predose (Baseline), at the end of infusion, and at 1 to 3 hours after the end of infusion.

<u>Key Inclusion Criteria</u> (selected by clinical reviewer)
Inclusion criteria include but are not limited to the following.

1. Is a male with an established clinical diagnosis of DMD and an out-of-frame deletion amenable to Exon 45 skipping, including but not limited to deletions of exons such as 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55, as documented prior to screening by a genetic report from an accredited laboratory defining deletion endpoints by multiplex ligation-dependent probe amplification or sequencing. The subject's amenability to exon 45 skipping must be confirmed prior to first dose using the genotyping results obtained during Screening.
2. Is between 7 and 13 years of age, inclusive, at randomization.
3. Has stable pulmonary function (FVC % of predicted ≥ 50% and no requirement for

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nocturnal ventilation) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.

4. Has intact right and left biceps brachii muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups.
5. Has been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1, and the dose is expected to remain constant throughout the study (except for modifications to accommodate changes in weight).
6. If taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), β adrenergic blockers, aldosterone receptor antagonists, potassium, or coenzyme Q, has been on a stable dose for at least 12 weeks prior to Week 1 and the dose is expected to remain constant throughout the study (except for modifications to accommodate changes in weight).
7. Achieved a mean 6MWT distance of ≥300 to ≤450 meters (without assistance) at both the Screening and Baseline visits (prior to Week 1). The mean 6MWT distance at the Screening and Baseline visits is the average of 2 separate assessments on 2 consecutive business days at each visit. The Baseline mean (average of Baseline Days 1 and 2) must be within 15% of the Screening mean distance (average of Screening Days 1 and 2).

<u>Key Exclusion Criteria</u> (selected by clinical reviewer)
Exclusion criteria include but are not limited to the following.

1. Treatment with any of the following investigational therapies according to the time frames specified:
   <u>At any time</u>:
   - Utrophin upregulating agents (except for Ezutromid)
   - Anti-myostatin agents except for Domagrozumab (PF-06252616) (e.g., BMS-986089 or other)
   - CRISPR/Cas9, or any other form of gene editing
   - Gene therapy
   - Cell-based therapy (e.g., stem cell transplantation)
   - Any form of nucleic acid antisense therapy, except PRO045 (BMN 045 [an exon 45 skipping therapy]; see below) or PRO053 (BMN 053 [an exon 53 skipping therapy]; see below)

   <u>Within 24 weeks prior to Week 1</u>:
   - Ezutromid (SMT C1100)
   - PRO045 (BMN 045)
   - PRO051 (BMN 051 [drisapersen, an exon 51 skipping therapy])
   - PRO053 (BMN 053)
   - Domagrozumab (PF-06252616)
   - Anti-fibrotic or anti-inflammatory agents including but not limited to:
   - rimeporide, vamorolone (VBP-15), epigallocatechin-gallate, TAS-205,

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- edasalonexent (CAT-1004), FG-3019, and halofuginone (HT-100)
- Mast cell activation inhibitor (e.g., CRD007 [pemirolast sodium])
- Idebenone (Raxone®)

Within 12 weeks prior to Week 1:

- Nitric oxide (NO)-active agents including, but not limited to, metformin and citrulline, isosorbide dinitrate, tadalafil, sildenafil, pentoxyfilline if taken as part of a DMD clinical trial and not for a medical indication. If taken for a medical indication, must be on a stable dose for at least 12 weeks prior to Week 1.

2. Treatment with any of the following non-investigational therapies according to the time frames specified:

   Within 12 weeks prior to Week 1:

   - Any pharmacologic treatment (other than corticosteroids) that may have an effect on muscle strength or function. Growth hormone for short stature and testosterone for delayed puberty are permitted if a physician has documented the diagnosis and medical necessity of treatment, and the subject started dosing at least 24 weeks prior to Week 1.

   Within 12 weeks prior to Week 1 or anticipated need during the study:

   - Statins
   - Aminoglycoside antibiotics

3. LVEF [Left Ventricular Ejection Fraction] < 50% on the Screening echocardiogram (ECHO) or QTcF ≥ 450 msec on the
   Screening and Baseline ECG.

4. During range of motion testing of ankle dorsiflexion, the mean bilateral loss of dorsiflexion is more than -10 degrees.

Other Prohibited Concomitant Treatments

In addition to the treatments detailed in the exclusion criteria, the following treatments were also prohibited during the study:

- Systemic or oral corticosteroids used for a condition other than DMD (short courses of systemic or oral steroids for acute exacerbations of asthma or dermatitis are permitted);
- Immunosuppressants other than the required and stable corticosteroid treatment for DMD in all subjects;
- Statins or aminoglycosides unless agreed by the site investigator and the medical monitor;
- Other investigational treatments for DMD;

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- New physiotherapy interventions unless the best interests of the subject are at stake.

Casimersen Dose Rationale

The casimersen dose of 30mg/kg weekly was chosen based upon several sets of nonclinical and clinical data. Surrogate ASOs in nonclinical models of DMD induced a dose-dependent increase in dystrophin production over a predicted human range that encompassed 30mg/kg of weekly IV casimersen. Eteplirsen, an approved exon-skipping ASO (Exondys 51) that shares a similar chemical backbone and similar exon-skipping design as casimersen, is dosed by IV infusion weekly at 30mg/kg IV to patients with DMD amenable to exon 51 skipping. Finally, clinical data from phase 1 studies show that the PK profiles of eteplirsen and casimersen are similar.

Dose Modification

There are no formal dose alteration provisions. When a subject has dose interruption for safety reasons, individual decisions about dose resumption are made by the site investigator and the medical monitor.

Subject and Study Stopping Criteria

The applicant or a site investigator could stop a subject's participation for many non-safety reasons, as well as for a safety reason such as unacceptable or intolerable treatment-emergent adverse event (TEAE).

The applicant, a site investigator, the medical monitor, the Data Monitoring Committee (DMC; see below), an IRB/IEC, or a regulatory authority could stop the study for a number of non-safety reasons, as well as the safety reason of the discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study.

Data Monitoring Committee (DMC)

An independent DMC (IDMC) periodically monitors safety, data quality, and integrity of study conduct. After reviewing safety data at each meeting, the IDMC may recommend that: the study may proceed; the study may resume with specified modifications; study enrollment or dosing should be interrupted for further evaluation; or the study should be discontinued. The applicant makes final decisions about IDMC recommendations.

Study Endpoints

Note that the following list of endpoints denotes the Change from Baseline (CFB) to Week 96 in the 6MWT as the primary efficacy endpoint, and a variety of measurements of dystrophin or dystrophin expression as secondary or additional efficacy endpoints. Per FDA's agreement at the pre-NDA meeting with the applicant on 6/5/19, the applicant has submitted data for a surrogate endpoint: the CFB to Week 48 in dystrophin expression as assessed using western

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blot methodologies in skeletal muscle biopsies obtained from subjects with DMD amenable to exon 45 skipping. The applicant has also submitted assessments of the effect of casimersen on exon-skipping, and IHC data that permit a qualitative assessment of the localization of truncated dystrophin in the muscle biopsy tissues. These latter assessments are intended by the applicant to support the endpoint of dystrophin expression for consideration for accelerated approval. The discussion below will therefore focus more on dystrophin measurements than on the 6MWT and other clinical endpoints.

Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Change from Baseline at Week 96 in 6MWT

Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- Change from Baseline at Weeks 48 or 96 in the quantity of dystrophin protein expression as measured by western blot of biopsied muscle tissue.
- Change from Baseline at Week 144 (Week 48 of the OL period) in 6MWT
- Change from Baseline at Weeks 48 or 96 in the intensity of dystrophin expression in biopsied muscle tissue, as measured by immunohistochemistry (IHC).
- Ability to rise independently from the floor (without external support) at Week 96 and Week 144, as indicated by a North Star Ambulatory Assessment (NSAA) sub-score of “2” (without modification) or “1” (Gower’s maneuver).
- Time to loss of ambulation (LOA) from randomization through Week 96 and Week 144.
- Change from Baseline at Week 96 and Week 144 in:
    - NSAA total score
    - Forced Vital Capacity (FVC) % predicted

Additional Efficacy Endpoints

Additional efficacy endpoints are:

- Change from Baseline at Week 48 or Week 96 in exon skipping by measurement and sequence verification of exon 45 skipped messenger RNA.
- Change from Baseline at Weeks 48 or 96 dystrophin protein expression in biopsied muscle tissue as measured by IHC (Percent Dystrophin Positive Fibers [PDPF]).
- Change from Baseline at Week 96 and Week 144 for the combined-active group in:
    - Frequency of falls
    - Left Ventricular Ejection Fraction (LVEF)
    - NSAA time to complete 10-meter run
    - Timed 4-step test
    - 9-hole peg test
    - Performance of Upper Limb (PUL)

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  - Quantitative Muscle Testing (QMT0 by hand-held myometry/dynamometry and Maximum Voluntary Isometric Contraction Testing (MVICT)
  - Maximum Inspiratory Pressure % predicted (MIP %p) and Maximum Expiratory Pressure % predicted (MEP %p)
  - Pediatric Outcomes Data Collection Instrument (PODCI) score
- Change from Baseline at Week 96 and Week 144 in Caregiver Questionnaire and Videography
- Change at Week 96 and Week 144 in Clinical Global Impression of Change (CGIC)

<u>Dystrophin Expression as a Surrogate Endpoint in DMD</u>
Per agreement at the pre-NDA meeting on 6/5/19 (Meeting Minutes sent by FDA to applicant on 6/27/19), the applicant has submitted for accelerated approval the pharmacodynamic effects of casimersen in the Change from Baseline (CFB) to Week 48 in dystrophin protein expression in muscle biopsy tissue, assessed using western blot techniques. Also submitted are the following assessments, each of which is intended to support casimersen's effects on dystrophin expression:

- CFB to Week 48 in casimersen-induced skipping of exon 45, assessed by RT-PCR methodology;
- CFB to Week 48 in the qualitative intensity of casimersen-induced dystrophin expression, assessed using immunohistochemical (IHC) techniques.

There are three recent precedents for the use of dystrophin measurements to support accelerated approval of treatments of patients with DMD that is amenable to the skipping of targeted exons.

1. The first ASO that was granted accelerated approval for the treatment for DMD was eteplirsen (Exondys 51; approved 2016). Exondys 51 "is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping (Exondys 51 Prescribing Information, June 2020 version)." The basis for accelerated approval was a small increase in dystrophin expression as measured by western blot techniques.

2. The second ASO to be granted accelerated approval was golodirsen (Vyondys 53; approved 2019), which is "indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping (Vyondys 53 Prescribing Information, December 2019 version)."

3. The most recent ASO that was approved as a treatment for DMD is viltolarsen (Viltepso; approved 2020). Viltepso is "an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping (Viltepso Prescribing Information,

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August 2020 version)."

The 6MWT as a Clinically Meaningful Endpoint in DMD

Upon completion, the ongoing study 4045-301 will measure as its primary endpoint the CFB to Week 96 in the 6MWT. These data are forthcoming and therefore were not submitted in this NDA, as agreed by FDA at the pre-NDA meeting on 6/27/19. A brief discussion about the 6MWT follows below.

The 6MWT measures the total distance in meters walked by a subject in six minutes. The test has been used as the primary endpoint in registration and approval studies for treatment of non-DMD indications (e.g., bosentan; see McDonald et al., 2010), but it has not been used as the basis for approval of drugs that are indicated for the treatment of DMD. The test can be straightforward to administer. However, test results are subject to bias and considerable variation as a result of numerous external factors, including coaching of patients by parents or by site staff. When test conventions are rigorously followed to help ensure the absence of bias and the minimization of variation, then the results can be clinically meaningful.

The 6MWT can detect change as shown by mean improvement in four randomized, controlled registration studies for: bosentan (approved as Tracleer for pulmonary arterial hypertension); laronidase (approved as Aldurazyme for mucopolysaccharidosis Type 1 [Hurler and Hurler-Scheie forms]); idursulfase (approved as Elaprase for mucopolysaccharidosis Type 2 [Hunter syndrome]); and alglucosidase-alfa [sic] (approved as Lumizyme for Pompe disease). In each of these studies, the mean baseline 6 Meter Walk Distance (6MWD) was between 300 and 400 meters, with a mean within-subject Standard Deviation (SD) of approximately 60 meters. The mean improvement in 6MWD across the four studies ranged from 28 – 44 meters. It has been suggested that a change of 10 – 15% in the 6MWD can improve a patient's sense of well-being, and the improvements measured in the four trials fell close to or within that range. (McDonald et al., 2010).

FDA agreed in a Type A meeting with the applicant on 11/18/14 that the 6MWT could be used as a primary endpoint.

Clinical Reviewer's Comments

The study's subject population, study design, and dystrophin expression as a surrogate endpoint are adequate and acceptable for FDA's evaluation of the submitted NDA for accelerated approval. The Biometrics review of the Statistical Analysis Plan is below.

Statistical Analysis Plan

The following text is from the Biometrics Staff, courtesy of Dr. Xiang Ling.

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Per the Statistical Analysis Plan (SAP), the interim muscle biopsy set will be used for this interim analysis, which includes subjects amenable to exon 45 skipping, with collection of two muscle biopsies for each subject in the interim analysis, both at Baseline and at Week 48. For each subject, two replicate tissue samples were obtained from each of the two muscle biopsies at Baseline, and two replicates were also obtained from each of the two biopsies at Week 48. The mean values of the four replicates were calculated for each subject to obtain a Baseline value, and the same procedure was used to obtain a value for Week 48.

A 2-sample permutation test was conducted to compare the treatment groups. A permutation of 10,000 re-randomizations was performed. The mean difference between treatment groups was computed from each permuted data set. The 2-sided nominal p-value was calculated as twice the proportion of permuted treatment difference estimates that were more extreme than the treatment difference estimate observed in the actual data set.

The primary statistical analysis of western blot results was based on the actual measured value, including measured values that were below the lower limit of quantification (LLOQ, 0.25%). Sensitivity analyses were conducted for assay results < LLOQ. Western blot values < LLOQ were imputed for each replicate using 1 of 2 methods: as 0 or 0.24 (level immediately below the LLOQ). An additional imputation method (imputing values less than lower limit of detection [LLOD, 0.05%] as 0.02 and values between the lower limit of detection and LLOQ as 0.15) was included after blind break for the interim analysis. The values represent midrange values based on values below the lower limit of detection (0 to 0.05) and between the lower limit of detection and LLOQ (0.24), respectively.

For the interim analysis, a Type I error of 0.01 was assigned to the comparison between casimersen and placebo in change from Baseline to Week 48 in the quantity of dystrophin expression as measured by western blot. Change from Baseline to Week 48 in exon 45 skipping by measurement and sequence verification of exon 45-skipped mRNA was analyzed as an exploratory endpoint for the interim analysis without formal adjustment of multiplicity. A gatekeeping testing procedure that covers the interim analysis and the final analysis will be used to adjust for multiplicity for in order to control the overall Type 1 error rate at a 2-sided significance level of 0.05.

To ensure the integrity of the study conduct and maintain the blinding of the trial, the interim analysis was performed by the contract research organization (CRO) unblinded statistical team, which was not otherwise be involved in the trial design or conduct of study 4045-301 (ESSENCE), other than the support of the DMC and the unblinded integrity safety summary. The treatment-level results summary and the subject-level muscle biopsy data were provided in de-identified fashion to Sarepta so that there was no link to study subjects, and the de-identified data were included in this NDA submission.

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Protocol Amendments

The pharmacodynamic efficacy data for the application were collected in study 4045-301. For this and other ongoing studies, May 31, 2019 was the cut-off date for the data submitted by the applicant in this NDA. The original protocol for study 4045-301 was signed by the applicant on 2/13/15. From this time until the cut-off date, there were 10 amendments to the protocol. Key features of the original protocol are listed below. Each successive amendment follows, listing only major revisions as selected by the clinical reviewer. Minor administrative or clarifying revisions that do not affect the subject population, safety monitoring, efficacy assessments, or statistical analyses are not included in this list. Although the study is recruiting subjects with DMD amenable to skipping of either exon 45 (for casimersen) or of exon 53 (for golodirsen), the study features that are listed pertain to aspects of the study that affect both ASOs, as well as aspects that affect only casimersen.

1. Original Protocol (Version 1, dated 2/13/15)
   - 99 subjects with DMD amenable to exon 45 skipping or exon 53 skipping
   - 48-week randomized, double-blind, placebo-controlled study with approximately 66 subjects randomized to casimersen (exon 45 skipping; 30mg/kg IV weekly) or golodirsen (exon 53 skipping; 30mg/kg IV weekly), and approximately 33 subjects randomized to placebo (IV weekly).
   - Muscle biopsies at Baseline, and either Week 24 (approximately 33%) or Week 48 (approximately 67%)
   - Primary endpoint CFB to Week 48 in 6MWT
   - Secondary endpoints CFB to Week 24 and Week 48 in percent dystrophin-positive fibers, assessed by IHC; and CFB to Week 48 in pulmonary function parameters
   - Among many additional efficacy endpoints is CFB to Week 24 and 48 of pooled casimersen and golodirsen treated subjects, assessed by western blot

2. Amendment 1, (Version 2, dated 10/19/15)
   - Increased monitoring for renal toxicity by adding measurements of serum cystatin C and urinary KIM-1 (based on nonclinical findings or renal toxicity)
   - Added an open-label extension (OLE) period to follow the 48-week double-blinded period (duration of OLE unspecified)

3. Amendment 2 (Version 3, dated 11/12/15)
   - Established an independent Data Monitoring Committee (DMC), with periodic meetings to monitor safety, data quality, and integrity of the study
   - Prohibited use of “implantable central venous catheters” for IV infusions (defined prior to this amendment as “implanted venous access ports”) for IV infusion

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4. Amendment 3 (Version 4, dated 6/7/16)
   - Increased duration of double-blind period to 96 weeks, and assigned a 96-week duration to the OLE
   - 6MWT and NSAA measured on two consecutive days at both Screening and at Baseline
   - Muscle biopsies only at Baseline and Week 48
   - Interim analysis at Week 48 of double-blind period when 75% of subjects have 6MWT data and muscle biopsy data
     - Primary endpoint is CFB to Week 48 in 6MWT for pooled group (both ASO treatments together)
     - Secondary endpoints analyzed hierarchically if primary positive; the top secondary endpoints are CFB to Week 48 in dystrophin expression (assessed by western blot), and then CFB to Week 48 in intensity of dystrophin expression (assessed by IHC)
   - Added CFB to Week 48 in percent of dystrophin positive fibers (PDPF)

5. Amendment 4 (Version 5; dated 3/15/17)
   - Added a co-primary endpoint of CFB to Week 96 in 6MWT to the original primary of CFB to Week 48 in 6MWT
   - If interim analysis at Week 48 is positive, all remaining subjects in double-blind portion to enter OLE
   - Added additional prohibited concomitant medications

6. Amendment 5 (Version 6; dated 6/1/17)
   - Following a public meeting of OPT, the following revision was made per the OPT recommendation. Implantation of a "totally implantable central venous access device (i.e., port) is allowed, if necessary or at the discretion of the parent(s)/guardian(s) after consultation with the investigator and the consulting surgeon, after provision of informed consent by investigators to subjects and caregivers."

7. Amendment 6 (Version 7; dated 12/13/17)
   - Increased overall sample size from 99 to 126
   - A subset of the first 45 subjects amenable to exon 45 skipping have muscle biopsies at Week 48, and the remainder at Week 96

8. Amendment 7 (Version 8; dated 8/23/18)
   - Interim analysis conducted using Week 48 muscle biopsies from the first 45 subjects amenable to exon 45 skipping

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Clinical Reviewer's Comment
This is consistent with Type C meeting comments from 8/1/18.

- One of the co-primary endpoints (CFB to Week 48 in 6MWT) removed, leaving the only primary endpoint as CFB to Week 96 in 6MWT

Clinical Reviewer's Comment
This is *consistent with Type C meeting comments from 8/1/18.*

- Added a new secondary endpoint of CFB to Week 144 in 6MWT
- Duration of OLE decreased from 96 weeks after the end of the 96-week double-blind period to 48 weeks after the end of the double-blind period

9. Amendment 8 (Version 9; dated 12/21/18)
   - As required by the French Regulatory Authority, added an algorithm for medical management of a treatment-emergent adverse event of tea-colored urine (i.e., potential rhabdomyolysis)
   - List of prohibited concomitant medications was lengthened

10. Amendment 9 (Version 10 and current global version except in UK; dated 2/27/19)
    - ECG recordings added before and after first dose of study drug for all new subjects
    - ECG recordings added before and after first dose of study drug at all visits in which samples for PK assessments are obtained
    - Exploration of PK effects on any changes in QTc cardiac conduction measurements

11. Amendment 10 (only in UK; dated 4/17/19)
    - The independent DMC to evaluate safety data at Week 96 (end of double-blind period) before subjects enter OLE

Clinical Reviewer's Comments
The design and size of study 4045-301 evolved considerably after the initial version of the protocol on 2/13/15. As regards the casimersen part of the study:

- *The planned number of subjects with DMD amenable to exon 45 skipping when enrollment completes has increased from approximately 50 to approximately 111; and the number of these subjects exposed to casimersen during the double-blind part of the study has increased from approximately 33 to approximately 74.*
- *The randomized double-blind part of the study has increased from 48 weeks to 96 weeks; and an OLE of another 48 weeks in duration has been added.*
- *The primary endpoint has been revised from the CFB to Week 48 in 6MWT to the CFB to Week 96 in 6MWT.*
- *An interim analysis of dystrophin expression, intensity of dystrophin expression, and*

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percent of exon-skipping has been conducted for the first 45 subjects to have muscle biopsies at Week 48; these data have been submitted for accelerated approval as the only efficacy data submitted in this NDA.

- *Additional safety monitoring for renal toxicity has been put into place; and a medical management algorithm for potential cases of rhabdomyolysis has been instituted.*

As regards the interim analysis at Week 48, these protocol revisions are acceptable for FDA's evaluation of the CBB to Week 48 in dystrophin parameters for accelerated approval, assuming acceptable safety. In principle, the revisions are also acceptable for FDA's future evaluation of the completed clinical study efficacy and safety data, in order to support an accelerated approval if granted. However, this cannot be concluded at present.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor has attested that "casimersen clinical studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements [Clinical Overview, section 1.7]." The following specific language pertains to the largest study (i.e., 4045-301), from which were derived the principle safety data and all of the dystrophin efficacy data that were submitted for consideration of accelerated approval.

> "This study will be conducted in full compliance with the IRB regulations in 21 CFR 56 and/or the European Clinical Trial Directive 2001/20/EC. Before enrollment of patients into the study, the protocol and informed assent (for patients, if applicable) and informed consent (for parents/legal guardians) documents will be reviewed and approved by the appropriate IRB/IEC and regulatory authority. Amendments to the protocol will be subjected to the same IRB/IEC and regulatory authority review requirements as the original protocol. The Investigator will promptly notify the IRB/IEC and Sponsor of any SAEs or of any other information that might affect the safe use of the IP during the study. IRB approvals/IEC positive opinions and regulatory authorities' approvals must be sent to the Sponsor, or its designee, before initiation of the study or before an amendment is instituted. All correspondence with the IRB/IEC and the regulatory authority must be retained in the study regulatory files [Protocol for Study 4045-301, section 14.2]."

Financial Disclosures

There are two covered studies: 4045-101 and 4045-301. The Bioresearch Monitoring (BIMO) Technical Conference Guide, version 1 (dated 12/28/17) was used to identify and to list all

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clinical sites that submitted data for this NDA. There were 3 US sites in study 4045-101, and 44 global sites (including US sites) in study 4045-301.

In study 4045-101, financial certifications for the 3 sites were submitted, and there were no financial disclosures.

In study 4045-301, financial certifications were originally lacking for 7 sites:

1. Gihan Tennekon, site 231 (US)
2. Han Phan, site 253 (US)
3. Craig Campbell, site 302 (Canada)
4. Wolfgang Mueller-Felber, site 412 (Germany)
5. Janbend Kirscher, site 417 (Germany)
6. Juan Vilchez Padilla, site 424 (Spain)
7. Lenka Jurikova, site 430 (Czech Republic)

In addition, two site investigators in study 4045-301 were listed on Form 3455 (Financial Disclosures) as having other significant payments (e.g.: grants to fund ongoing research projects; compensation in form of equipment; retainer for consultation; or honoraria). However, there were no attachments to the originally submitted Form 3455 that included details of these payments. The two site investigators are:

(b) (6)

In response to an Information Request sent by FDA (sent 9/21/20) , the applicant supplied the requested financial information for the seven above-listed investigators in study 4045-301, and there were no financial disclosures. The applicant also supplied the requested details of financial payments for the two above-listed investigators. The financial payments to each of these investigators were made long before the onset of the study. These payments were for (b) (6)

Clinical Reviewer's Comment

It is unlikely that the (b) (6) payments to 2 investigators has caused bias or compromised the data integrity of study 4045-301, for the following reasons. First, the key safety data that is discussed in section 8 and that will be used to construct the Adverse Reactions table in section 6 of the Prescribing Information, should accelerated approval be granted, are from the double-blind period of the study. Without knowledge of treatment assignments, neither of the investigators would be able to assess safety data in a biased manner. Second, the only submitted efficacy data were derived from muscle biopsy tissue that was analyzed in a blinded manner. For the reason just elaborated, the absence of knowledge of treatment assignment could not alter the quantitative western blot data that form the basis for a decision about accelerated approval.

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Subject Disposition

Study 4045-301 is ongoing, and for that reason there is no study report. As described further below, the subset of subjects (n = 45) from this study who completed Week 48 of the 96-week double-blind period had muscle biopsies at Baseline and again at Week 48. These subjects comprised the Interim Analysis (IA) dataset, and they provided the basis for all efficacy data submitted for a consideration of accelerated approval. No subject disposition information has been provided for the 45 subjects in the IA dataset. A full disposition of all subjects who comprised the safety database of study 4045-301 will be provided in the safety section.

Protocol Violations/Deviations

The IA report states in section 11 that there were no deviations from the IA protocol.

Demographic Characteristics

The pre-specified plan for this interim analysis was to study muscle biopsy tissue from the first 45 subjects to reach Week 48 and to have muscle biopsies at both timepoints. However, of the first 45 patients with mutations amenable to exon 45 skipping, one patient was randomized in error, discontinued without receiving study drug, and had no muscle biopsies. A total of 44 patients had both Baseline and Week 48 muscle biopsies. Of these 44 patients, one patient had a genetic mutation that was predicted to produce a truncated dystrophin isoform that lacked the epitope of currently validated antibodies for Western blot (per Muscle Biopsy Study Report SR-19-002). Therefore, the dystrophin expression of this patient was not available by the time of the interim analysis, and the interim analysis set consisted of 43 evaluable patients (27 treated with casimersen, and 16 treated with placebo) with mutations amenable to exon 45 skipping. In order to assure the integrity of blinding for individual patients, treatment assignments are not provided for the two patients excluded from the Interim Muscle Biopsy Set due to discontinuation or unevaluable data.

The table below shows the demographic and other baseline characteristics of the 43 subjects who participated in the interim analysis of dystrophin expression, based upon muscle biopsy samples that were obtained at Baseline and at Week 48.

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Table 12. Baseline Characteristics of Subjects in the Interim Analysis of Efficacy

Variable	Statistic	Placebo (N=16)	Casimersen (N=27)	Total (N=43)
Age (years)	n	16	27	43
	Mean (SD)	9.3 (1.82)	9.1 (1.88)	9.2 (1.83)
	Median	9.0	9.0	9.0
	Minimum, maximum	NR	NR	7, 13
	7 to 8.5 years, n (%)	5 (31.3)	7 (25.9%)	12 (27.9)
	> 8.5 to 13 years, n (%)	11 (68.8)	20 (74.1%)	31 (72.1)
Race, n (%)	White	NR	NR	37 (86.0)
	Other	NR	NR	6 (14.0)
Ethnicity, n (%)	Hispanic or Latino	NR	NR	2 (4.7)
	Not Hispanic or Latino	NR	NR	41 (95.3)
Weight[a]	< median	7 (43.8)	14 (51.9%)	21 (48.8)
	≥ median	9 (56.3)	13 (48.1%)	22 (51.2)
Body mass index, kg/m^2[a]	n	15	26	41
	Mean (SD)	19.348 (4.1148)	18.859 (4.4255)	19.038 (4.2689)
	Median	19.267	17.882	18.643
	Minimum, maximum	NR	NR	12.64, 29.76
Mutation, n (%)	Deletion 44	30%[b]	20%[b]	10 (23.3)
	Deletion 46-47	30%[b]	20%[b]	10 (23.3)
	Deletion 46-48	20%[b]	30%[b]	10 (23.3)
	Remaining combined	30%[b]	30%[b]	13 (30.2)
	Deletion 46	NR	NR	3 (7.0)
	Deletion 46-49	NR	NR	1 (2.3)
	Deletion 46-51	NR	NR	6 (14.0)
	Deletion 46-55	NR	NR	3 (7.0)
Time Since DMD Diagnosis (months)	n	16	27	43
	Mean (SD)	68.12 (36.639)	65.55 (35.562)	66.51 (35.551)
	Median	74.35	57.86	60.48
	Minimum, maximum	NR	NR	2.2, 152.5
Duration of Corticosteroid Use (months)	n	16	26	42
	Mean (SD)	43.08 (22.226)	48.89 (27.172)	46.68 (25.280)
	Median	39.75	49.82	41.28
	Minimum, maximum	NR	NR	6.3, 112.9
Corticosteroid Type, n (%)	Deflazacort	NR	NR	32 (74.4%)
	Prednisone	NR	NR	10 (23.3%)
Corticosteroid Frequency, n (%)	Daily	NR	NR	37 (86.0%)
	Intermittent	NR	NR	5 (11.6%)

DMD=Duchenne muscular dystrophy; ISS = Integrated Summary of Safety; NR=not reported in order to preserve blinding of individual patients; SD=standard deviation

[a] Baseline was the last recorded value prior to the first dose of study drug (placebo or casimersen).

[b] Percentages of patients in the placebo and casimersen treatment groups are rounded to the nearest 10% and exact counts are not presented in the placebo and casimersen treatment groups to protect integrity of the ongoing study

Source: Summary of Clinical Efficacy, Table 2

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Clinical Reviewer's Comment

There appear to be no differences in baseline characteristics that would affect objective measurements of dystrophin protein expression skipping of exon 45, or the anatomic location of truncated dystrophin produced via exon-skipping.

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

These characteristics are shown in the above table.

6.2. Efficacy Results

6.2.1. Primary Endpoint of Interim Analysis

Effects of Casimersen and Placebo on the CFB to Week 48 in Dystrophin Expression as Quantitated by Western Blot Methodology

Note on Subject IDs in the Muscle Biopsy Interim Analysis that Constitutes the Efficacy Assessments

Because study 4045-301 is ongoing, all subjects from whom efficacy or safety data were obtained for this NDA have been de-identified to prevent staff or site unblinding. A second randomization was then performed on all muscle biopsy tissue obtained from the 43 subjects who provided muscle biopsies for the interim analyses of dystrophin expression, exon-skipping, and dystrophin localization. As described further below, the muscle biopsy tissue was randomized using a list produced by an unblinded CRO statistical team. In the analyses described in the next three efficacy sections, all subjects will be denoted using their randomized muscle biopsy IDs.

Note on Text Authorship:
In the following sections on endpoint analyses, text was written by the clinical reviewer unless otherwise noted.

This section will describe first the applicant's analyses of the data, followed by FDA's analyses of the data.

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6.2.1.1. Agreements between Applicant and FDA on Data to be Submitted in this NDA

The SAP for the Integrated Summary of Studies (ISS) for the Interim Analysis is dated 2/7/19. The SAP for Study 4045-301 is dated 2/26/19, and it was signed by the applicant's staff on 2/26/19 and 2/27/19. These dates are well before the data cut-off of 5/31/19 for the Interim Analysis of study 4045-301. In the SAP for Study 4045-301 (section 6.1), the primary endpoint for the study is denoted as the change from Baseline (CFB) to Week 96 in the 6-Minute Walk Test (6MWT).

However, in the pre-NDA meeting between the applicant and FDA on 6/5/19, the applicant proposed:

> "The NDA for accelerated approval of casimersen will be based on an interim analysis of the *de novo* dystrophin protein data at Week 48 for the first 43 enrolled patients with exon 45 skip amenable mutations and evaluable dystrophin data in Phase 3 double-blind placebo-controlled Study 4045-301; functional data from 4045-301 will not be presented in the NDA [Question 1, pre-NDA Meeting Minutes, sent on 6/27/19]."

FDA responded to this question as follows.

> "We agree that functional data may not need to be presented in your planned NDA submission if Study 4045-301 is still ongoing at the time of submission. See response to Question 2 regarding the analysis of dystrophin data [pre-NDA Meeting Minutes]".

Other FDA responses during this meeting or in post-meeting notes that were sent to the applicant on 6/9/19 acknowledged the following:

1. "In general, your approach for using Western blot and exon skipping bioassays for measuring dystrophin protein expression is acceptable…Response to Question 2]." There were also descriptions in this response and in subsequent responses about the methodology. These descriptions are included as needed further below.
2. "Dystrophin quantification using immunohistochemistry, by (b) (4) or manual pathology scoring, is not required for a complete NDA submission [post-meeting note].
3. "The absence of supportive quantitative immunohistochemistry would not impact the potential approvability of the NDA [post-meeting note]."
4. "Representative samples of immunohistochemistry images, to support proper localization of dystrophin in the sarcolemma, would not need to be accompanied by quantitative datasets [post-meeting note]."

6.2.1.2. Collection of Muscle Biopsies and Sample Processing

The Protocol for Study 4045-301 specifies that a muscle biopsy will be obtained at Baseline

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from all subjects amenable to exon 45 skipping. A second muscle biopsy will be obtained from subjects either at Week 48 for approximately the first 45 subjects, or at Week 96 for all remaining subjects [section 10.3.2.1].

Per the Biopsy Surgical Protocol [Appendix A of the Muscle Biopsy Report Interim Analysis, SR-19-003], the preferable biopsy site at Baseline was biceps brachii in one arm, or alternatively from triceps brachii or deltoid, if necessary. At Weeks 48 or 96, the biopsy site was the corresponding muscle in the contralateral arm. In each biopsy procedure, a surgeon excised two cylindrical samples (A and B) of at least 0.5 cm in diameter or width and at least 1.0 cm in length, from adjacent regions in the belly of the muscle, avoiding fatty or fibrotic areas or tendon insertion sites. Samples were excised in a manner such that muscle fibers would run primarily lengthwise.

Within 30 minutes of surgical excision, the muscle biopsy samples were to be transported to the Histology Lab and fixed to a cork base using Tissue-Tek O.C.T. compound. Each sample was to be oriented so that the muscle fibers would run vertically, in order that fibers are viewed in cross-section after they are sectioned at a later time. The cork-affixed samples were then frozen in isopentane that was chilled in a dewar of liquid nitrogen. This procedure was described in the Biopsy Laboratory Manual (Appendix B of SR-19-003). After freezing, the samples were stored in a -80° C freezer until they were shipped on dry ice (b) (4)

At (b) (4) samples were removed from their dry ice shipping container and immediately stored in a -80°C freezer until time for sample preparation, as described in the Tissue Allocation Study Report SC-19-002. A histotechnologist removed the cork base from each sample at the time of freezing. Each set of samples for each subject was prepared (b) (4) in two phases: Phase I to prepare material that was sent to the Sarepta Translational Development Lab (Andover, MA for analyses using Western blot and RT-PCR methodologies; and Phase II to prepare material that was sent to (b) (4) for analyses using immunohistochemistry (IHC) methodology. Following each phase of sample preparation, frozen block remnants were stored in a -80°C freezer.

In Phase A, a histotechnologist removed the samples from the -80°C freezer and placed them in a cryostat. OCT compound was used to fix the samples to the cryostat chuck so that muscle fibers will be oriented in cross-section following sectioning. The following figure depicts how Blocks A and B were sectioned in Phase I.

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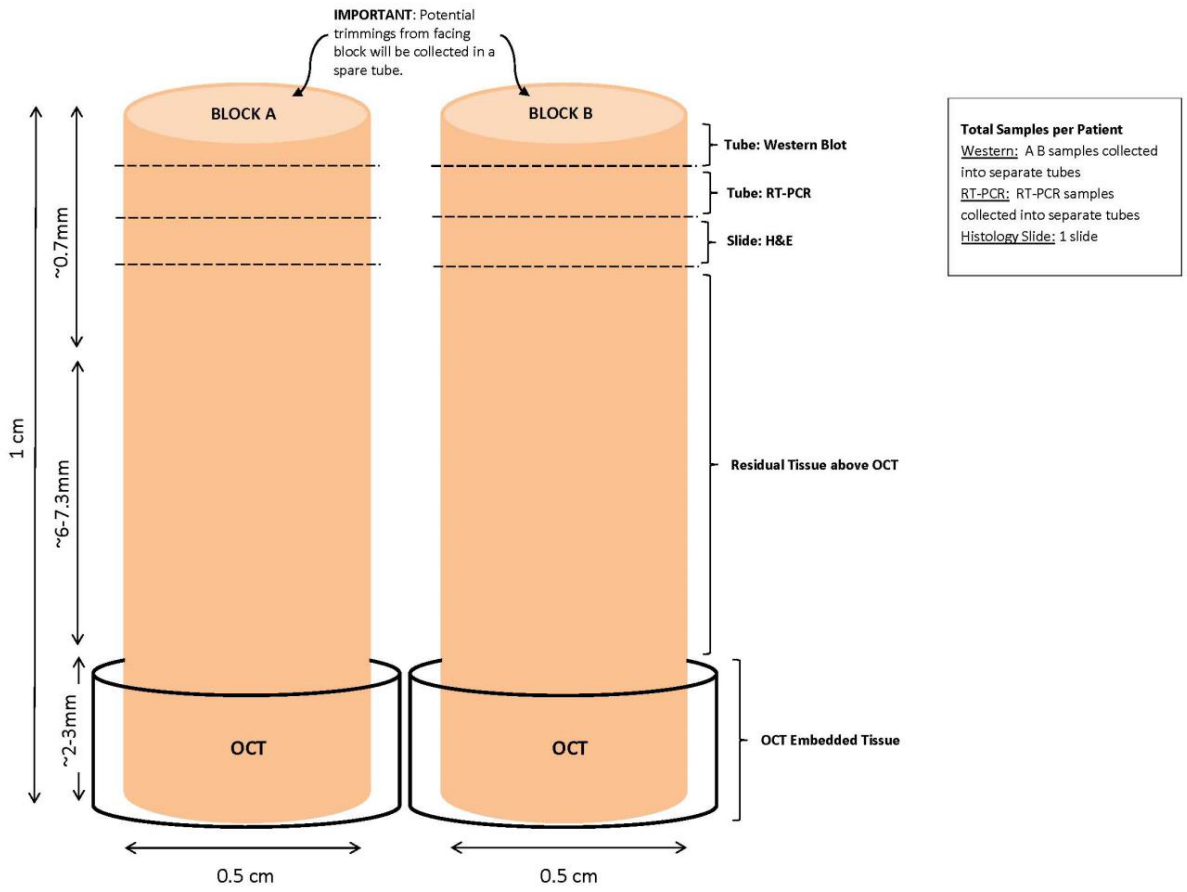
Figure 4. Tissue Allocation During Phase I



[Source: Tissue Allocation Technical Report, AR-19-002, Fig. 2]

For the Western blot methodology, the tissue sections were placed into separate tubes for Block A and Block B. A similar procedure was used for the RT-PCR methodology, as described further below. Finally, a slide was prepared for histologic evaluation. All tissue samples were randomized at (b) (4) staff by using a randomization list produced (b) (4) (b) (4) The randomized muscle biopsy "live ID" numbers for each subject consisted of a 4-digit number. The sample randomization lists were maintained by (b) (4) unblinded statistics team. All tissue was frozen in a -80^{0}C freezer until later shipment on dry ice to Sarepta Translational Development Lab (Andover, MA) for analysis using western blot methodology.

6.2.1.3. Applicant's Western Blot Method [From Drs. Thomas Biel and Ashutosh Rao, OBP]

NOTE: Text that was written by Drs. Thomas Biel and Ashutosh Rao from the Office of Biotechnology Products (OBP) is designated in some of the sections below. If undesignated, the section was written by the clinical reviewer.

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In the applicant's current western blot methodology (3rd version as developed by the applicant and used in this NDA submission), all dystrophin protein measurements using western blot analyses were quantified against a standard curve generated from 0.25%, 0.5%, 1.0%, 4.0% and 8.0% dystrophin of normal control and quality control (QC samples). The preparation of the human biopsy samples and the standard curve samples were appropriate for quantifying dystrophin levels in human muscle biopsies specimens (DOC-01875, DOC-01181, and DOC-02262). All dystrophin gels and immunoblots contained a DMD pooled sample quality control and the standard curve to quantify the dystrophin protein in human muscle homogenate samples. Following the dystrophin detection, the membranes were reblotted with an anti-alpha-actinin antibody to measure the actinin protein. To determine equal protein loading, alpha-actinin variation between the quality control, 5-point standards, and human specimens were compared and immunoblots with actinin variation less than or equal to ± 50% were deemed appropriate for quantifying the relative dystrophin protein levels.

6.2.1.4. Applicant's Gel Design for Western Blot Analyses [From OBP]

A total of 89 gels were run to accommodate all the baseline and on-treatment samples. Homogenates from cryosection tissue from blocks A and B at baseline and 48-week treatment were run in duplicate. In total 344 specimens were analyzed (43 subjects x 2 timepoints x 2 tissue blocks x 2 duplicates = 344 specimens). Four homogenates from baseline or on-treatment samples were run on separate gels using a 12-well 1.0 mm Tris Acetate gel. As demonstrated in the assessor-generated schematic below, the gel designed included four lanes for homogenized tissue lysates from subjects (Samples a-d), two lanes for a molecular weight marker (MWM), one lane with a DMD pooled quality sample (DMD pool), and 5 lanes for the healthy standard curve samples (SCP 0.25% - 8 %).

Figure 5. Diagram of Western Blot Lane Design

3-8% Tris-Acetate Gel Design											
LANE 1	LANE 2	LANE 3	LANE 4	LANE 5	LANE 6	LANE 7	LANE 8	LANE 9	LANE 10	LANE 11	LANE 12
MWM	DMD Pool	Sample a	Sample b	Sample c	Sample d	SCP 0.25%	SCP 0.5%	SCP 1.0%	SCP 4%	SCP 8%	MWM

In the assessor-generated composite figure below, nine representative dystrophin and alpha-actinin immunoblots are shown. The legend that denotes the gel lanes uses the term "unknown sample" for the 4 lanes that were loaded with samples from a single subject: two replicates from Block A; and two replicates from Block B at a single timepoint (i.e., either Baseline or Week 48).

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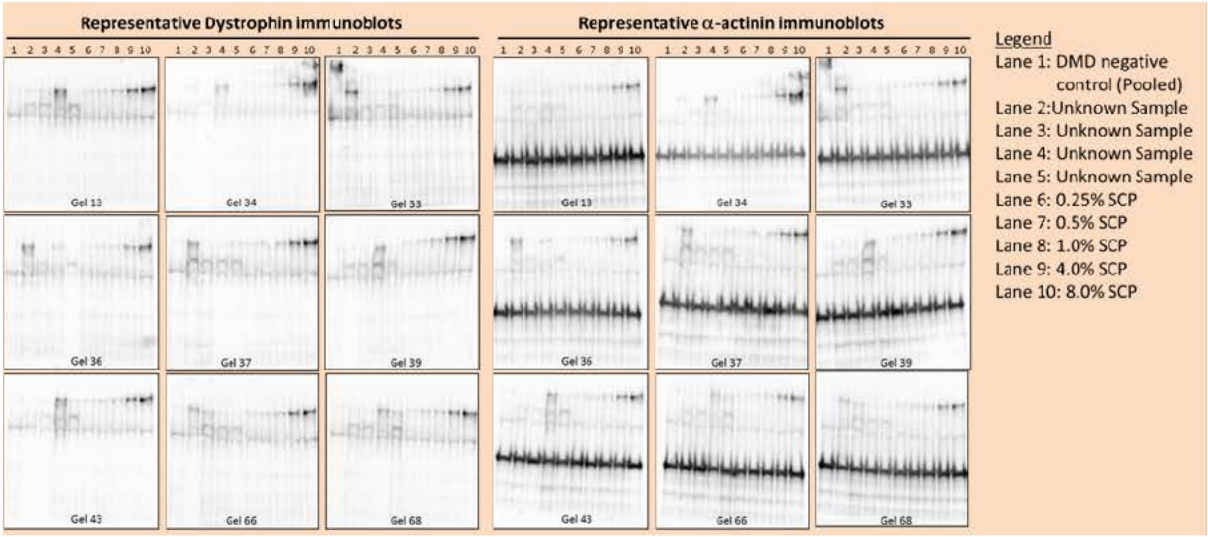
Figure 6. Representative Dystrophin and Alpha-actin Immunoblots



6.2.1.5. Applicant's Western Blot Evaluation [from OBP]

We reviewed over 20 individual anti-dystrophin immunoblots and 20 individual anti-actinin immunoblots. All the anti-dystrophin immunoblots demonstrated a % dystrophin standard curve at the expected molecular weight of the intact dystrophin protein with no blemishes and artifacts that would be expected impact the quantification of % dystrophin from clinical samples. All the anti-actinin immunoblots were relatively free of artifacts or blemishes and appeared to be have visually similar band intensity between samples supportive of the claim that the protein loading was equal or within the ± 50% variation cutoff limit. The western blotting method is inherently considered semiquantitative because it relies on relative quantitation compared to a healthy control standard curve, which can be variable in its dystrophin content, and not an absolute quantitation because it does not report absolute concentrations of dystrophin protein. Collectively, the dystrophin protein raw data reported by quantifying the relative % dystrophin band intensity against a % dystrophin standard curve was appropriately measured per their validated method.

6.2.1.6. Applicant's Method of Statistical Analyses of the Primary Dystrophin Endpoint

In the Muscle Biopsy section (section 7) of the SAP for Study 4045-301, the applicant provides the following method for analysis of dystrophin protein expression.

In the Muscle Biopsy section (section 7) of the SAP for Study 4045-301, the applicant provided the biopsy sampling methodology and statistical analysis plan. In addition, that section described several imputation methods that were used for dystrophin values that were below

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the Lower Limit of Quantitation (LLOQ) or below the Lower Limit of Detection (LLOD). See the Biometrics description of these procedures in the above section that is entitled "Statistical Analysis Plan."

Clinical Reviewer's Comment

How to impute a value to observed values below LLOQ (i.e., 0.25%) is inherently difficult. This reviewer believes that the two pre-specified imputation methods are not entirely valid ways to evaluate data that are below LLOQ, because the uncertain accuracy of observed values increases as a function of the extent to which these values are below LLOQ. In this reviewer's opinion, it is not appropriate to assume that any observed value below 0.25% NL should be assigned a value as high as 0.24% NL, as was done in the second prespecified imputation method (denoted as method 3 in Table 12). Likewise, it is not entirely appropriate to assume that any observed value below 0.25% NL should be assumed to be absent, and hence to assign a value of zero % NL, as is done in the first prespecified imputation method (denoted as method 2 in Table 12). However, this method does acknowledge the fact that values below the LLOQ are inaccurate, and therefore it is somewhat less faulty than method 3.

The third method, which was not prespecified and was developed after database lock, uses the LLOD (i.e., 0.05% NL) as a threshold for assigning observed values above LLOD but below LLOQ to a value of 0.15% NL; and for assigning observed values below LLOD a value of 0.02 % NL. Observed values below the LLOD have such high inaccuracy that they are essentially uninterpretable. It is not valid to use the LLOD to discriminate between imputation values. Moreover, because this method was not prespecified, it is also invalid for use irrespective of its method of imputation.

In sections further below that present FDA's analyses, this clinical reviewer will use the main analysis that was pre-specified by the applicant (i.e., using all measured values). The reviewer will use as a sensitivity analysis only the second prespecified imputation method (i.e., assigning any observed value below LLOQ a value of zero). FDA's statistical reviewer (Dr. Xiang Ling) will use other methods to ascertain the effects of baseline values above and below LLOQ on the principle analyses.

6.2.1.7. Applicant's Analysis of Dystrophin Expression by Treatment Group [clinical reviewer]

The following table shows the applicant's analysis of mean dystrophin protein expression for each treatment group (placebo, n = 16 vs. casimersen, n = 27) at Baseline and at Week 48, as well as the CFB to Week 48. The analysis method was that described above as the main analysis method, in which all observed values were used. All p-values were calculated from t-tests using datasets constructed after 10,000 permutations, as cited above.

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Table 13. Applicant's Analysis of CFB to Week 48 by Treatment Group

	Statistic	Placebo (N=16)	Casimersen (N=27)
Baseline	Mean	0.538	0.925
	SD (SE)	0.7941 (0.1985)	1.6738 (0.3221)
	Median	0.139	0.283
	Min, Max	0.04, 2.55	0.04, 6.51
Week 48	Mean	0.756	1.736
	SD (SE)	1.1523 (0.2881)	1.9671 (0.3786)
	Median	0.166	1.235
	Min, Max	0.04, 3.73	0.10, 7.38
Change to Week 48	Mean	0.217	0.811
	SD (SE)	0.4897 (0.1224)	0.7046 (0.1356)
	Median	0.016	0.670
	Min, Max	-0.31, 1.57	0.05, 2.96
	Within-group p-value[a]	0.089	<0.001
	Difference of means	0.594	
	Between-group p-value[b]	0.004	
Fold Change From Baseline to Week 48 Based on Individual Patients	Mean	1.662	4.714
	SD (SE)	1.5841 (0.3960)	5.4324 (1.0455)
	Median	1.257	2.735
	Min, Max	0.21, 5.97	1.08, 23.52
Fold Change of Mean Part 2 Week 48 Over Mean Baseline		1.404	1.877

Max=maximum; Min=minimum; SD=standard deviation; SE=standard error
[a] Based on 1-sample permutation t-test.
[b] Based on 2-sample permutation t-test.

[Source: Summary of Clinical Efficacy, Table 3]

Note that the mean Baseline dystrophin expression was 0.54% NL at Baseline in the placebo group and 0.93% NL in the casimersen group. Individual subject dystrophin expression at Baseline was as high as 2.6% NL in the placebo group and as high as 6.5% NL in the casimersen group. It is possible that measurable pre-treatment dystrophin expression indicates the presence of revertant fibers and/or heterogeneity as a function of biopsy. These possibilities will be discussed in a section below.

There was greater mean dystrophin expression at Week 48 in both treatment groups, although

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substantially higher in the casimersen group (1.74% NL) than in the placebo group (0.76% NL). Note that the maximum observed value at Week 48 in dystrophin expression in the placebo group (3.7% NL) is approximately half of the maximum Week 48 value in the casimersen group (7.4% NL). Similar to the dystrophin expression that was observed at Baseline, measurable dystrophin in the placebo group at Week 48 may suggest the presence of revertant fibers.

Within-group mean change from Baseline (CFB) to Week 48 in dystrophin was statistically significantly increased in the casimersen group (0.81% NL; $p < 0.001$) but not in the placebo group (0.22% NL; $p = 0.09$). The maximum CFB to Week 48 in dystrophin expression in the placebo group was 1.57% NL. This placebo-treated subject had approximately half of the maximum CFB to Week 48 observed in a subject in the casimersen group (2.96% NL).

The overall between-group difference in mean CFB to Week 48 in dystrophin expression was statistically significant in favor of casimersen (0.594% NL; $p = 0.004$).

Clinical Reviewer's Comment
Based upon the applicant's analyses, casimersen increased dystrophin expression by Week 48 (0.594% NL) in a statistically significant way ($p = 0.004$) as compared to placebo. FDA analyses of these data are presented further below.

6.2.1.8. Applicant's Sensitivity Analyses of Dystrophin Expression by Treatment Group

The applicant provided two pre-specified methods of imputation, and also used a third method that was not pre-specified. The table below shows the results of the pre-specified sensitivity analyses.

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Table 14. Applicant's Analyses of Dystrophin Expression Using Two Prespecified Methods of Imputation

	Statistic	Placebo (N=16)	Casimersen (N=27)
Values <LLOQ Analyzed as 0			
Baseline	Mean (SD)	0.475 (0.8183)	0.880 (1.6961)
Week 48	Mean (SD)	0.701 (1.1814)	1.702 (1.9942)
Change to Week 48			
	Mean (SD)	0.226 (0.5041)	0.822 (0.7199)
	Within-group p value[a]	0.083	<0.001
	Difference in means	0.596	
	Between-group p value[b]	0.005	
Values <LLOQ Analyzed as 0.24			
Baseline	Mean (SD)	0.640 (0.7370)	1.006 (1.6329)
Week 48	Mean (SD)	0.844 (1.1001)	1.753 (1.9530)
Change to Week 48			
	Mean (SD)	0.204 (0.4744)	0.747 (0.7306)
	Within-group p value[a]	0.097	<0.001
	Difference in means	0.543	
	Between-group p value[b]	0.009	

LLOQ=lower limit of quantitation; SD=standard deviation
[a] Based on 1-sample permutation t-test.
[b] Based on 2-sample permutation t-test.

[Source: Summary of Clinical Efficacy, Table 4]

Both of these prespecified sensitivity analyses support the main analysis.

The imputation method that was not pre-specified assigned observed dystrophin values that were between 0.05% NL and < 0.25% NL a value of 0.15% NL. Observed values that were below 0.05% NL (i.e., the LLOD) were assigned a value a value of 0.02% NL. The table below shows the results of this analysis method.

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Table 15. Applicant's Third Imputation Method (Not Pre-specified) for Analysis of CFB to Week 48 in Dystrophin Expression

Parameter	Statistic	Placebo (n = 16)	Casimersen (n = 27)
Baseline	Mean % NL (SD)	0.56 (0.78)	0.94 (1.66)
Week 48	Mean % NL (SD)	0.77 (1.14)	1.73 (1.97)
CFB to Week 48	Mean % NL (SD)	0.21 (0.49)	0.79 (0.71)
	Within-group test of Mean CFB to Week 48 % NL [a]	p = 0.09	p < 0.001
	Difference in Group Mean CFB to Week 48 % NL [b]	0.58	
	Between-group test of CFB to Week 48	p = 0.006	

[a] based on 1-sample permutation t-test
[b] based on 2-sample permutation t-test
[Source: Muscle Biopsy Interim Table MBI.2.7.1]

The results of the main analysis method are qualitatively similar to those of the two pre-specified imputation methods and also to that of the third sensitivity analysis that was not pre-specified. All methods showed a statistically significant between-groups increase in mean dystrophin expression at Week 48 in favor of casimersen treatment (p-values ranging from 0.004 to 0.009).

6.2.1.9. Applicant's Evaluation of Two Subgroups (Age and Weight) for CFB to Week 48 in Dystrophin Expression

The applicant evaluated two subgroups for descriptive purposes but not for formal statistical analyses: age (7 to 8.5 years, and > 8.5 years); and weight (< median, and ≥ median). Evaluation of these subgroups was not mentioned in the protocol for study 4045-301 (section 13) nor in the SAP for study 4045-301 (section 7.1), but they provide a useful function.

The applicant's subgroup analysis of age is presented in the figure below. The subgroup of subjects who were between 7 to 8.5 years of age, inclusive, consists of 7 subjects in the casimersen group and 5 subjects in the placebo group. The subgroup of subjects who were between greater than 8.5 years of age consists of 20 subjects in the casimersen group and 11 subjects in the placebo group.

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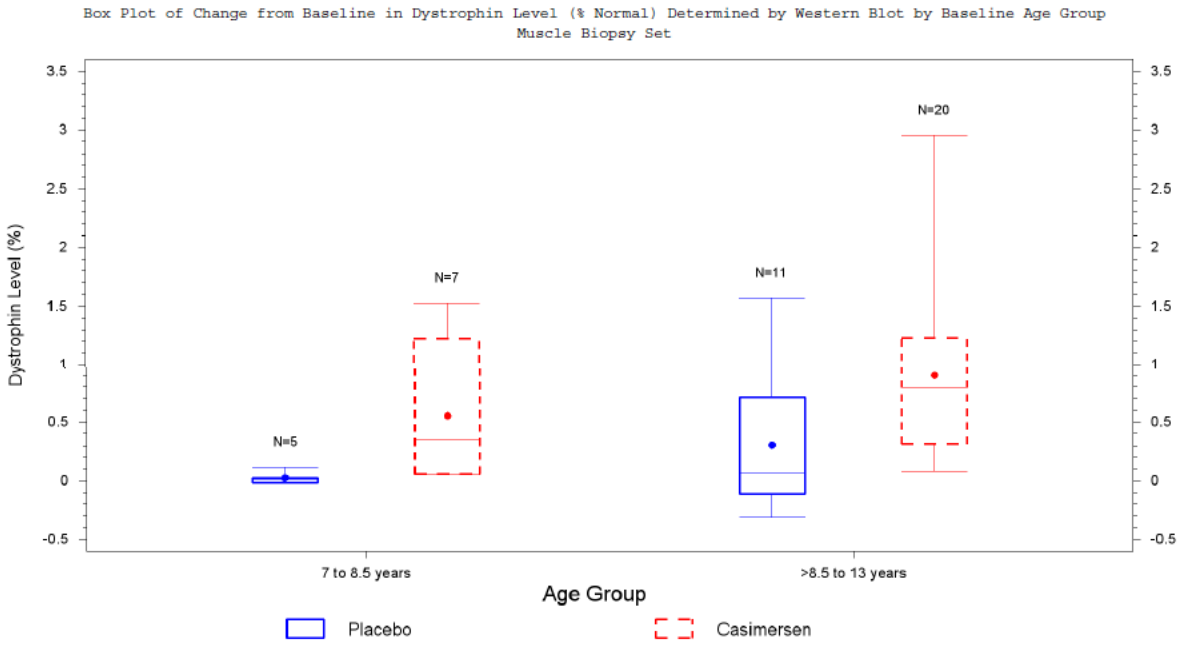
Figure 7. Subgroup Analysis of CFB to Week 48 in Dystrophin Expression by Age



[Source: Figure MBI.2.4.1, Biopsy Interim Analysis]

The applicant's subgroup analysis of weight is depicted below. There were 14 casimersen-treated subjects and 7 placebo-treated subjects in the subgroup with less than the median weight. The subgroup of ≥ median weight consisted of 13 casimersen-treated subjects and 9 placebo-treated subjects.

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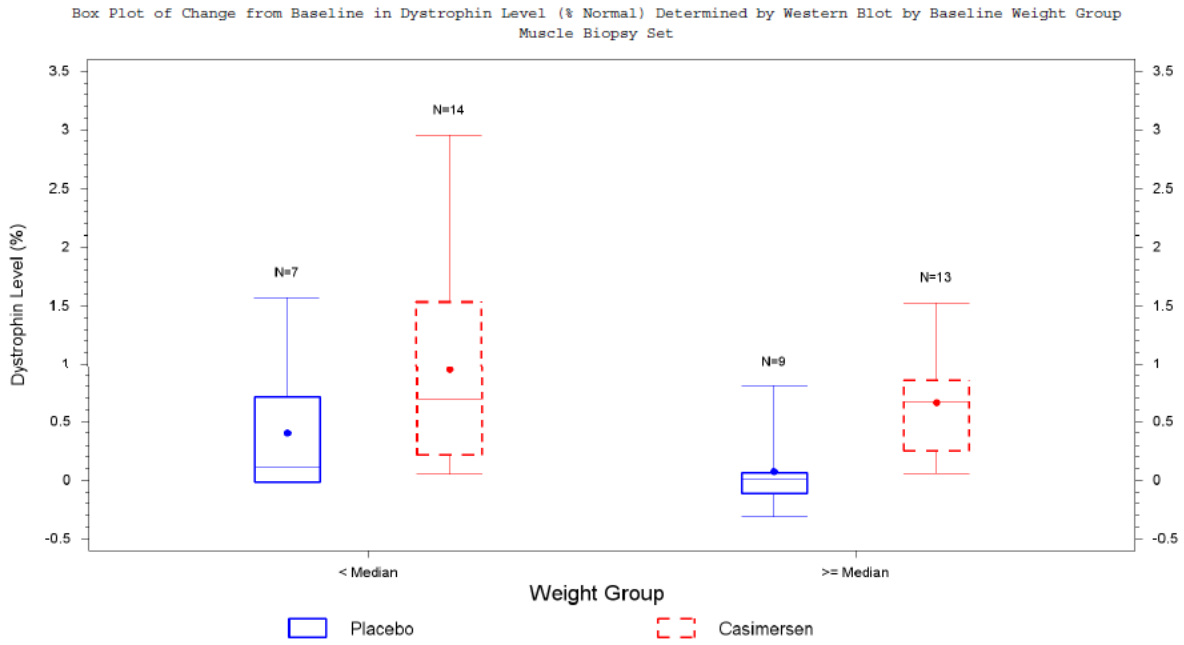
Figure 8. Subgroup Analysis of CFB to Week 48 in Dystrophin Expression by Weight



[Source: Figure MBI.2.4.2, Biopsy Interim Analysis]

Clinical Reviewer's Comments

In both age subgroups, the median (denoted by a horizontal line) and the mean (denoted by a dot) CFB to Week 48 in dystrophin expression in casimersen-treated subjects (red dashed box) were greater than the mean and the median in placebo-treated subjects (blue solid box). In a similar fashion, in both weight subgroups, the median and the mean CFB to Week 48 in dystrophin expression were greater in casimersen-treated subjects than in placebo-treated subjects.

The subgroups are necessarily small in size. Nevertheless, it appears that casimersen-treated subjects in each subgroup had a qualitatively greater CFB to Week 48 in dystrophin expression, compared to placebo-treated subjects.

6.2.1.10. FDA's Clinical Analyses of Dystrophin Expression by Treatment Group [by Dr. David A. Hosford]

NOTE: All analyses below are from the clinical reviewer unless otherwise stated. Analyses by the clinical reviewer were performed using JMP Clinical 7.1 and the applicant's ADMI.xpt dataset. All analyses use the applicant's SAP-prespecified main analysis method (i.e., all observed values without imputation) unless otherwise specified. All plots or figures that show casimersen-treated subjects are in red, and all that show placebo-treated subjects are in blue.

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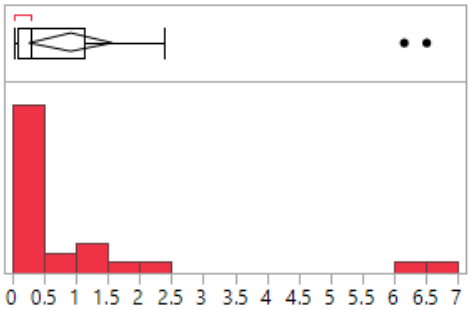
6.2.1.10A. FDA's Analysis of Baseline Distribution of Dystrophin Expression by Treatment Group [Clinical Reviewer]

The following figure is the distribution of baseline dystrophin expression as % NL for each subject within the casimersen group. The x-axis shows bins of dystrophin values, and the y-axis is proportional to the number of subjects within each bin. The Tukey outlier box-and-whiskers plot above the distribution displays the following:

- The vertical line within the box is the median of the group.
- The diamond in the box shows the mean (middle of the diamond) and the upper and lower 95% confidence levels of the mean (ends of the diamond).
- The ends of the box represent the 25th quantile on the left, and the 75th quantile on the right. The interquartile range (IQR) is the difference between the 25th and 75th quantiles.
- The left whisker extends from the left end of the box to the lowest subject value (in all of the plots in this review), and the right whisker extends from the right end of the box (i.e., the 75th quantile) to the highest subject value, with one exception. If subject values exceed 1.5 X IQR, then the right whisker will end at the highest subject value that is within 1.5 X IQR of the 75th quantile. Any subject values with values that exceed 1.5 X IQR above the 75th quantile are conventionally defined as outliers, and they are displayed as black dots corresponding to the outlier values.
- The red bracket outside of the box shows the quantile with the densest number of observations.

Figure 9. Distribution and Summary Statistics of Baseline Dystrophin Expression in the Casimersen Group



Mean	0.9247222
Std Dev	1.6738191
Std Err Mean	0.3221266
Upper 95% Mean	1.586863
Lower 95% Mean	0.2625814
N	27

[Source: ADMI.xpt analyzed with JMP Clinical 7.1]

Figure 10. Distribution and Summary Statistics of Baseline Dystrophin Expression in the Placebo Group

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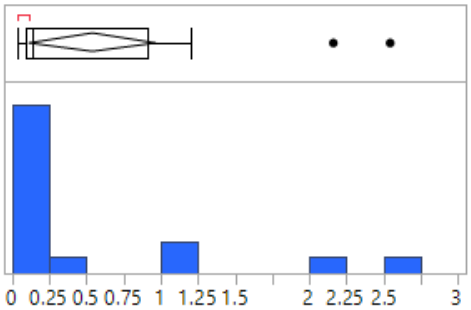

Mean	0.5384375
Std Dev	0.7940791
Std Err Mean	0.1985198
Upper 95% Mean	0.9615724
Lower 95% Mean	0.1153026
N	16

[Source: analysis using ADMI.xpt]

Both distributions are positively skewed. The summary statistics replicate the applicant's analyses for Baseline dystrophin expression in each group.

In the casimersen group, there are two subjects with Baseline dystrophin values that have high outlier values: subject (b) (6) (high) and then subject (b) (6) (higher). In the placebo group there are also two subjects with high outlier values: subject (b) (6) (high) and then subject (b) (6) (higher).

Clinical Reviewer's Comment
It is worth noting that the placebo group and the casimersen group have Baseline mean dystrophin expression of 0.54% NL (placebo) and 0. 92% NL (casimersen). The between-group difference in Baseline mean dystrophin expression is not statistically significant (p = 0.31, parametric 2-sample t-test analysis using the applicant's ADMI.xpt dataset; and p = 0.72, using the nonparametric Wilcoxon Rank Sum Test). Baseline pre-treatment dystrophin expression may indicate the presence of revertant fibers. This possibility will be explored in a section further below.

6.2.1.10B. FDA's Analysis of the Distribution of CFB to Week 48 in Dystrophin Expression by Treatment Group [Clinical Reviewer]

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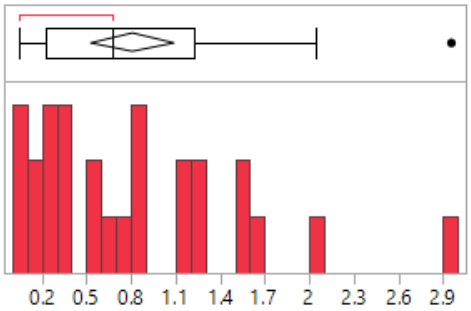
Figure 11. Distribution, Summary Statistics, and Goodness-of-Fit of CFB to Week 48 in Dystrophin Expression in the Casimersen Group



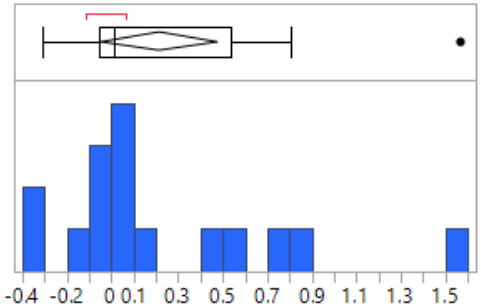
Mean	0.8109259
Std Dev	0.7046498
Std Err Mean	0.1356099
Upper 95% Mean	1.0896761
Lower 95% Mean	0.5321758
N	27

Shapiro-Wilk Goodness-of-Fit Test

W	Prob<W
0.887512	0.0070*

[Source: analysis using ADMI.xpt]

Figure 12. Distribution and Summary Statistics of CFB to Week 48 in Dystrophin Expression in the Placebo Group



Mean	0.2173438
Std Dev	0.489712
Std Err Mean	0.122428
Upper 95% Mean	0.4782929
Lower 95% Mean	-0.043605
N	16

Shapiro-Wilk Goodness-of-Fit Test

W	Prob<W
0.830475	0.0071*

[Source: analysis using ADMI.xpt]

As was apparent with baseline dystrophin expression, the distribution by subject of CFB to Week 48 is positively skewed in each group. Neither distribution is normally distributed per the Shapiro-Wild test for goodness-of-fit (casimersen: p = 0.0071; placebo: p = 0.0070).

In both groups, the summary statistics replicate the applicant's analyses for the CFB to Week 48 in dystrophin expression. In each group there is a single outlier with high observed values: subject (b) (6) in the casimersen group, and subject (b) (6) in the placebo group.

Clinical Reviewer's Comment
The applicant's summary statistics for the casimersen and placebo groups were replicated. However, the lack of normality in each treatment group in the CFB to Week 48 in dystrophin

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expression raises a question about the validity of using statistical tests that rely upon the assumption of normally distributed data (e.g., 2-sample t-tests). In the following sections, FDA's statistical analysis will first use all observed values without imputation (i.e., the applicant's main analysis method), followed by an analysis using a nonparametric test, the Wilcoxon Rank Sum Test (also termed the Mann-Whitney U test). This test is valid to use when analyzing data that are not normally distributed.

6.2.1.10C. FDA's Analysis of CFB to Week 48 in Dystrophin Expression by Treatment Group [Clinical Reviewer]

The following scatterplot shows the distribution by subject of CFB to Week 48 in dystrophin expression (% NL) in each treatment group. The y-axis shows the values of CFB to Week 48 from lowest to highest.

NOTE: All statistical analyses use a calculation of (placebo) minus (casimersen), and therefore the analyses will show a negative value when the casimersen group result is greater than the placebo group result.

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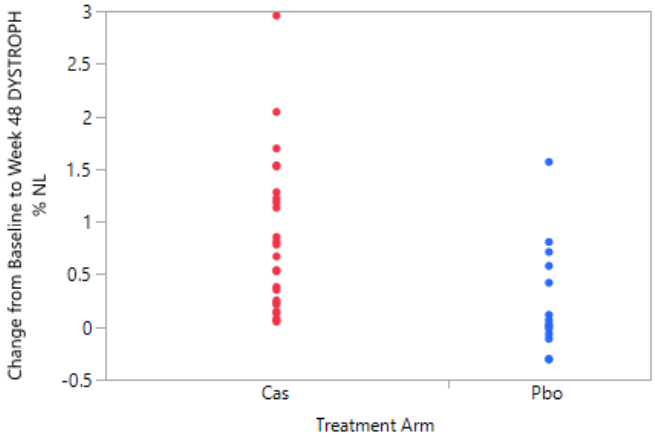
Figure 13. Analysis of Between-Group CFB to Week 48 in Dystrophin Expression



2-sample t Test (placebo – casimersen)
Assuming unequal variances

Difference	-0.59358	t Ratio	-3.24897
Std Err Dif	0.18270	DF	39.8123
Upper CL Dif	-0.22428	Prob > |t|	0.0024*
Lower CL Dif	-0.96288	Prob > t	0.9988
Confidence	0.95	Prob < t	0.0012*

Wilcoxon Rank Sum (same as Mann-Whitney U test)

Level	Count	Score Sum	Expected Score	Score Mean	(Mean-Mean0)/Std0
Cas	27	728.000	594.000	26.9630	3.355
Pbo	16	218.000	352.000	13.6250	-3.355

2-Sample Test on Rank Sum, Normal Approximation

S	Z	Prob>|Z|
218	-3.35457	0.0008*

[Source: analysis using ADMI.xpt]

The FDA's summary statistics for the between-group difference in CFB to Week 48 in dystrophin expression replicate the applicant's summary statistics. In the FDA's between-group statistical analysis of the difference in means in dystrophin expression, note that the difference of 0.59% NL is statistically significant in favor of casimersen (parametric 2-sample t-test using unequal variances: p = 0.002; Wilcoxon Rank Sum Test, p = 0.0008). This analysis yields a similar but not identical p-value to that obtained by the applicant when they used a 2-sample permutation t-test (p = 0.004). JMP Clinical 7.1 lacks the capability to perform a 2-sample permutation test. Nevertheless, both of these statistical tests show that casimersen increased the CFB to Week 48 in mean dystrophin expression in a statistically significant manner compared to placebo. In a section below, the FDA's statistical reviewer will show the results that were independently obtained when using the applicant's 2-sample permutation t-test.

The nonparametric Wilcoxon Rank Sum Test also showed that casimersen statistically significantly (p = 0.0008) increased mean dystrophin expression by Week 48, compared to placebo.

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Clinical Reviewer's Discussion of Statistical Test Results

As noted in the section above, there is a limitation in applying the 2-sample t-test or the 2-sample permutation test to analyze these datasets due to the non-normal distribution of the data. For that reason, the nonparametric Wilcoxon Rank Sum Test was used to analyze the between-group difference in means. Both the parametric 2-sample t-test and the nonparametric Wilcoxon Rank Sum Test showed similar and statistically significant results to those obtained by the applicant when using the 2-sample permutation test. In other words, casimersen statistically significantly increased the CFB to Week 48 in mean dystrophin expression when compared to placebo expression (0.59% NL; p = 0.0008, Wilcoxon Rank Sum Test).

6.2.1.10D. Possible Explanations for High Observed Values of CFB to Week 48 in the Placebo Group [Clinical Reviewer]

Placebo-treated subject (b) (6) had the second highest Baseline observed value for dystrophin expression (2.2% NL) in the placebo group, and the highest CFB to Week 48 in dystrophin expression (1.6% NL) in the placebo group. In section 9A, it was noted that a possible explanation for high observed values in the placebo group may be the presence of revertant fibers and/or biopsy heterogeneity. Another possibility may be inaccurate western blot results. Each of these possibilities is investigated below.

Recall that for every measurement of dystrophin expression, there are two blocks (A and B) from the muscle biopsy obtained at each time point (i.e., at both Baseline and at Week 48). There are also two replicates that are run on each gel for each subject, making a total of four Baseline measures that are averaged to obtain the mean Baseline value for each subject. Likewise, there are four Week 48 measures that are averaged to obtain the Week 48 value for each subject.

The applicant provided the following table showing a high degree of variability in the Baseline measures of dystrophin expression in subject (b) (6)

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Table 16. Baseline and Week 48 Measures of Dystrophin Expression in Subject (b) (6)

Table 10: Placebo Patient (b) (6) Block and Replicate variation, 4045-301 Interim Analysis

Timepoint	Block A (WB % of normal)	Block B (WB % of normal)	% RSD
Baseline	0.315	4.01	99.63
Baseline Technical Replicates	0.4, 0.23	3.65, 4.37	38.16 (Block A), 12.70 (Block B)
Week 48	4.66	2.8	30.82
Week 48 Technical Replicates	4.95, 4.37	2.39, 3.21	8.80 (Block A), 20.71 (Block B)

[Source: Table 10 in Applicant's Study Report on Assessment of Dystrophin Protein (SR-19-006)]

Outlined in blue, note the more than 10-fold variability in Baseline dystrophin measurements in Block A (0.31% NL) as compared to Block B (4.0% NL). The Week 48 measurements are not as highly variable. These results suggest not only the presence of revertant fibers at Baseline in this subject, but also the variability that can arise from heterogeneity of different Blocks at each timepoint.

An alternative possibility is that the applicant's measurements of dystrophin expression by western blot methods suffer from such a high variability that both Baseline and Week 48 measurements are suspect. The OBP reviewers (Drs. Biel and Rao) commented above (section 3) that "the dystrophin protein raw data obtained by quantifying the % dystrophin band intensity against a % dystrophin standard curve was appropriately measured per their [the applicant's] method but contains inherent variability."

To evaluate this possibility, subjects in the placebo group with the 5 highest measurements of CFB to Week 48 in dystrophin expression were compared to their measurements of Baseline dystrophin expression. If the subjects with the highest CFB to Week 48 in dystrophin expression do not also have the highest Baseline values, this may suggest that the measured values at Baseline and at Week 48 are independent of the presence of high amounts of revertant fibers, but instead are the results of random variability in measurements. On the other hand, if the subjects with the highest CFB to Week 48 in dystrophin expression are among those with the highest Baseline values, then a more likely explanation is that these subjects actually have the highest amounts of revertant fibers, and that these values were accurately measured. The following table shows the values for CFB to Week 48 in the subjects with the 5 highest measurements, and also the Baseline values for these subjects.

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Table 17. Subjects from the Placebo Group with the Highest CFB to Week 48 Dystrophin Expression, and Baseline Expression

Subject Number in ADMI.xpt Dataset	Five Highest Measurements of CFB to Week 48 Dystrophin (% NL)	Baseline Dystrophin (% NL)
(b) (6)	1.57% NL	2.16 % NL (2nd highest)
	0.81% NL	0.16% NL (6th highest)
	0.71% NL	1.08% NL (4th highest)
	0.58% NL	2.55% NL (highest)
	0.42% NL	0.11% NL (5th highest)

[Source: analysis using ADMI.xpt]

The five subjects with the highest CFB to Week 48 in dystrophin expression had four of the five highest Baseline dystrophin expression. The exception is subject (b) (6), in whom the Baseline dystrophin expression was the sixth highest, and therefore just missed having one of the top five measurements.

Clinical Reviewer's Comments

It appears that the subjects with high amounts of dystrophin expression at Week 48 in the placebo group are in large part the subjects with the highest amounts at Baseline. This outcome suggests the presence of high amounts of revertant fibers at both Baseline and Week 48 in these subjects, rather than a random variability in the applicant's measurements of dystrophin expression. Even subject (b) (6), who had a large variability of measurements between two blocks from his Baseline muscle biopsy, had the second highest CFB to Week 48 in dystrophin expression. Hence, even assuming that there may be occasional sample heterogeneity, the applicant's measurement methodology appears to be sufficiently accurate to rely upon the measurements as observed.

6.2.1.10E. FDA's Tests of CFB to Week 48 in Dystrophin Expression: Outlier Exclusion and Sensitivity Analysis [Clinical Reviewer]

In the casimersen group's distribution of CFB to Week 48 in dystrophin expression, subject (b) (6) had a high outlier value. In the same distribution in the placebo group, and as discussed in the section above, subject (b) (6) had a high outlier value. Data from these subjects were excluded from the following analyses.

Using the applicant's main analysis method (i.e., using all observed values without any imputation method), the between-group difference in the mean CFB to Week 48 in dystrophin expression was evaluated (plots not shown) after excluding data from the two outliers. The between-group difference in means was 0.60% NL. The parametric 2-sample t-test showed that this difference was statistically significant in favor of casimersen ($p = 0.0001$). The

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nonparametric Wilcoxon rank sum test also showed a statistically significant difference in favor of casimersen (p = 0.0002).

A sensitivity analysis method in which all dystrophin values < LLOQ were imputed a value of 0% NL was used to evaluate the CFB to Week 48 in dystrophin expression, after also excluding the two subjects with outlier values (i.e., subjects (b) (6)). The between-group difference in means was 0.61 % NL. The 2-sample t-test showed that this difference was statistically significant in favor of casimersen (p = 0.0002). Likewise, the nonparametric Wilcoxon rank sum test showed that this difference was statistically significant in favor of casimersen (p = 0.0006).

Clinical Reviewer's Comment
These sensitivity analyses and outlier analyses support the applicant's results.

6.2.1.10F. FDA's Analysis of CFB to Week 48 in Dystrophin Expression by Age and by Weight [Clinical Reviewer]

Although not planned by the sponsor for formal statistical analysis, the groupings by age and by weight were analyzed using the applicant's ADMI.xpt dataset. The table below shows for each subgroup the difference in the mean CFB to Week 48 in dystrophin expression, as well as statistical analyses using a parametric 2-sample t-test and a nonparametric Wilcoxon Rank Sum Test.

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Table 18. Subgroup Analyses by Age and by Weight of CFB to Week 48 in Dystrophin Expression

SUBGROUP	PARAMETER		
	Difference in Mean CFB to Week 48 in Dystrophin Expression	2-sample t-test (p-value)	Wilcoxon Rank Sum Test (p-value)
AGE			
7 to 8.5 years N = 5, placebo N = 7, casimersen	0.53% NL (favors casimersen)	p = 0.06	p = 0.015
> 8.5 years N = 11, placebo N = 20, casimersen	0.60% NL (favors casimersen)	p = 0.02	p = 0.016
WEIGHT			
< Median N = 7, placebo N = 14, casimersen	0.55% NL (favors casimersen)	p = 0.10	p = 0.080
≥ Median N = 9 placebo N = 13, casimersen	0.59% NL (favors casimersen)	p = 0.004	p = 0.004

[Source: analysis using ADMI.xpt]

Clinical Reviewer's Comments
With one exception, the subgroup analyses of the between-group difference in mean CFB to Week 48 in dystrophin expression favored casimersen in a statistically significant manner at the 0.05 level. The exception was in the subgroup of subjects with less than median weight. In this subgroup, casimersen was favored but not in a statistically significant way (p = 0.104, 2-sample t-test; p = 0.080, Wilcoxon Rank Sum Test). Nonetheless, these statistical analyses reinforce the applicant's descriptive evaluation through the use of box-and-whisker plots. There does not appear to be a meaningful difference by subgroups of age or weight in the effect of casimersen on CFB to Week 48 in dystrophin expression.

6.2.1.10G. FDA's Statistical Review on the CFB to Week 48 in Dystrophin Expression [by Dr. Xiang Ling]

The statistical reviewer confirmed the results for the change from baseline in dystrophin levels as measured by western blot. The casimersen group had a statistically significantly greater increase in dystrophin protein levels from Baseline to Week 48 than the placebo group (mean difference of 0.594%; p = 0.004; see Table below). The statistical reviewer also conducted a

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sensitivity analysis using a Wilcoxon Rank Sum test, which is a nonparametric test with very few assumptions. The analysis result (p-value = 0.0008, not shown in table), supported the primary analysis.

Table 19. Change from Baseline in Dystrophin Levels Determined by Western Blot

		Placebo (N=16)	Casimersen (N=27)
Baseline	Mean	0.538	0.925
	SD	0.7941 (0.1985)	1.6738 (0.3221)
	Median	0.139	0.283
	Min, Max	0.04, 2.55	0.04, 6.51
Week 48	Mean	0.756	1.736
	SD (SE)	1.1523 (0.2881)	1.9671 (0.3786)
	Median	0.166	1.235
	Min, Max	0.04, 3.73	0.10, 7.38
Change to Week 48	Mean	0.217	0.811
	SD (SE)	0.4897 (0.1224)	0.7046 (0.1356)
	Median	0.016	0.670
	Min, Max	-0.31, 1.57	0.05, 2.96
	Within-group p value[a]	0.087	<0.001
	Difference of means	0.594	
	Between-group p value[b]	0.004	

Max=maximum; Min=minimum; SD=standard deviation; SE=standard error
[a] Based on 1-sample permutation t-test.
[b] Based on 2-sample permutation t-test.
[Source: FDA statistical reviewer]

As shown in the figure below, the majority of the subjects (24 out of 43; 56%) had baseline dystrophin levels below the lower limit of quantification (LLOQ, 0.25%), and only 5 placebo-treated-subjects had baseline dystrophin level above the LLOQ. Therefore, the handling of the data points below LLOQ may impact the results. The prespecified sensitivity analyses conducted by the applicant imputed dystrophin levels < LLOQ using 1 of 2 methods: as 0 or 0.24. However, these sensitivity analyses may not be interpretable given the large proportion of the dystrophin data < LLOQ.

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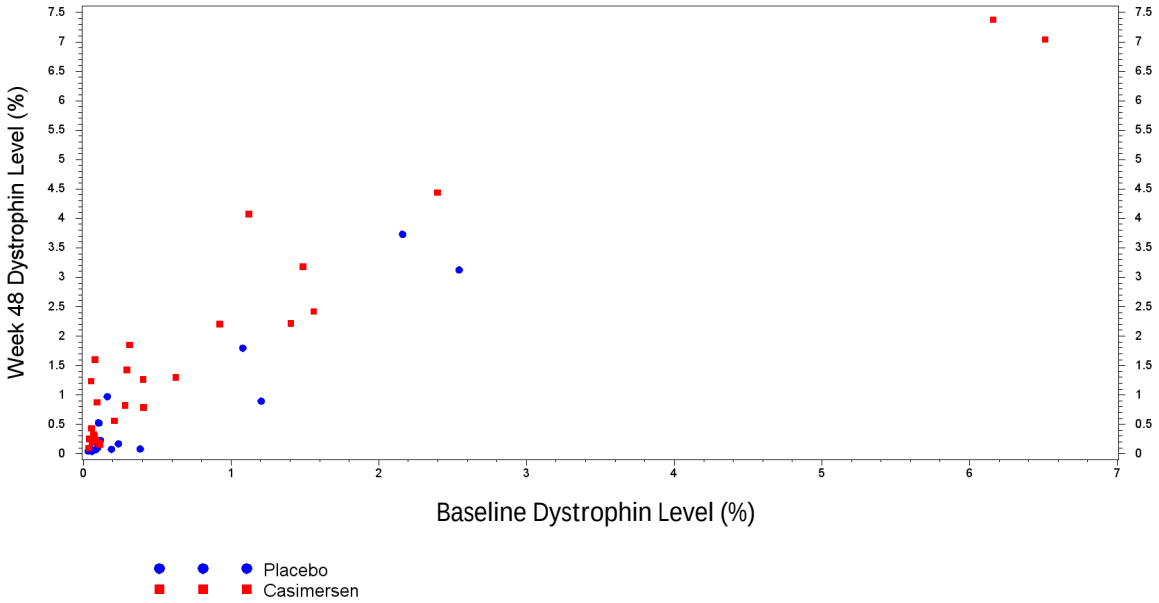
Figure 14. Dystrophin Levels Determined by Western Blot at Baseline and Week 48



[Source: FDA statistical reviewer]

Instead of imputing values < LLOQ, the reviewer conducted a sensitivity analysis on the binary dystrophin data (< LLOQ vs. ≥ LLOQ). In the subset of subjects with a baseline dystrophin data < LLOQ, there was a higher proportion of subjects in the casimersen group who had Week 48 dystrophin levels that were increased to ≥ LLOQ, compared to placebo (62% vs 18%; odds ratio = 9.0). A similar estimated odds ratio for the overall population was obtained by the analysis stratified by baseline dystrophin level (< LLOQ vs. ≥ LLOQ), supporting the treatment effect of casimersen in increasing dystrophin level at Week 48.

Table 20. Proportion of Subjects with Dystrophin Levels above LLOQ at Week 48

		Placebo n (%)	Casimersen n (%)	Casimersen vs. Placebo Odds Ratio (95% CI)	
Baseline Dystrophin < LLOQ (n=24)					Estimated Odds Ratio for Overall Population 9.0 (1.4, 56.0)
Dystrophin at Week 48	< LLOQ	9 (82%)	5 (38%)	9.0 (1.4, 56.0)	
	≥ LLOQ	2 (18%)	8 (62%)		
Baseline Dystrophin ≥ LLOQ (n=19)					
Dystrophin at Week 48	< LLOQ	1 (20%)	0 (0%)	9.7 (0.3, 281.3)**	
	≥ LLOQ	4 (80%)	14 (100%)		

An odds ratio > 1 is in favor of the casimersen group.
** Logit estimators with a correction of 0.5 in every cell of those tables that contain a zero were used.
[Source: FDA statistical reviewer]

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6.2.1.10H. FDA Clinical and Statistical Reviewers' Conclusions About the CFB to Week 48 in Dystrophin Expression

FDA has replicated the summary statistics of Baseline observed values of dystrophin expression in each group, and also the observed values in CFB to Week 48 in each group. Using the entire dataset, FDA's analyses verified that casimersen significantly increased CFB to Week 48 in mean dystrophin expression when compared to placebo (0.59% NL; p = 0.0008 [Wilcoxon Rank Sum Test]). A sensitivity analysis conducted by removing outliers and assigning a value of 0 to all values < LLOQ showed that casimersen significantly increased CFB to Week 48 in mean dystrophin expression compared to placebo (0.61% NL; p = 0.0002 [Wilcoxon Rank Sum Test]). This supports the results of the main analysis.

Because more than half of the 43 subjects in this interim analysis had baseline dystrophin values that were below LLOQ, the FDA statistical reviewer also used an independent sensitivity analysis to calculate odds ratios for the CFB to Week 48 in two subsets: the subset with a baseline dystrophin < LLOQ (n = 24); and the subset with a baseline dystrophin ≥ LLOQ (n = 19). In both subsets, casimersen increased baseline values to ≥ LLOQ compared to placebo, with an odds ratio of 9.0. The overall odds ratio for the entire population was similar. Together, the FDA analyses support the applicant's analyses. The mean CFB to Week 48 in dystrophin levels in the casimersen group were statistically significantly greater than in the placebo group.

The applicant's analysis of the primary endpoint for accelerated approval has been verified, and the endpoint has been met.

Data Quality and Integrity

OBP staff (Drs. Thomas Biel and Ashutosh Rao) evaluated data quality and integrity of the muscle biopsy assessments as described in a section above, and they determined that the data quality were sound. OSI staff evaluated the integrity of muscle biopsy collection and other data integrity properties through an inspection of three study sites, as described in a section above. These FDA staff determined that "the data generated by these sites appear acceptable in support of the respective indication."

6.2.2. Additional Efficacy Results

Effects of Casimersen and Placebo on the Mean CFB to Week 48 in Percent Exon-skipping as Analyzed by RT-ddPCR and Endpoint RT-PCR Methodology

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This section will begin with the applicant's analyses of % skipping of exon 45 as a function of treatment. FDA's analyses of these data will conclude this section.

6.2.2.1. Muscle Biopsy Tissue Allocation for RT-PCR Analyses

The same Blocks of tissue (A and B) that were used by histotechnologists (b) (4) to process tissue for western blot analyses of dystrophin expression at each time point (i.e., those from Baseline and those from Week 48) were also used to process tissue for RT-PCR at each time-point. These tissues were frozen before being sent on dry ice to Sarepta Translational Development Laboratory (Andover, MA) for their RT-PCR analyses.

6.2.2.2. Evaluation of Applicant's RT-PCR methodology [by OBP reviewers, Drs. Thomas Biel and Ashutosh Rao]

The applicant used two RT-PCR methods for measuring dystrophin mRNA: a more traditional reverse transcriptase-PCR using an Endpoint methodology (Endpoint RT-PCR) and a reverse transcriptase digital droplet PCR (RT-ddPCR) method. The Endpoint PCR method was not validated. As stated by the applicant, "the Endpoint PCR method is intended to provide only a relative measure of increase in skipping from baseline." It is not an accurate quantitative measure of absolute skipping. For a quantitative measurement, the applicant has validated and performed RT-ddPCR.

Frozen muscle tissue taken from DMD subjects with known relevant mutations at baseline were used to validate the RNA isolation portion of the RT-ddPCR method. The RNA was extracted and analyzed from the tissue sections obtained from each subject, as follows. Two baseline and two on-treatment samples were analyzed in quadruplicate for each of the 43 subjects with exon 45-amenable genotypes to determine the skipped and un-skipped RNA concentration using RT-ddPCR. For quality control, a positive (50PC) and negative test (water) control are included on each plate and predefined criteria are listed in the methodology. The 50PC positive control is an equal mix of skipped and un-skipped in vitro transcript.

Validation studies were performed in quadruplicates using 8 different contrived RNA samples that were designed to contain known deletions in the dystrophin protein from clinical specimens. All the validation studies passed the predefined acceptance criteria to support that the methods are appropriate for quantifying the skipped and un-skipped dystrophin mRNA transcripts using RT-ddPCR. The accuracy, precision, and linearity validation studies were appropriately performed, and the results demonstrated that the percent concentrations of skipped dystrophin mRNA transcripts can be determined between 0.5% to 99.5% with low variability. Compared to the validation studies, the 4045-301 study delivered a multitude of specimens (86 samples) for quantifying the % skipped dystrophin mRNA transcripts. Muscle biopsy samples per time point (Baseline or Week 48) were analyzed in quadruplicate for each of

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the 43 subjects (2 replicates per sample, 2 samples per plate). Each assay contained a negative and positive control to ensure data quality, and clinical specimens to quantify the % of skipped dystrophin mRNA transcript. Based on the standard deviation at baseline and after 48 weeks of treatment, both the Placebo and the Casimersen cohorts are demonstrating minor variability. Collectively, the RT-ddPCR method to quantify the skipped and unskipped mRNA dystrophin transcript appears to be appropriate for reporting the dystrophin mRNA transcript in the clinical specimens obtained from the 4045-301 clinical study.

6.2.2.3. Applicant's Method of Analysis of Exon-skipping using RT-ddPCR [Clinical Reviewer]

The following table denotes the number of subjects in the study with each genotype that was amenable to exon 45 skipping. Because study 4045-301 is still ongoing, the specific genotype of each of the 43 subjects included in the interim analysis has not been provided.

Table 21. Genotypes of Subjects in the Muscle Biopsy Interim Analysis

Table 4: Patient Genotype and Amplicon Size of Mutation Specific Primers

Number of patients	Genotype (exons deleted)	Primers Exon Location	Unskipped amplicon (bp)	Skipped amplicon (bp)
10	44	43, 46	450	274
10	46-47	44, 48	436	260
10	46-48	44, 50	411	235
3	46	43, 47	468	299
1	46-49	43, 50	479	303
6	46-51	43, 52	478	302
3	46-55	44, 56	436	260

[Source: Week 48 Interim RT-PCR Report, SR-19-007, Table 4]

Per the applicant's Interim RT-PCR Report [SR-19-007), "during RT-ddPCR analysis of subject biopsy samples, each sample was analyzed in quadruplicate as technical replicates and averaged at the time of data reporting. An average across each replicate was reported to (b) (4) for analysis. The reported result of "percent skipped" for RT-ddPCR was calculated by dividing the quantity of skipped dystrophin mRNA molecules by the total number of dystrophin mRNA molecules (skipped + un-skipped) as shown below:

% skipped = (skipped mRNA copies) / (skipped + un-skipped mRNA copies) X 100."

Following the generation of blinded datasets at the Sarepta Translational Development Lab, these datasets were sent to an unblinded statistical analysis team at (b) (4)

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(b) (4) as described in the Interim RT-PCR Report (SR-19-007). The applicant's prespecified method of between-group comparisons of exon-skipping was the 2-sample permutation test using 10,000 permutations (sections 7.5 and 7.2, study 4045-301 SAP).

6.2.2.4. Applicant's Analysis of Percent Exon-skipping Using RT-ddPCR

The following table shows the % exon-skipping as measured by this technique.

Table 22. Applicant's Assessment of Percent Exon-skipping using RT-ddPCR

	Statistic	RT-ddPCR	
		Placebo (N=16)	Casimersen (N=27)
Baseline	n	16	27
	Mean	0.275	0.413
	SD	0.1060	0.3749
	(SE)	(0.0265)	(0.0721)
	Median	0.252	0.242
	Min, Max	0.08, 0.43	0.07, 1.35
Week 48	n	16	27
	Mean	0.283	2.019
	SD	0.1634	1.1224
	(SE)	(0.0408)	(0.2160)
	Median	0.239	1.825
	Min, Max	0.09, 0.69	0.75, 5.98
Change from Baseline to Week 48	n	16	27
	Mean	0.007	1.606
	SD	0.1199	1.1294
	(SE)	(0.0300)	(0.2174)
	Median	-0.045	1.275
	Min, Max	-0.11, 0.27	0.50, 5.48
	Within-group p-value[a]	0.808	<0.001
	Difference in means	1.599	
	Between-group p-value[b]	< 0.001	

[a] Based on 1-sample permutation t-test.

[b] Based on 2-sample permutation t-test.

[Source: Applicant's Week 48 Interim RT-PCR Report, SR-19-007, Table 10]

The mean Baseline % exon-skipping is measurable in both the placebo (rounded up to 0.28%) and casimersen (0.41%) groups. This is consistent with the presence of pre-treatment revertant fibers, as discussed in several of the above sections. Mean Week 48 measurements of % exon-skipping were virtually unchanged within the placebo group (rounded down to 0.28%), but

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substantially higher within the casimersen group (2.0%).

The mean CFB to Week 48 was virtually unchanged within the placebo group (0.01%; within-group one-sample permutation test: p-value = 0.81) but was higher in the casimersen group (1.6%; within-group one-sample permutation test: p-value < 0.001). The between-group difference in the means was 1.6% (p < 0.001, 2-sample permutation test).

Clinical Reviewer's Comments
There appears to be evidence of pre-treatment (i.e., Baseline) revertant fibers in both groups. Although the mean Baseline exon-skipping was greater in the casimersen group (0.41%) than in the placebo group (0.28%), the between-groups difference in the Baseline means was not statistically significant (p = 0.81 using a parametric 1-sample permutation t-test).

The much greater increase in % exon-skipping in the casimersen group at Week 48 but not in the placebo group is consistent with the proposed exon-skipping mechanism of action of casimersen in subjects with DMD amenable to exon 45 skipping. The between group difference in means for the CFB to Week 48 (1.6%) is statistically significant (p < 0.001; 2-sample permutation t-test). This is also consistent with the exon-skipping design of this ASO.

6.2.2.5. Applicant's Percent Exon-skipping Using Endpoint RT-PCR

As discussed above (section 2), the applicant's validation of the Endpoint RT-PCR was not provided. Per the applicant, the results of the Endpoint RT-PCR method were intended only to provide a qualitative assessment of % exon-skipping. The applicant provided the following summary of results using the Endpoint RT-PCR measurements of % exon-skipping in the two treatment groups.

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Table 23. Applicant's Evaluation of Percent Exon-Skipping as Measured by Endpoint RT-PCR

	Statistic	RT-PCR	
		Placebo (N=16)	Casimersen (N=27)
Baseline	n	16	27
	Mean	0.461	1.048
	SD	0.6024	1.4584
	(SE)	(0. 1506)	(0.2807)
	Median	0.000	0.633
	Min, Max	0.00, 1.31	0.00, 5.15
Week 48	n	16	27
	Mean	0.544	9.036
	SD	0.7450	5.2341
	(SE)	(0.1863)	(1.0073)
	Median	0.321	8.308
	Min, Max	0.00, 2.43	2.95, 25.24
Change from Baseline to Week 48	n	16	27
	Mean	0.083	7.988
	SD	0.6968	5.2642
	(SE)	(0.1742)	(1.0131)
	Median	0.000	6.207
	Min, Max	-1.19, 1.17	2.95, 23.82
	Within-group p-value[a]	0.630	<0.001
	Difference in means	7.905	
	Between-group p-value[b]	<0.001	

[a] Based on 1-sample permutation t-test.

[b] Based on 2-sample permutation t-test.

[Source: Applicant's Week 48 Interim RT-PCR Report, SR-19-007, Table 9]

The mean CFB to Week 48 in exon-skipping in the placebo group was 0.08%, whereas the corresponding mean CFB to Week 48 in the casimersen group was 8.0%. The difference in means (7.9%) was statistically significant ($p < 0.001$; 2-sample permutation t-test).

Clinical Reviewer's Comments

The applicant's statistical analysis of the mean CFB to Week 48 in % exon-skipping using the qualitative Endpoint RT-PCR method supports the quantitative RT-ddPCR analysis. Both methods show a statistically significant effect of casimersen to increase the % exon-skipping as compared to placebo. It is interesting to note that the RT-ddPCR measurement of the difference between the group means was 1.6%, whereas the Endpoint RT-PCR measurement of this difference was substantially larger (7.9%). Endpoint RT-PCR is known to over-estimate exon-skipping to a greater degree than RT-ddPCR, and these results may stem from this this type of over-estimation.

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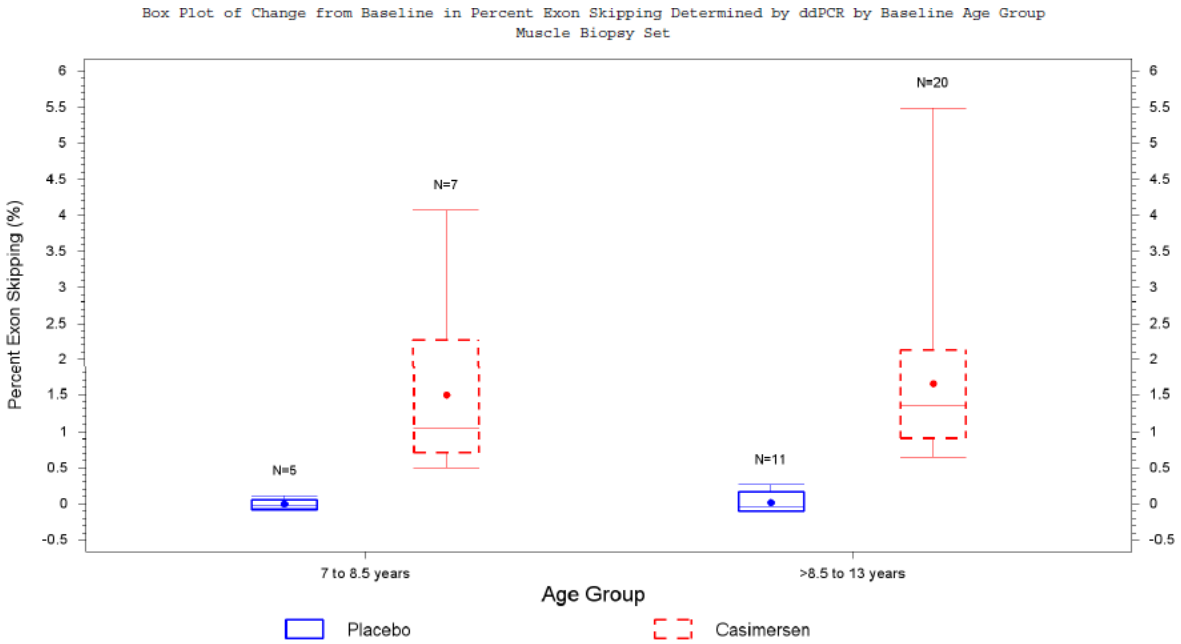
6.2.2.6. Applicant's Analysis of the CFB to Week 48 in Percent Exon-skipping by Age and Weight

The figure below depicts the CFB to Week 48 in % exon-skipping by two subgroups of age: subjects from 7 to 8.5 years of age; and subjects greater than 8.5 years of age. There were 12 subjects in the younger subgroup (n = 7 casimersen and n = 5 placebo), and 31 subjects in the older subgroup (n = 20 casimersen and n = 11 placebo). The assessments were made using RT-ddPCR methodology.

Figure 15. Applicant's Analysis of CFB to Week 48 in Percent Exon-skipping By Age



[Source: Figure MBI.4.2.1, Biopsy Interim Analysis]

The figure below shows the effect of weight sub-groups on the CFB to Week 48 in % exon-skipping, assessed by RT-ddPCR. There were 21 subjects in the lower weight group (n = 14 casimersen, and n = 7 placebo), and 22 subjects in the higher weight group (n = 13 casimersen and n = 9 placebo).

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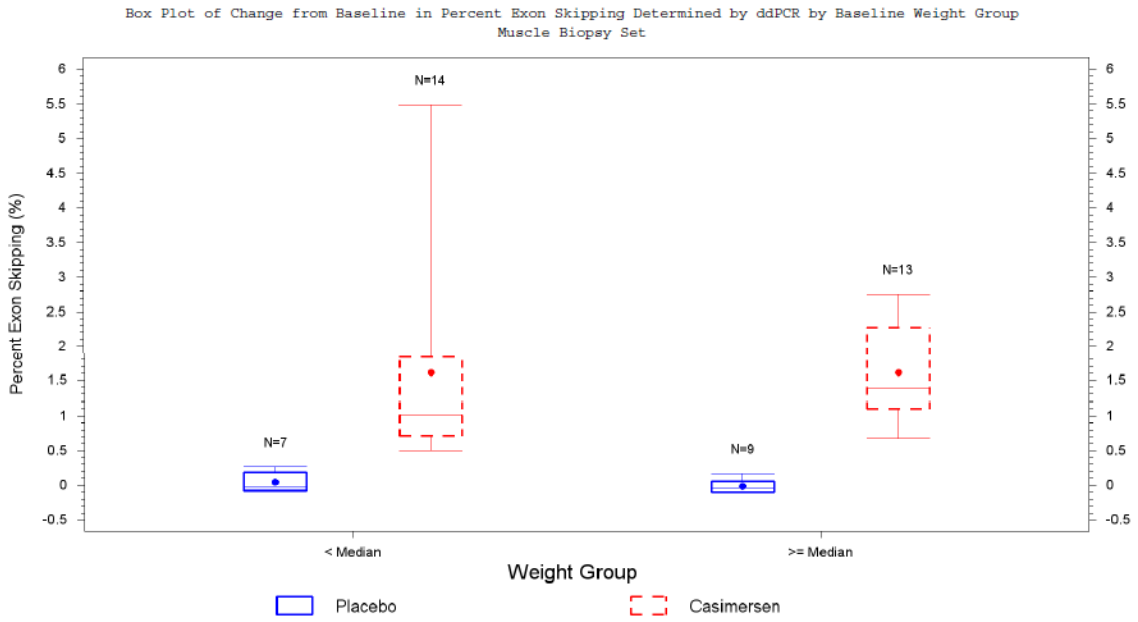
Figure 16. Applicant's Assessment of the CFB to Week 48 in Percent Exon-skipping by Weight



[Source: Figure MBI.4.2.2, Biopsy Interim Analysis]

Clinical Reviewer's Comments

These box-and-whiskers plots show that in each age subgroup and in each weight subgroup, the median and mean difference in CFB to Week 48 in % exon-skipping are greater in casimersen-treated subjects than in placebo-treated subjects. Moreover, in each subgroup, all casimersen-treated subjects had observed values that were greater than any placebo-treated subject. There appears to be no qualitative effect of age or weight on casimersen's greater CFB to Week 48 in % exon-skipping, as compared to placebo.

6.2.2.7. FDA's Clinical Analyses of Percent Exon-skipping using RT-ddPCR [Clinical Reviewer]

All of the following analyses used JMP Clinical 7.1 to analyze the applicant's ADMI.xpt dataset. Only RT-ddPCR measurements were analyzed unless otherwise stated.

6.2.2.7A. Within-Group Distributions of CFB to Week 48 in Percent Exon-skipping

The following plot shows the distribution of subjects in the CFB to Week 48 in exon-skipping in the casimersen group, along with summary statistics and the goodness of fit to a normal distribution.

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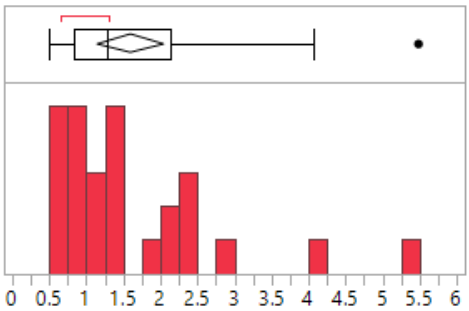
Figure 17. Distribution of CFB to Week 48 in Percent Exon Skipping in the Casimersen Group



Mean	1.6061296
Std Dev	1.1294327
Std Err Mean	0.2173594
Upper 95% Mean	2.0529183
Lower 95% Mean	1.1593409
N	27

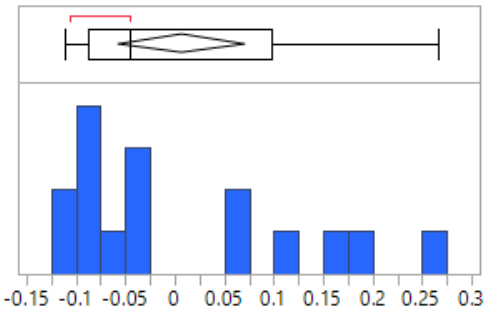
Shapiro-Wilk Goodness of Fit Test

W	Prob<W
0.792392	0.0001*

[Source: analysis using ADMI.xpt]

The plot below shows the distribution of subjects in the CFB to Week 48 in exon-skipping in the placebo group, as well as displays of summary statistics and the goodness of fit to a normal distribution.

Figure 18. Distribution of CFB to Week 48 in Percent Exon Skipping in the Placebo Group



Mean	0.0073125
Std Dev	0.1198789
Std Err Mean	0.0299697
Upper 95% Mean	0.0711915
Lower 95% Mean	-0.056566
N	16

Shapiro-Wilk Goodness of Fit Test

W	Prob<W
0.854533	0.0159*

[Source: analysis using ADMI.xpt]

The summary statistics show that FDA's analysis of each treatment group replicate those of the applicant. Note that there is a single outlier in the casimersen group (subject [redacted] (b) (6)). Note also that neither group has a normal distribution in the CFB to Week 48 in % exon-skipping.

Clinical Reviewer's Comment
The non-normal distributions in each group will affect the robustness of using a 2-sample t-test to analyze the between-group difference in means.

6.2.2.7B. FDA's Analysis of Between-Group Difference in CFB to Week 48 of Percent Exon-

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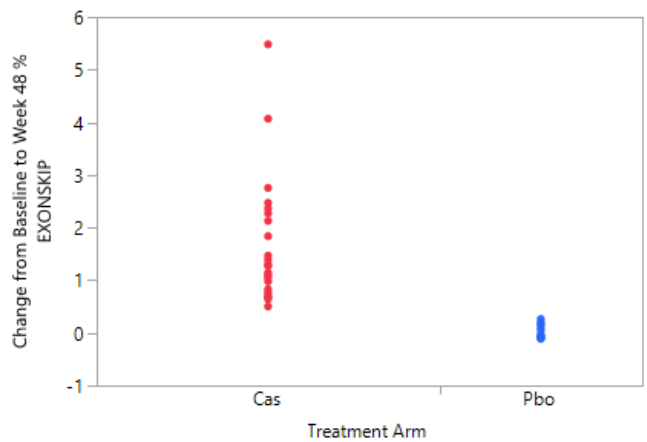
skipping [Clinical Reviewer]

The plot below is a vertical scatterplot of the CFB to Week 48 in & exon-skipping by group. The plot is accompanied by both a parametric 2-sample t-test and a nonparametric Wilcoxon Rank Sum Test of the between-group difference in means.

Figure 19. Scatterplot of Between-group CFB to Week 48 in Exon-skipping



2-sample t-test (placebo – casimersen)
Assuming unequal variances

Difference	-1.5988	t Ratio	-7.2867
Std Err Dif	0.2194	DF	26.98108
Upper CL Dif	-1.1486	Prob > |t|	<.0001*
Lower CL Dif	-2.0490	Prob > t	1.0000
Confidence	0.95	Prob < t	<.0001*

Wilcoxon Rank Sum Test

Level	Count	Score Sum	Expected Score	Score Mean	(Mean-Mean0)/Std0
Cas	27	810.000	594.000	30.0000	5.415
Pbo	16	136.000	352.000	8.5000	-5.415

Z-test on Rank Sum, Normal Approximation

S	Z	Prob>|Z|
136	-5.41485	<.0001*

[Source: analysis using ADMI.xpt]

These analyses of the between-group difference in mean CFB to Week 48 in exon-skipping verified the applicant's between-group analyses. Note that the applicant obtained a between-group difference of 1.6% exon-skipping, and this difference was statistically significant in favor of casimersen ($p < 0.001$; 2-sample permutation t-test). The FDA analysis obtained the same between-group difference of 1.6% exon-skipping, which was also statistically significant in favor of casimersen although with a slightly different statistic ($p < 0.0001$; 2-sample t-test). As was the case with the dystrophin protein comparisons for the primary endpoint, this slight difference in statistical results is accounted for by the applicant's use of a 2-sample permutation t-test, as opposed to FDA's use of a 2-sample t-test. The FDA statistical reviewer's analysis, further below, uses a 2-sample permutation t-test.

The parametric 2-sample t-test is not as valid when comparing groups that do not have a normal distribution. However, use of the nonparametric Wilcoxon Rank Sum Test also showed

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a significant difference in favor of casimersen ($p < 0.0001$).

Clinical Reviewer's Comment
The FDA clinical reviewer's analyses, both parametric and nonparametric, verify the applicant's statement that casimersen produced a statistically significant increase in % exon-skipping by Week 48, when compared to placebo.

6.2.2.7C. FDA's Clinical Analyses of CFB to Week 48 in Percent Exon-skipping Without the Outlier in the Casimersen Group: RT-ddPCR and Endpoint RT-PCR [Clinical Reviewer]

Recall that subject (b) (6) (casimersen group) demonstrated a high outlier value in the CFB to Week 48 in % exon-skipping. The same analysis as was shown in the section above was repeated with the exception that subject (b) (6) was excluded. Two analyses are described in this section. The first analysis used RT-ddPCR to evaluate the between-group difference in mean CFB to Week 48 in % exon-skipping, excluding subject (b) (6) The second analysis used Endpoint RT-PCR to evaluate the mean CFB to Week 48 in % exon-skipping, including all subjects and then excluding subject (b) (6)

Using the RT-ddPCR method, the between-group difference in the mean CFB to Week 48 in % exon-skipping was 1.4% without the high casimersen outlier value, in comparison to the value of 1.6% when all subjects were included in the analysis. Nonetheless, after subject (b) (6) was excluded, the between-group difference in mean CFB to Week 48 in % exon-skipping was still statistically significant in favor of casimersen ($p < 0.0001$, 2-sample t-test; and $p < 0.0001$, Wilcoxon Rank Sum Test).

Using the Endpoint RT-PCR method, the between-group difference in mean CFB to Week 48 in % exon-skipping was 8.0% when all subjects were included. This difference was statistically significant ($p < 0.0001$) using both a 2-sample t-test and the Wilcoxon Rank Sum Test. When the casimersen outlier subject (b) (6) was excluded, the difference in means decreased to 7.3%, but the difference was still statistically significant in favor of casimersen ($p < 0.0001$, both 2-sample t-test and Wilcoxon Rank Sum Test).

6.2.2.7D. FDA's Clinical Analysis of Age and Weight Subgroup Effects on the CFB to Week 48 in Percent Exon-skipping

The table below show the between-group difference in the mean CFB to Week 48 in % exon-skipping as a function of age subgroups and of weight subgroups.

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Table 24. Exon-skipping as a Function of Age and BMI Subgroups

SUBGROUP	PARAMETER		
	Difference in Mean CFB to Week 48 in % Exon-skipping	2-sample t-test (p-value)	Wilcoxon Rank Sum Test (p-value)
AGE			
7 to 8.5 years N = 5, placebo N = 7, casimersen	1.5% (favors casimersen)	p = 0.02	p = 0.006
> 8.5 years N = 11, placebo N = 20, casimersen	1.6% (favors casimersen)	p < 0.0001	p < 0.0001
WEIGHT			
< Median N = 7, placebo N = 14, casimersen	1.6% (favors casimersen)	p = 0.001	p = 0.0003
≥ Median N = 9 placebo N = 13, casimersen	1.6% (favors casimersen)	p < 0.0001	p = 0.0001

[Source: analysis using ADMI.xpt]

Clinical Reviewer's Comments
In each subgroup of age and each subgroup of weight, casimersen produced a statistically significantly greater increase in the mean CFB to Week 48 in % exon-skipping. This set of subgroup results verifies the descriptive box-and-whiskers plots that were submitted by the applicant in their subgroup analysis.

6.2.2.7E. Statistical Review on the CFB to Week 48 in Percent Exon-skipping by RT-ddPCR [by Dr. Xiang Ling]

The statistical reviewer confirmed the results for the change from baseline in percent exon-skipping as measured by RT-ddPCR. The casimersen group had a statistically significantly greater increase in percent exon-skipping from Baseline to Week 48 than the placebo group (mean difference of 1.599; $p < 0.001$; Table 28), although all baseline percent exon-skipping values > 0.05 were in the casimersen group, there was clear separation between the two group for the subjects with baseline percent exon-skipping ≤ 0.05, indicating that the result was not driven by the relatively larger baseline values in the casimersen group.

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Table 25. Change from Baseline in Percent Exon-skipping by RT-ddPCR

		Placebo (N=16)	Casimersen (N=27)
Baseline	Mean	0.275	0.413
	SD (SE)	0.1060 (0.0265)	0.3749 (0.0721)
	Median	0.252	0.242
	Min, Max	0.08, 0.43	0.07, 1.35
Week 48	Mean	0.283	2.019
	SD (SE)	0.1634 (0.0408)	1.1224 (0.2160)
	Median	0.239	1.825
	Min, Max	0.09, 0.69	0.75, 5.98
Change to Week 48	Mean	0.007	1.606
	SD (SE)	0.1199 (0.0300)	1.1294 (0.2174)
	Median	-0.045	1.275
	Min, Max	-0.11, 0.27	0.50, 5.48
	Within-group p value[a]	0.811	< 0.001
	Difference of means	1.599	
	Between-group p value[b]	< 0.001	

Max=maximum; Min=minimum; SD=standard deviation; SE=standard error

[a] Based on 1-sample permutation t-test.

[b] Based on 2-sample permutation t-test.

[Source: FDA statistical reviewer]

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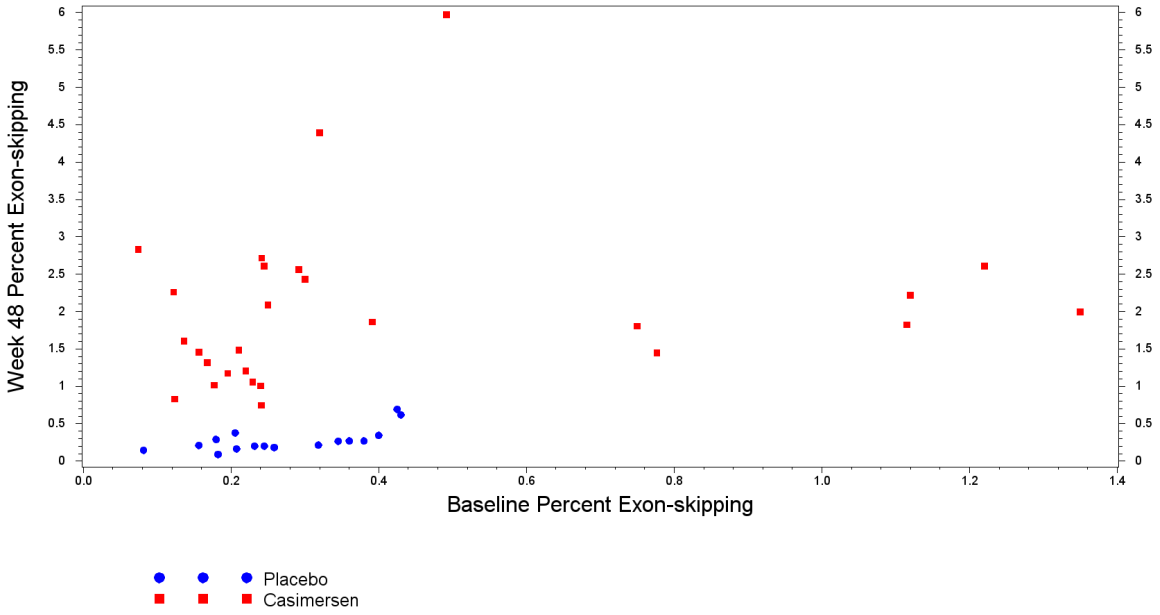
Figure 20. Percent Exon-skipping by RT-ddPCR at Baseline and Week 48



[Source: FDA statistical reviewer]

6.2.2.7F. FDA Clinical and Statistical Reviewers' Conclusion about CFB to Week 48 in Percent Exon-skipping by Group, RT-ddPCR

FDA's analyses using RT-ddPCR data to analyze % exon-skipping verified the applicant's finding that casimersen increased the mean CFB to Week 48 in % exon-skipping in a statistically significant way, compared to placebo (p < 0.0001, 2-sample t-test; p < 0.0001, Wilcoxon Rank Sum Test). Moreover, even though all Baseline percent exon-skipping values > 0.05 were in the casimersen group, there was clear separation between the two group for subjects with baseline percent exon-skipping ≤ 0.05, indicating that the result was not driven by the relatively larger baseline values in the casimersen group. Additional FDA analyses that excluded casimersen outlier values for subject (b) (6) *yielded similar results. Each analysis favored casimersen over placebo in the mean CFB to Week 48 in % exon-skipping in a statistically significant way (p < 0.0001; Wilcoxon Rank Sum Test).*

The applicant's exon-skipping analysis has been verified, and the endpoint is met.

Dose/Dose Response

Only the single dose of 30mg/kg/week was tested in Study 4045-301. This dose and weekly regimen are the same as those used in the applicant's studies for accelerated approval of two

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other ASOs, eteplirsen (Exondys 51) and golodirsen (Vyondys 53). The similarity in the ASO backbones for each of the three ASOs may account for the statistically significant increase in dystrophin expression and in exon-skipping using this regiment.

In the absence of muscle biopsies from subjects who were administered other doses of casimersen, it is not possible to make any statement about dose-response.

Durability of Response

Only two time points were examined in respect to dystrophin expression in this NDA: Baseline and Week 48. Study 4045-301 is still ongoing, and the muscle biopsies to be obtained at Week 96 may provide additional data that can be used to discuss durability of response as regards dystrophin expression.

Persistence of Effect

The design of study 4045-301 does not allow this type of analysis.

6.2.3. Additional Analyses Conducted on the Individual Trial

Effects of Casimersen and Placebo on Dystrophin Localization as Assessed Using Immunohistochemistry (IHC) Methodology

As in the preceding efficacy sections, this section will first present the applicant's IHC assessments, followed by FDA's assessments.

6.2.3.1. Tissue Allocation for IHC Assessments

Muscle biopsies were performed by surgeons as described in earlier sections, and then frozen at each Histology Lab before their shipment on dry ice to (b) (4) the samples were frozen. In Phase I, the samples were processed by (b) (4) histotechnologists for assessments that would be made at Sarepta Translational Development Lab using western blot and RT-PCR methodologies.

In Phase II, Sarepta Therapeutics instructed (b) (4) histotechnologists to process the biopsy tissue for IHC assessments that would be made (b) (4) histotechnologists used the following tissue allocation scheme to section tissues for (b) (4)

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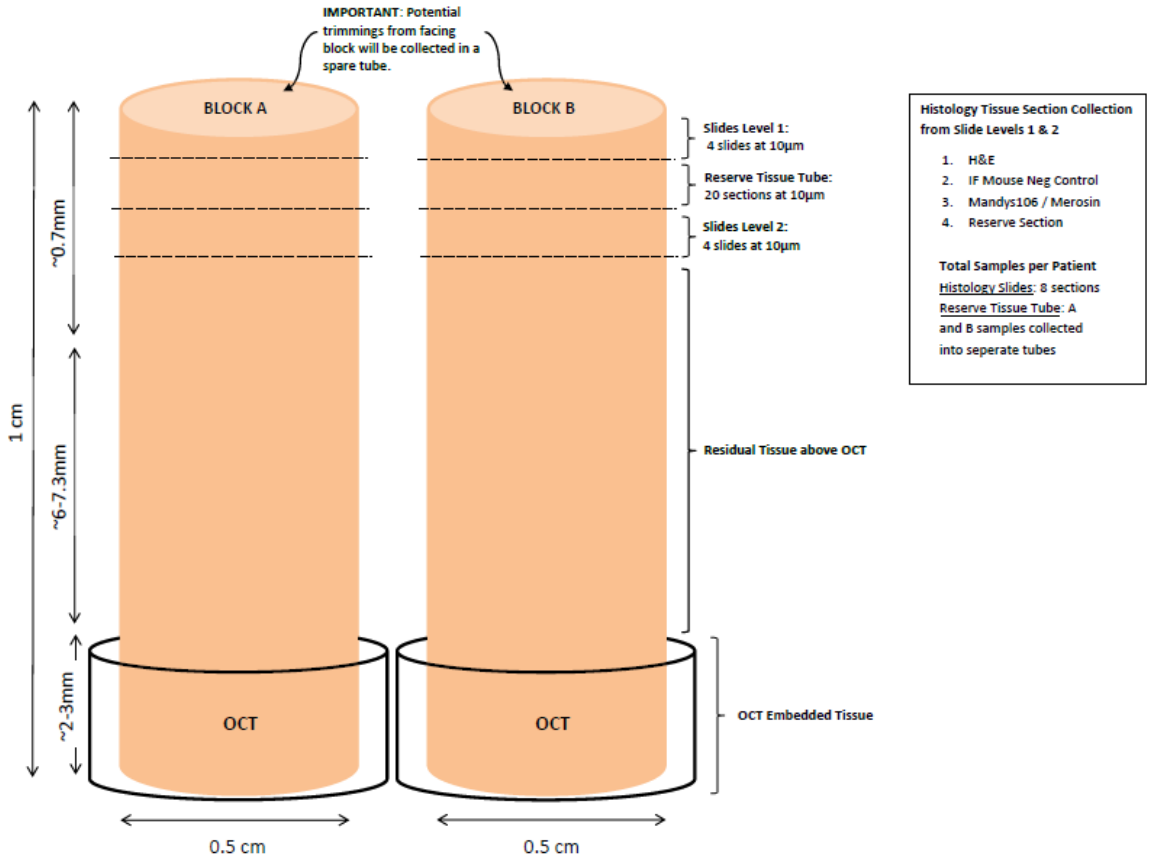
IHC analysis.

Figure 21. Tissue Allocation for Phase II



[Source: Tissue Allocation Technical Report, SR-19-002, Fig. 3]

After the appropriate cryosections were collected from Blocks A and B at each time point (i.e., Baseline and Week 48) and stored in separate tubes, the samples from each subject were randomized using a unique 4-digit "live ID" number supplied by the unblinded statistical team [redacted] (b) (4) Samples were frozen until their eventual shipment on dry ice [redacted] (b) (4) performed all IHC analyses.

6.2.3.2. Evaluation of the IHC methodology [by Drs. Thomas Biel and Ashutosh Rao, OBP staff]

All biopsies collected in 4045-301 were cryosectioned [redacted] (b) (4) They were immunolabeled at

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(b) (4) using an antibody (MANDYS106) that targets an epitope in exon 43 of dystrophin (Kodippili et al., 2014), and an antibody that targets merosin, a protein that forms the heavy chain of the skeletal muscle basement membrane protein, laminin. Over 345 slides were produced (2 per biopsy plus 1 reserve). Five batches of slides were scanned into images that were reviewed by board-certified pathologist to determine the quality of the digital image.

As discussed during the pre-NDA meeting on 6/5/19, the quantitative analysis of IHC, including dystrophin intensity and percent dystrophin-positive fibers, was not submitted. Instead, the applicant provided representative images that are purported to demonstrate the correct localization of dystrophin to the sarcolemma. Subjects were categorized into two groups based on the dystrophin expression as determined by western blot (< 1% NL, and ≥ 1% NL). The applicant selected representative tissue sections of high quality using the following criteria.

For the treatment group, tissue images from three subjects with the largest dystrophin changes from Baseline to Week 48 were reviewed and one single representative subject was selected based on 2 aspects:

1. Quality of the tissue section to allow visualization of muscle fibers;
2. Ability to visually recognize the difference in intensity of dystrophin at the sarcolemma between the timepoints.

These subject and the selected images are to have the largest CFB to Week 48 in dystrophin % NL.

The selected images in the < 1% NL dystrophin group were from two casimersen-treated subjects (b) (6) and from one placebo-treated subject (b) (6) The selected images in the ≥1% NL dystrophin group were from two casimersen-treated subjects (b) (6) (b) (6) and from one placebo-treated subject (b) (6) For each representative image, the sectioned tissue was dual-immuno-stained for merosin and for dystrophin (MANDYS106 antibody).

We evaluated 12 representative immunofluorescent (IF) images for dystrophin localization (i.e., images from BL and from Week 48 for the 6 applicant-selected patients), and an additional twenty images for artifacts and blemishes that would prevent the qualitative assessment for dystrophin location to the sarcolemma. The minor artifacts and blemishes present in these images would not interfere with the visual assessment for dystrophin's location. The applicant does not provide quantitative data that demonstrates dystrophin localized to the sarcolemma in patient biopsy tissue. The provided images demonstrate that dystrophin may localize to the sarcolemma, but quantitative measures using the entire study set were not provided as agreed at the pre-NDA meeting on 6/5/19.

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6.2.3.3. Applicant's IHC Images from Representative Subjects [Clinical Reviewer]

The applicant provided images from muscle biopsies obtained at Baseline and at Week 48 from the 43 subjects who were evaluated in this interim analysis. Images from the six representative subjects that were listed by Drs. Biel and Rao, above, were also included in the applicant's Summary of Clinical Efficacy. Shown in succession below are images from four of these six representative subjects: in two subjects with Baseline dystrophin expression < 1% NL, subjects (b) (4) (casimersen) and (b) (4) (placebo); and in two subjects with Baseline dystrophin expression above 1% NL, subjects (b) (4) (casimersen) and (b) (4) (placebo). The images from these subjects illustrate the extent to which qualitative observations may or not be made about the localization of dystrophin. These images also illustrate whether it is possible to make semi-quantitative observations about the level of dystrophin expression.

All images are magnified from biopsy sections that were stained for dystrophin using the MANDYS106 antibody, which targets an epitope in exon 43 of dystrophin. This exon is present in full-length dystrophin, as well as in truncated dystrophin in subjects with DMD amenable to exon 45 skipping provided that deleted exon 45 has actually been skipped. Without skipping of exon 45, the translation of dystrophin protein would be terminated by stop codons.

Only dystrophin immuno-stained sections will be shown below. Inverted red images were chosen for display so that stained dystrophin appears red against a fainter background. For each subject, the images are from small selected areas in the whole section, and the images are magnified. The three images on the left side in each figure below are from an immuno-stained section obtained from the Baseline biopsy tissue, and the three images on the right are from an immuno-stained section taken from the Week 48 biopsy tissue.

<u>Subject (b) (6) (casimersen)</u>
This subject had a Baseline dystrophin expression of 0.09% NL and a Week 48 expression of 0.9% NL, as measured in other biopsy sections from this subject using western blot techniques.

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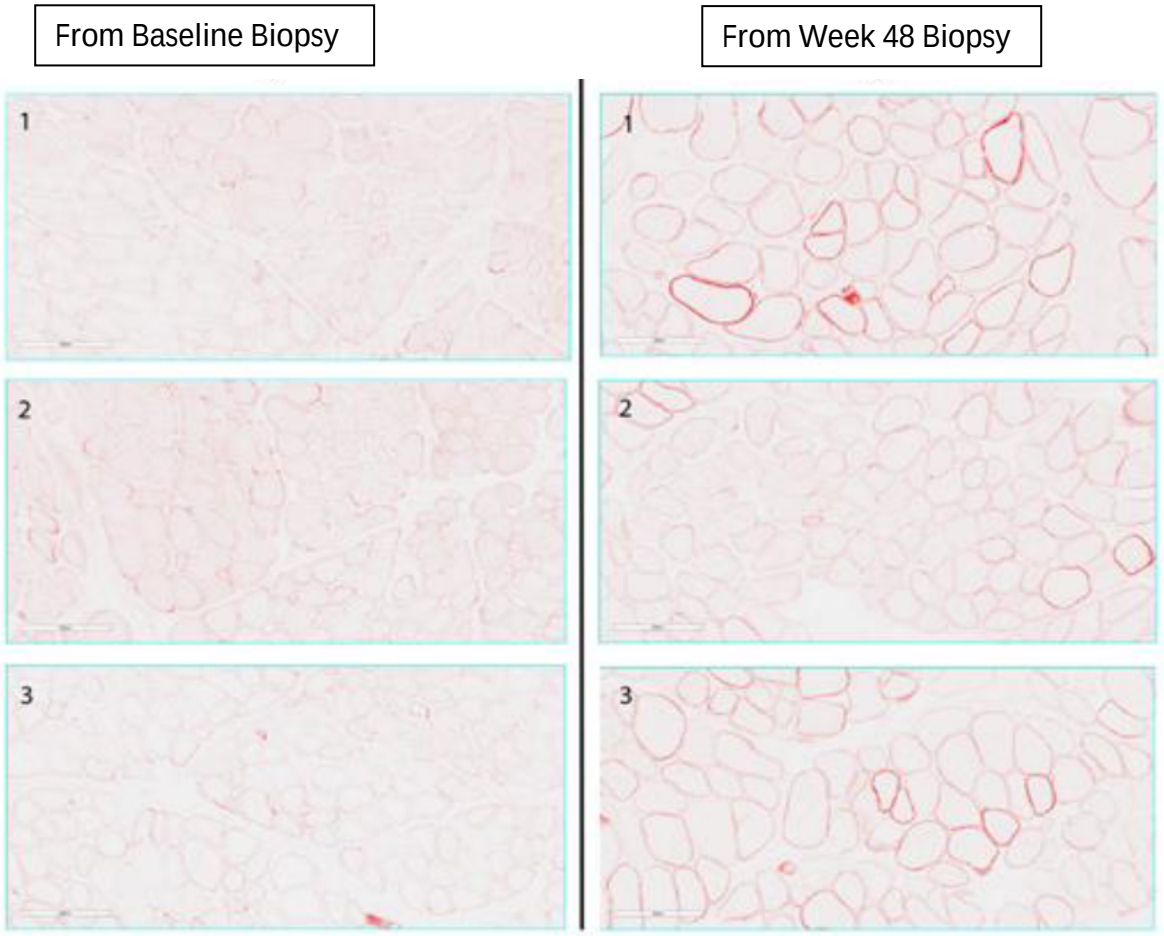
Figure 22. Immuno-stained Dystrophin Images from Subject (b) (6) (casimersen)



[Source: Summary of Clinical Efficacy, Fig. 14]

It is apparent that dystrophin expression is higher and somewhat broadly distributed in the three images on the right (Week 48; dystrophin expression 0.9% NL as measured separately by western blot techniques), as compared to its absence or near-absence in the three images on the left (Baseline; dystrophin expression 0.09% NL, as measured in separate sections). In the images on the right, it appears that dystrophin (the darker red regions) is outlining the cross-sections of muscle fibers, which would appear to indicate a sarcolemmal localization. Note also that there is a degree of heterogeneity in stained dystrophin across the three images on the right. Images 1 and 3 appear to show a greater degree of stained dystrophin than Image 2.

Clinical Reviewer's Comments

These images show the near-absence of pre-treatment (i.e., Baseline) dystrophin expression, which may also correlate with a near-absence of revertant fibers in these images. Images 1 and 3 on the right, from a section taken from the Week 48 biopsy, show a fairly broad distribution

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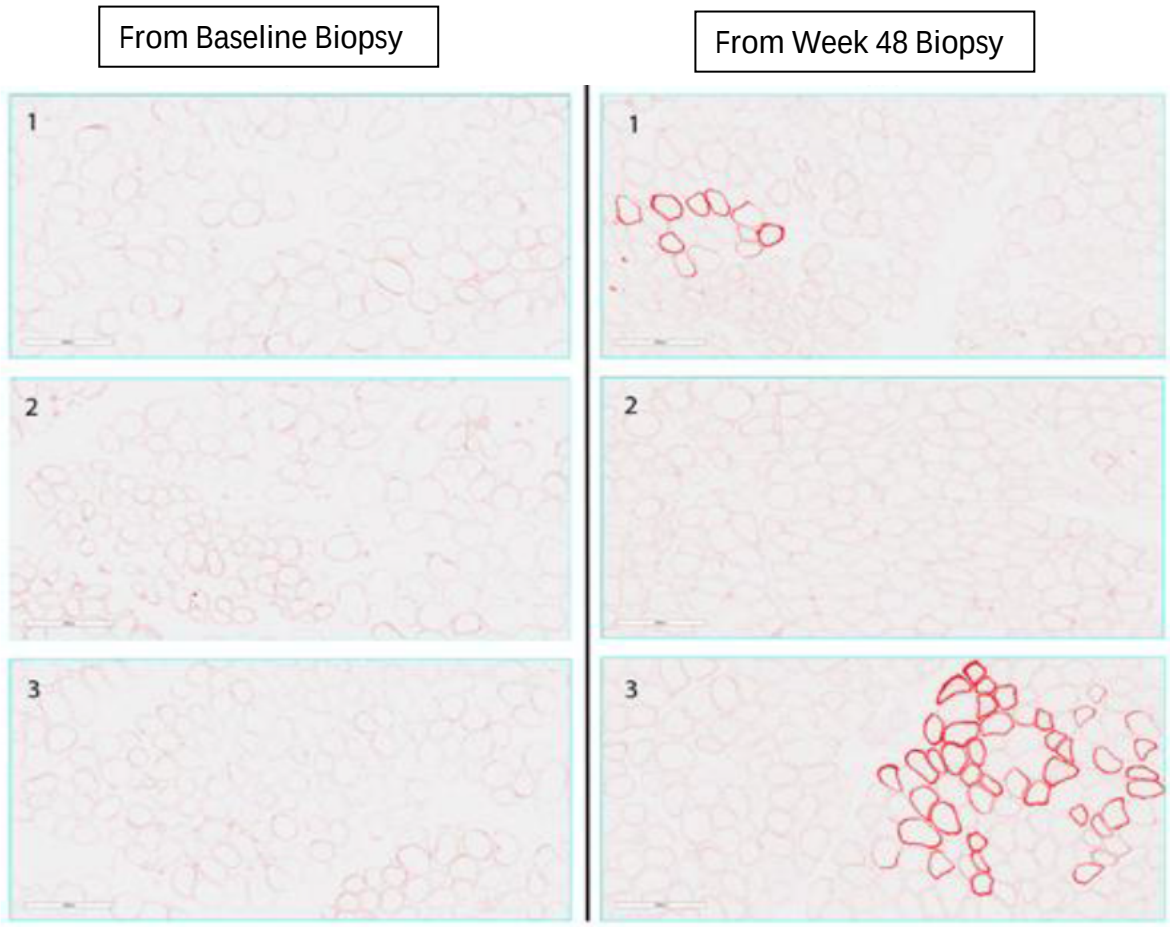
across many muscle fibers. Note, however, that the images are taken from a small portion of an entire immune-stained section, and that the images may not be entirely representative of the entire section, nor of the entire biopsy tissue. This feature is illustrated by the heterogeneity of dystrophin staining across the three images on the right (Week 48) side of the figure.

Subject (b) (6) (placebo)
This subject had a Baseline dystrophin expression that was 0.12% NL, and a Week 48 expression that was 0.23% NL.

Figure 23. Immuno-stained Dystrophin Images from Subject (b) (6) (Placebo)



[Source: Summary of Clinical Efficacy, Fig. 15]

Dystrophin expression is observable in some of the images on the right, but in restricted regions (Week 48; dystrophin expression 0.23% NL as measured separately by western blot techniques), as compared to the three images on the left (Baseline; dystrophin expression 0.12% NL as measured in separate sections). In the images on the right, it appears that

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dystrophin has a sarcolemmal localization. Note also that there is a degree of heterogeneity in stained dystrophin across the three images on the right. Images 1 and 3 show dystrophin expression in contrast to Image 2.

Clinical Reviewer's Comment

These images show an absence or near-absence of dystrophin expression at Baseline, in contrast to a visible but restricted pattern of expression in the images from Week 48. Note that these latter images show that not all fibers in a single fascicle show dystrophin immunostaining. This may indicate the presence of revertant fibers in this placebo-treated subject at Week 48, but within restricted muscle fibers.

Subject (b) (6) (casimersen)

This subject had a Baseline dystrophin that was 2.4% NL, and a Week 48 expression that was 4.4% NL.

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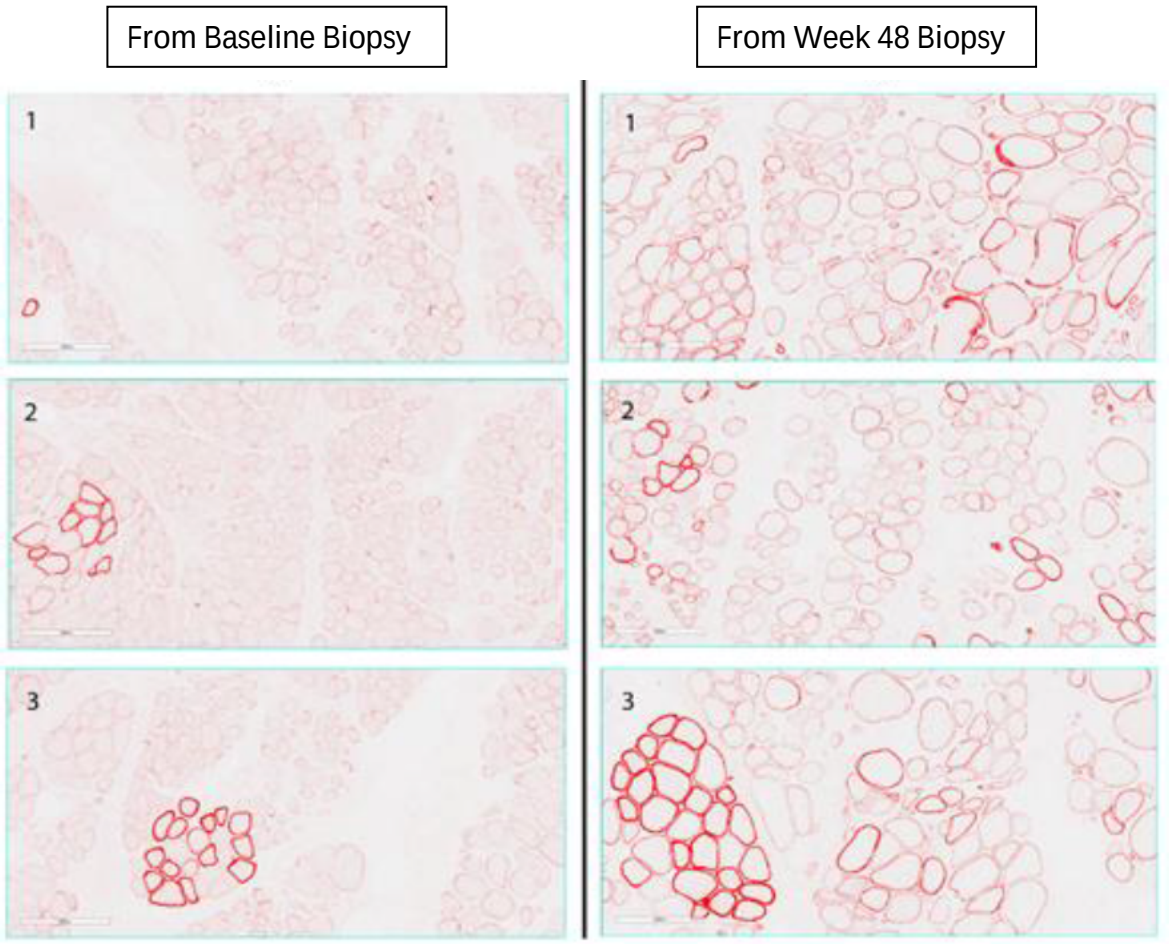
Figure 24. Immuno-stained Dystrophin Images from Subject (b) (6) (casimersen)



[Source: Summary of Clinical Efficacy, Fig. 19]

Dystrophin expression is higher and more broadly distributed in the three images on the right (Week 48; dystrophin expression 4.4% NL as measured separately by western blot techniques), as compared to the three images on the left (Baseline; dystrophin expression 2.2% NL as measured in separate sections). In all images, it appears that dystrophin is in the region of the sarcolemma.

Clinical Reviewer's Comments

Note that the presence of stained dystrophin at Baseline is restricted to some but not all fibers in a muscle fascicle. This pattern is similar to the restricted pattern of dystrophin staining in the Week 48 images from the placebo-treated subject above (Fig. 18), and it may indicate the presence of pre-treatment revertant fibers in these images. Note also that the degree of dystrophin staining in the images on the right side (i.e., at Week 48) does not appear to be appreciably greater that the degree of dystrophin-staining in the images on the left side (i.e., at

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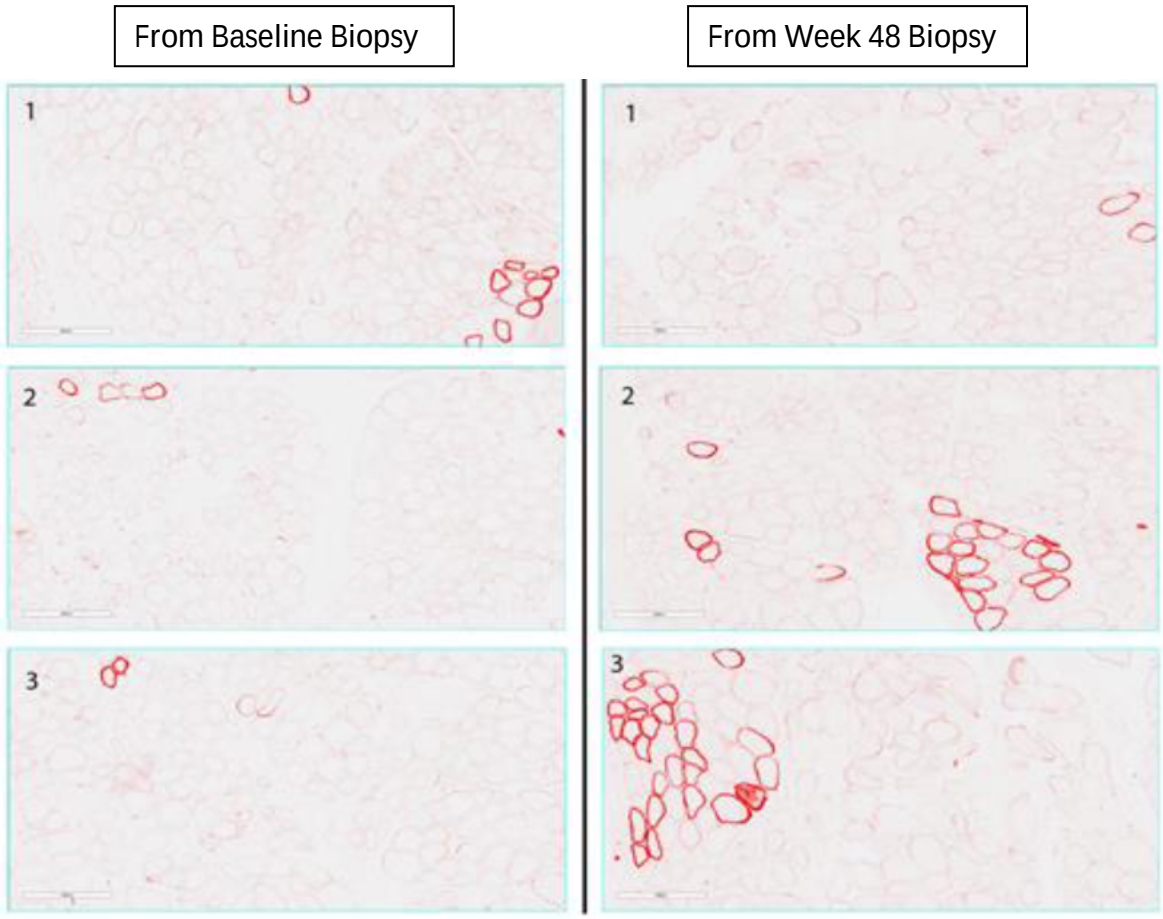
Baseline), even though the observed values of % dystrophin expression in this subject were 0.44% NL at Week 48 and 0.22% NL at Baseline. This is one illustration that these immune-stained images are adequate to determine the approximate dystrophin protein localization and also to observe whether the stained dystrophin has a restricted or a more broadly distributed pattern, but not to serve as a quantitative measure of the level of dystrophin expression.

Subject (b) (6) (placebo)

This subject had a Baseline dystrophin expression that was 2.2% NL, and a Week 48 expression that was 3.7% NL.

Figure 25. Immuno-stained Dystrophin Images from Subject (b) (6) (Placebo)



[Source: Summary of Clinical Efficacy, Fig. 18]

Dystrophin staining is observable in all Baseline images and in all Week 48 images from this placebo-treated subject, possibly indicating the presence of revertant fibers. The staining is

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greater in the images within sections taken from the Week 48 biopsy. In all images, the stained fibers are restricted in localization. It appears that stained dystrophin is localized to the sarcolemma.

Clinical Reviewer's Comments
Similar to images from the placebo-treated subject in Figure 17, dystrophin staining is restricted to some but not all muscle fibers in their muscle fascicle. This may support the premise that revertant fibers in non-treated (i.e., placebo-treated) subjects, whether at Baseline or at Week 48, are generated randomly within muscle fascicles of these subjects, in contrast to the broader pattern of stained fibers in casimersen-treated subjects at Week 48.

6.2.3.4. Clinical Reviewer's Evaluation of IHC Images from Additional Subjects

Using the images that were provided by the applicant for each subject in the interim review, approximately half of the subjects (i.e., 14 from the 27 casimersen-treated subjects, and 8 from the 16 placebo-treated subjects) were evaluated in a partially blinded manner by this reviewer in order to make three assessments about the images from each subject. For this exercise, "partially blinded" refers to the reviewer's lack of knowledge of Baseline and Week 48 dystrophin expression for the reviewed subjects, as measured by separate western blot methodology. This reviewer was not blinded to the treatment groups, however, because all image filenames included the terms "placebo" or "casimersen" to indicate the treatment assignment. Likewise, this reviewer was not blinded to whether the images were from biopsy samples obtained at Baseline or at Week 48, because all image filenames included "BL" or "48" to indicate the time point.

The three assessments were as follows.

a) The apparent localization of immuno-stained dystrophin in each image, if staining was visible.

b) A subjective assessment of the degree of dystrophin staining using the following 6 categories:
   i. Very low
   ii. Low
   iii. Low to medium
   iv. Medium
   v. Medium to high
   vi. High

c) The directionality of the subjectively-determined degree of dystrophin staining from images taken at Baseline in relationship to the degree of staining from images taken at

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Week 48. For example, if the reviewer rated images from Baseline as Low, and images at Week 48 as Medium (or any higher degree than Low), then the directionality was "increased." Conversely, if images at Baseline were rated Medium to High and images at Week 48 were rated Low to Medium (or any lower degree than Medium to High), then the directionality was "decreased." For subjects in whom the Baseline and Week 48 values were the same (e.g., both time points rated as Low), directionality could not be determined.

The results of this subjective evaluation were as follows.

1. Every image from the 22 reviewed subjects appeared to show sarcolemmal localization of staining at Baseline and/or at Week 48, in both casimersen-treated and placebo-treated subjects.

2. After completion of all subjective assessments of the degree of dystrophin expression in all images, directionality was then assigned where possible. Directionality was not evaluable in 8 subjects for whom there was no change in the subjective rating between Baseline and Week 48 images. In 14 subjects, directionality was evaluable.

   After all assessments of directionality were made, each subject's image (at Baseline and at Week 48) was then coupled to the quantitatively determined dystrophin expression for that subject at each time point, as measured by the applicant using separate western blot methodology.

   The results were that 11 of 14 assessments of directionality were correct when compared to the directionality of the Baseline and Week 48 measurements of dystrophin expression.

   Clinical Reviewer's Comment
   The lack of full concordance between subjective ratings by this reviewer of directionality and the actual directionality as measured by western blot techniques illustrates that the IHC images are not fully adequate for a qualitative assessment by this reviewer of the direction of change in dystrophin expression (i.e., increased or decreased) between Baseline and Week 48.

3. All images were then grouped into their subjectively rated category (i.e., one of the six categories listed above, as rated for degree of dystrophin expression). Because there were 22 subjects evaluated by this reviewer, there were 44 images (i.e., both Baseline and Week 48 images for each subject) that were grouped. The quantitative measurements of dystrophin expression at Baseline and at Week 48 for each subject in each category were then used to calculate a mean for all images in that subjectively

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rated category. The results are shown in the table below.

Table 26. Comparison of Subjectively Evaluated Degree of Dystrophin Expression with Measured Dystrophin Expression in Immuno-stained Images

Subjective Evaluation of the Degree of Dystrophin Expression	Images in each category (N)	Mean dystrophin expression (% NL) per WB data for the subjects in the subjectively rated category
Very low	2	0.07% NL
Low	12	0.68% NL
Low to medium	5	0.93% NL
Medium	17	1.4% NL
Medium to high	4	3.1% NL
High	4	1.5% NL

[Source: Clinical reviewer's subjective evaluations of IHC images from all subjects]

There was an increase of mean measured dystrophin expression in each category through the subjective rating of medium dystrophin. Although the two higher categories (i.e., medium to high and high) had mean measured dystrophin expression that was greater than in any lower category, this reviewer was unable to perceive a difference in the degree of dystrophin in higher categories.

This categorization does not make apparent the very wide range of measured dystrophin expression within each category. For example, in the medium category, the measured dystrophin expression ranged from 0.05% NL in one subject, the second lowest measured value for any subject in the interim analysis, to 6.51 in another subject, the second highest measured value in the analysis.

Clinical Reviewer's Comments

It is clear that this reviewer cannot distinguish even a semi-quantitative degree of dystrophin expression using the immuno-stained images. This illustrates and confirms the observations made by OBP staff (Drs. Thomas Biel and Ashutosh Rao) regarding the qualitative nature of the immune-staining methods. These images appear to be adequate for a qualitative evaluation of the localization of immuno-stained dystrophin, but they are not adequate for other purposes.

6.2.3.5. Clinical Reviewer's Conclusion about IHC Qualitative Localization of Dystrophin

In every image in which immuno-stained dystrophin was visible, staining appeared to be localized to the sarcolemma. This supports the premise that casimersen has the potential ability to increase the amount of truncated dystrophin within muscle fibers, and that the ultimate

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cellular location of truncated dystrophin may be relevant to dystrophin's cellular function in skeletal muscle.

That conclusion, although important, appears to be the only conclusion that this reviewer can make about the use of these immune-stained sections. This reviewer was unable to use the images to assess the degree of dystrophin expression, or even whether dystrophin expression was increased or decreased from Baseline to Week 48. That assessment must rely upon changes in dystrophin expression as measured using western blot technologies, as described further above.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Section 7.1 is not applicable because the efficacy endpoints that were submitted for evaluation of accelerated approval are derived from a single clinical trial (i.e., study 4045-301). However, sections 7.2 and 7.3 will assess the potential clinical benefits and risks for the potential use of casimersen, if approved, in subjects with DMD amenable to exon 45 skipping.

7.1.1. Primary Endpoints

7.1.2. Secondary and Other Endpoints

7.1.3. Subpopulations

7.1.4. Dose and Dose-Response

7.1.5. Onset, Duration, and Durability of Efficacy Effects

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-market Setting

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This NDA was submitted for consideration of accelerated approval on the basis of increased expression of dystrophin in skeletal muscle tissue that was obtained from subjects with DMD amenable to exon 45 skipping. As such, there are no clinical data in the submission. If accelerated approval is granted by FDA, then a key post-marketing requirement will be to submit the results of a study or studies in this subject population that assess the effect of casimersen on clinically meaningful endpoints. For this reason, it is somewhat premature to consider how casimersen may be used in the marketplace.

Nonetheless, there may be differences between the subject population that was enrolled in study 4045-301 and the potential patient population that may be prescribed casimersen post-approval. Examples of these differences are listed below.

1. Race and Ethnicity
   Approximately 86% of the subjects enrolled in the interim analysis dataset were white, and approximately 95% were not of Hispanic or Latino origin. It is possible although unlikely that casimersen may act differently in patients of other races and/or ethnicity. The exon-skipping mechanism of action of the product is anticipated to be independent of race and ethnicity.

2. Age of Subjects
   All subjects in this interim analysis dataset were between 7 and 13 years of age, inclusive (inclusion criterion 1). Moreover, all subjects in the study, and not just in this interim analysis dataset, had less severe features or consequences of DMD at enrollment, including the following:

   a. Forced Vital Capacity (FVC) $\geq$ 50% predicted and not requiring night-time ventilation (inclusion criterion 3);
   b. 6-Minute Walk Test (6MWT) distance of at least 300 meters and $\leq$ 450 meters at Screening and at Baseline (inclusion criterion 7);
   c. Left Ventricular Ejection Fraction (LVEF) must not be < 50% (exclusion criterion 6).

   The use of these criteria to enroll a slightly younger and a less severely affected subject population makes it difficult to predict the clinical effect of casimersen in older and more severely affected patients.

3. Concomitant Medications with Restricted Use
   A variety of medications that are sometimes prescribed in patients with DMD were restricted per exclusion criterion 2. For example, “any pharmacologic treatment (other than corticosteroids) that may have an effect on muscle strength or function” could not be used within 12 weeks prior to Week 1, or during the study. In a clinical setting, it is

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> likely that a number of these restricted medications will be prescribed as standard of care to patients who are being treated with casimersen. The potential benefits or risks of casimersen in patients using these medications cannot be predicted.

However, there are also features of the subject population in study 4045-301 that are similar to those of patients in a clinical setting. In study 4045-301, inclusion criterion 5 specifies that subjects must have "been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1, and the dose is expected to remain constant throughout the study (except for modifications to accommodate changes in weight)." The majority of patients with DMD in a clinical setting are treated with corticosteroids. Hence the required use of corticosteroids in this study ensures that these study participants should be representative of the majority of patients in a clinical setting who are also treated with corticosteroids.

7.2.2. Other Relevant Benefits

The key benefit of casimersen is that it is a genetically targeted treatment for patients with DMD amenable to exon 45 skipping. None of the approved ASOs target this specific subgroup of patients with DMD. However, regarding formulation of method of administration, casimersen offers no benefit in comparison to other targeted ASO treatments. The requirement for weekly IV infusions will be burdensome for patients and caregivers. However, the other marketed ASOs (Exondys 51 [eteplirsen], Vyondys 53 [golodirsen], and Viltepso [viltolarsen]) are also administered by IV infusion.

7.3. Integrated Assessment of Effectiveness

This section begins with a discussion on whether the applicant's intended patient population and the surrogate endpoint chosen for interim analysis meet the statutory evidentiary standard for accelerated approval. Subsequent discussions will address the extent to which the applicant has demonstrated an effect on this endpoint, and then the potential clinical benefit of casimersen's effects on this endpoint in patients with DMD amenable to exon 45 skipping.

7.3.1. Statutory Evidentiary Considerations as Regards Accelerated Approval

The features and requirements for accelerated approval are described in FDA's 2014 Guidance, "*Expedited Programs for Serious Conditions – Drugs and Biologics.*" Per section VII of this guidance, "The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to:

> . . . a product for a serious or life-threatening disease or condition . . . upon a determination

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that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

The qualifying criteria used to consider a drug or biologic for accelerated approval include the following (sections VII and III of the 2014 Guidance).

a) Serious condition.
DMD satisfies the definitions of a serious condition. The condition has a substantial impact on day-to-day functioning, and affected patients have a relentlessly progressive decline that leads to the loss of ambulation, the need for ventilation, total disability, and death that is typically caused by cardiac, pulmonary, or infectious etiologies.

b) Meaningful Advantage over Available Therapies.
Casimersen is a targeted therapy that is intended for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping. Currently available treatments for any patient population include Emflaza, an approved corticosteroid, and a variety of other corticosteroids and symptomatic treatments (e.g., foot and/or ankle braces, or tendon release surgery). However, there is no approved targeted treatment for patients with DMD amenable to exon 45 skipping.

c) Demonstrates an Effect on an Endpoint that is Reasonably Likely to Predict Clinical Benefit.
The surrogate endpoint for which the applicant has submitted clinical trial evidence is increased dystrophin expression in skeletal muscle, based upon an interim analysis of muscle biopsy tissue that was obtained from subjects during ongoing study 4045-301. Compared to its expression in individuals not affected by DMD, dystrophin is completely absent or expressed at a very low level in patients with DMD, due to mutations in the *DMD* gene. From a pathophysiologic standpoint, the correlation between total or near-total loss of dystrophin expression and the progression of muscle disease in DMD is clear (Guiraud et al., 2015). From a therapeutic point of view, the use of targeted therapies that promote exon-skipping of mutated exons that cause DMD in a chosen patient population is a rational way to treat those populations (Aartsma-Rus and Van Omen, 2007).

The pathophysiologic and therapeutic considerations stated above were used to support the recent approval of three exon-skipping treatments for targeted populations of patients with DMD. These treatments (i.e., Exondys 51 for patients with DMD amenable to exon 51 skipping; Vyondys 53 for patients with DMD amenable to exon 53 skipping; and Viltepso for patients with DMD amenable to exon 53 skipping) were granted

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accelerated approval based upon a statistically significant increase from Baseline in dystrophin expression, but with a post-marketing requirement that continued approval may be contingent upon further verification of a clinical benefit in confirmatory trials. It would appear that the chosen surrogate endpoint is consistent with those used for accelerated approval of the therapies just cited.

Clinical reviewer's comments
This reviewer judges that casimersen meets the qualifying criteria for accelerated approval. The next section will discuss the extent to which casimersen's effects on dystrophin expression in ongoing study 4045-301 meet the statutory evidentiary standards. A subsequent section will then discuss the potential clinical benefit of an effect on dystrophin expression in the intended patient population.

7.3.2. Review of Casimersen's Effects on Dystrophin Expression in the Interim Analysis of Study 4045-301

Section 6 of this review describes the applicant's data regarding the effect of casimersen on dystrophin expression as measured via western blot techniques, on percent exon-skipping via RT-ddPCR methodology, and on sarcolemmal localization of truncated dystrophin via microscopic analysis of muscle sections processed with IHC methodology. A summary of the findings is below.

a) Effect of Casimersen versus Placebo on Dystrophin Expression
FDA staff verified that casimersen significantly increased CFB to Week 48 in mean dystrophin expression when compared to placebo (0.59% NL; p = 0.004 [2-sample permutation t-test]; p = 0.0008 [Wilcoxon Rank Sum Test]). Even after removing outliers and using the nonparametric Wilcoxon Rank Sum Test for observed values, casimersen significantly increased CFB to Week 58 in mean dystrophin expression compared to placebo (0.60% NL; p = 0.0002 [Wilcoxon Rank Sum Test]). A pre-specified method of sensitivity analysis, adjusted by removing data from the outlier subjects, was supportive of the applicant's results. An independent sensitivity analysis conducted by FDA Biometrics staff also supported the applicant's results.

Clinical Reviewer's Comments
These effects of casimersen on dystrophin expression in subjects with DMD amenable to exon 45 skipping are qualitatively similar to the applicant's findings for eteplirsen's effect on dystrophin expression in subjects with DMD amenable to exon 51 skipping, and to the applicant's findings for golodirsen's effect on dystrophin expression in subjects with DMD amenable to exon 53 skipping. The table below shows data about dystrophin expression from the Prescribing Information for Exondys 51 and for Vyondys 53, alongside the submitted data for casimersen. But note that it is not always possible to

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directly compare these results across studies because of differences in the particular western blot methodologies used in each study.

Table 27. Effects of Three ASOs on Dystrophin Expression

	Baseline Dystrophin % NL	Week 48 Dystrophin % NL	CFB to Week 48 Dystrophin Within ASO Treatment Group % NL	CFB to Week 48 Dystrophin Compared to Placebo % NL
Eteplirsen (Label Study 3) *	0.16%	0.44%	0.28% ($p < 0.05$)	No placebo
Golodirsen (Label Study 1)	0.10%	1.02%	0.92% ($p < 0.001$)	No placebo
Casimersen (Study 4045-301)	0.93%	1.74%	0.81% ($p < 0.001$ within casimersen group, applicant)	Versus placebo: CFB = 0.59% ($p = 0.004$, applicant)

* Eteplirsen study 3 was the only study with available Baseline values. Eteplirsen study 2 (no Baseline) showed a Week 180 dystrophin value of 0.93% NL.

[Source: Prescribing Information for Exondys 51 and Vyondys 53; Summary of Clinical Efficacy for casimersen]

The column that is denoted "CFB to Week 48 Dystrophin Within ASO Treatment Group, % NL" is the most comparable measurement, because it shows the measured mean dystrophin expression as a function of ASO treatment, without any comparison to placebo. The studies of eteplirsen and golodirsen did not include a comparison of those ASOs vs. placebo. In this context, note that the CFB to Week 48 of dystrophin expression in the casimersen group (0.81% NL) is qualitatively similar to those for eteplirsen (0.28% NL) and for golodirsen (0.92% NL).

This clinical reviewer judges that the applicant's analysis of the primary endpoint for accelerated approval has been verified, and that the effects of casimersen on dystrophin expression are statistically significant and in keeping with the effects of other ASOs on dystrophin expression.

b) Effect of Casimersen versus Placebo on Percent Exon-skipping

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FDA's analyses of the applicant's use of RT-ddPCR methodology to analyze % exon-skipping verified the applicant's finding that casimersen increased the mean CFB to Week 48 in % exon-skipping in a statistically significant way, compared to placebo ($p < 0.0001$; Wilcoxon Rank Sum Test). Additional FDA analyses that excluded casimersen outlier values, using both the RT-ddPCR method and the Endpoint RT-PCR method, yielded similar results. Each analysis favored casimersen over placebo in the mean CFB to Week 48 in % exon-skipping in a statistically significant way ($p < 0.0001$; Wilcoxon Rank Sum Test). Additional sensitivity analyses conducted by FDA's Biometric staff also supported the applicant's findings.

Clinical Reviewer's Comments
Compared to placebo, casimersen produced a statistically significant increase of exon-skipping in this study population. Casimersen's increase in exon-skipping provides pharmacodynamic support for the agent's increase in dystrophin expression.

c) Muscle Fiber Localization of Dystrophin at Week 48 in Subjects Treated with Casimersen
This reviewer verified that in every image in which immuno-stained dystrophin was visible, staining appeared to be localized to the sarcolemma.

Clinical Reviewer's Comments
This result supports the premise that casimersen has the potential ability to increase the amount of truncated dystrophin within muscle fibers, and that the ultimate cellular location of truncated dystrophin in the sarcolemma should be relevant to dystrophin's cellular function in skeletal muscle.

This finding is supportive of the effect of casimersen to increase dystrophin expression and to increase exon-skipping. In this reviewer's opinion, the applicant has met the statutory evidentiary standards for accelerated approval.

7.3.3. The Potential Clinical Benefit of Increased Dystrophin Expression in the Intended Patient Population

For decades there have been widespread scientific and clinical discussions about the threshold of dystrophin expression that is needed in skeletal muscle fibers in order to increase or to normalize muscle function in patients with DMD. The discussions have reached no consensus, and hence this reviewer will not provide an exhaustive review or summary of the pertinent biomedical literature. However, it is instructive to consider several points about the relative dystrophin expression in DMD and in the less severe condition of BMD, in which dystrophin production is also reduced due to mutations in the *DMD* gene. The following examples from patients with BMD or DMD reveal that measured dystrophin expression in each patient population, when assessed using western blot techniques, may vary widely due to differences in: the particular western blot methodology; the location and type of the exon mutations; the

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skeletal muscles chosen for biopsy; and a complex interaction between age and clinical severity.

a. Anthony et al., 2011.

Anthony and colleagues (2011) studied 17 subjects with BMD, ranging in age from 10 to 76 years. Of the 17 subjects, 4 were asymptomatic, 12 had mild symptoms, and 1 was severely affected. The measured dystrophin expression in these subjects ranged from 57% that of normal controls to levels similar to those in normal controls. Dystrophin expression correlated with both clinical severity and with the location of the deleted exons, as follows.

- In asymptomatic subjects compared to mildly affected subjects, mean dystrophin expression was statistically significantly higher mean (p = 0.013). Moreover, the most severely affected subject had the lowest dystrophin expression (44% NL) as quantitated using the Dys2 antibody, which targets epitopes located in C-terminal exons 77-79 (Kodippili et al., 2014).

- The level of expression also varied by the pattern of exon deletions, with a mean expression of:
    - approximately 56% NL in the exon 53 group, comprised of 5 subjects with multi-exon deletions ending at exon 53 (including the most severely affected subject);
    - approximately 70% in the exon 55 group, comprised of 4 subjects with large exon deletions ending at exon 55;
    - approximately 80% in the exon 51 group, comprised of 8 subjects with multi-exon exon deletions ending at exon 51.

The mean dystrophin expression was statistically significantly higher in the exon 51 group than in the exon 53 group (p = 0.034). By way of comparison, the dystrophin expression in three subjects with DMD, who were included as a negative control group, ranged from 4 to 9% NL.

The measured dystrophin expression in these 17 subjects also varied as a function of the antibody used for quantification. Dys2 targets dystrophin epitopes in exons 77-79, and MANDYS106 targets epitopes in exon 43 [Kodippili et al., 2014]). The table below displays the above data by exon group and by the antibody used for quantification.

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Table 28. Mean Dystrophin Expression in 17 Subjects with BMD by Exon Deletion Pattern and by the Antibody Used for Detection

Deletion Group	Dystrophin Expression Using Dys2 Antibody: Mean (Range)	Dystrophin Expression Using MANDYS106 Antibody: Mean (Range)
Exon Deletion Group 53 n =5 with deletions: 42 – 53 [n = 1] 45 – 53 [n = 3] 52 – 53 [n = 1]	~ 56% NL (44% NL – 89% NL) Note: The most severely affected subject in the study had an expression of 44% NL by Dys2, and of 57% NL by MANDYS106.	~ 56% NL (0 – 69% NL) Note: The subject with an expression of 0 had deletions in exons 42 – 53, and the epitopes which MANDYS106 targets (exon 43) were absent.
Exon Deletion Group 55 n = 4 with deletions: 45-55 [n = 4]	~ 70% NL (59% NL – 85% NL)	~ 70% NL (62 – 87% NL)
Exon Deletion Group 51 n = 8 with deletions: 45-51 [n = 3] 48-51 [n = 5]	~ 80% NL (66% NL – 112% NL [sic])	~ 80% NL (48% NL - 104% NL [sic])

[Source: data from Anthony et al (2011); table prepared by clinical reviewer]

Clinical Reviewer's Comments
These data illustrate the variability in dystrophin expression as a function of both the antibody used for detection and also the location of exon deletions. The most severely affected subject also had the lowest measured dystrophin expression, but overall there was no clear relationship between dystrophin expression and clinical severity.

b. van den Bergen et al., 2014
As another example, van den Bergen and colleagues (2014) measured dystrophin expression and muscle strength in 33 subjects with genetically defined BMD. Dystrophin expression as measured with western blot techniques ranged from 3% NL - 78% NL. There was no linear relationship between dystrophin expression and muscle strength, although subjects with dystrophin expression less than 10% NL had a more severe clinical course.

Clinical Reviewer's Comment
An extremely wide range of dystrophin expression was not shown to have a linear relationship to muscle strength. It is intriguing that subjects with BMD, some of whom had dystrophin expression as low as 3% NL, could have normal muscle strength albeit with a more severe clinical course. As a corollary, this may suggest that in subjects with DMD, raising dystrophin expression into this range might be adequate to provide them with greater muscle function. However, the caveat for this suggestion is that the number of subjects with BMD who were

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described in this paper was small, particularly in the lower range of dystrophin expression.

c. Arechavala-Gomeza et al., 2010

To put the range of dystrophin expression in BMD into context with the range of dystrophin expression that has been measured in DMD, Arechavala-Gomeza and colleagues (2010) made a number of interesting observations in a retrospective review of 65 subjects with genetically confirmed DMD. Subjects were followed over a period of 8 years, and muscle biopsies were obtained from a subset of 35 of these subjects before the initiation of corticosteroid treatment. Muscle function was also assessed in these subjects using the Hammersmith Motor Activity Scale (HMAS) before the onset of corticosteroid therapy. In each of the 35 subjects, the same pathologist assessed cryosectioned muscle biopsy tissue that was immuno-stained for dystrophin using either the Dys-1, Dys-2, or Dys-3 antibody. In the 35-subject subset, residual dystrophin was identified in 18 subjects, and 17 subjects had no residual dystrophin. There was no difference between the HMAS scores in the groups with vs. without residual dystrophin.

Clinical Reviewer's Comments

The key finding in this paper may be that there was no difference in muscle function as assessed by the HMAS irrespective of whether these subjects with DMD had observable dystrophin. This may suggest that residual dystrophin plays no functional role in the clinical presentation of DMD at a particular point in time. If these subjects with no residual dystrophin are representative of a larger population of patients with DMD, then one might assign a value that is near zero for dystrophin expression in spite of functional muscle activity at that point in time. The caveat for this assumption is not only that this study was small, but also that all assessments were made using qualitative IHC techniques, and no quantitative western blot assessments were performed.

Nevertheless, this study of DMD and the above-described studies of BMD may provide a context in which to assess functional levels of dystrophin expression. A key point is that a subject with BMD and a dystrophin expression of 3% NL had no difference in clinical severity at a point in time, albeit with a more severe clinical course, as compared to subjects with higher levels of dystrophin expression (van den Bergen et al., 2014). It is conceivable that raising dystrophin expression from 0% NL (i.e., a baseline level of "functional" dystrophin in DMD) to a level of 3% NL may provide a clinical benefit in patients with DMD. There are many caveats to this suggestion. First, different methods using different anti-dystrophin antibodies produced the results in the studies cited above, and in many other studies that will not be reviewed here. Second, it is uncertain if subjects were assessed for muscle strength in a uniform manner across the studies. Third, the numbers of subjects assessed in these studies were small.

7.3.4. *Clinical Reviewer's Overall Efficacy Conclusion*

Multiple FDA analyses support the applicant's finding of a small but statistically significant increase from Baseline to Week 48 in dystrophin expression in casimersen-treated subjects compared to placebo-treated subjects. FDA analyses also verified the applicant's findings that

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casimersen-treated subjects had a small but significantly higher percentage of exon-skipping compared to placebo-treated subjects. The applicant used IHC techniques to demonstrate that dystrophin was localized to the sarcolemma in casimersen-treated subjects, which supports the premise that casimersen increased dystrophin expression at a cellular location in which it may have an effect on muscle fiber function. These findings appear to meet the statutory evidentiary standards for an accelerated approval for casimersen in the treatment of DMD that is amenable to exon 45 skipping. However, this statement is made solely in the context of casimersen's effects on a surrogate marker. The safety and tolerability of casimersen will be described and discussed in section 8 of this review.

Whether the small but statistically significant effect of casimersen on dystrophin expression when compared to placebo (0.6% NL) purports an improvement in clinically meaningful endpoints will not be known until the completion of ongoing study 4045-301. Submission of these results will be a post-marketing requirement for casimersen if it is granted accelerated approval.

8. Review of Safety

8.1. Safety Review Approach

The expert assistance of safety specialists within Division of Neurology, Dr. Sally Jo Yasuda and Dr. Rui Li, is gratefully acknowledged. They contributed immensely to the following safety review.

8.1.1. Safety Database for Review

This safety review is indication-specific, and the review describes the safety and tolerability of casimersen when used to treat subjects with DMD amenable to exon 45 skipping.

The three studies that the applicant has completed are described in section 5.1.1, and the two studies that are ongoing are described in section 5.1.2. Of these five completed or ongoing studies, three studies enrolled subjects in the indicated population.

1. Completed study 4045-101 enrolled 12 subjects with DMD amenable to exon 45 skipping. The first 12-week period of this study were randomized, double-blind, and

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placebo-controlled. During this period, 4 subjects received weekly IV infusions of placebo, and eight subjects received weekly IV infusions of casimersen at doses of 4mg/kg (2 weeks), 10mg/kg (2 weeks), 20mg/kg (2 weeks), and then 30mg/kg for the remainder of this period of the study. All 12 subjects then entered a 132-week open-label extension period, during which each subject received weekly IV infusions of casimersen at a dose of 30mg/kg. Following the end of the study, subjects were eligible to enter an additional open-label extension study (4045-302; see below).

2. Ongoing study 4045-301 is a 144-week, two-period study that is enrolling subjects with DMD amenable to exon 45 skipping. During the initial 96-week randomized, double-blind, placebo-controlled part of the study, subjects are randomized to either weekly IV infusions of placebo, or to weekly IV casimersen at a 30mg/kg dose. During the final 48-week open-label extension period, all subjects are treated with weekly IV casimersen at 30mg/kg. At the end of the 144-week study, all subjects are eligible to enter an additional open-label extension study (4045-302; see below).

   At the data cut-off date of 5/31/19, 88 subjects were enrolled in the study; 57 were receiving casimersen and 31 were receiving placebo. None had completed the study.

   Before its initiation, this study was placed on a partial clinical hold on 11/9/15 as described in section 3.2.4, over a concern that investigator discretion about the placement of a central venous catheter for IV infusions could expose subjects to more than a normal increase in risk. The partial hold was lifted on 12/17/15 when the applicant precluded the use of central venous catheters for IV infusions. However, after a public meeting of the Office of Pediatric Therapeutics in June 2017, the placement and use of central venous catheters was allowed under certain circumstances. A revision to the study protocol (Amendment 5) describes this renewed allowance for port placement.

3. Ongoing study 4045-302 is an open-label extension study for subjects who complete studies 4045-101 or 4045-301. All subjects who enroll receive weekly IV infusions of casimersen, 30mg/kg. As of the data cut-off date of 5/31/19, 11 subjects from study 4045-101 were enrolled in this study.

Two other completed studies evaluated either healthy adults or subjects with chronic kidney disease (CKD); none of these subjects had DMD. Study 4045-102 enrolled eight healthy adult, each of whom received a single radiolabeled dose of casimersen in order to study the drug's absorption, metabolism, and distribution. Study 4045-102 enrolled 25 subjects, 9 of whom were healthy and 16 of whom had stage 2 or stage 3 CKD, in order to study the pharmacokinetic profile of a single dose of casimersen in renally impaired subjects in comparison to subjects with normal renal function.

During the pre-NDA meeting on 6/5/19, FDA agreed with the sponsor's proposal that the NDA

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safety database would consist of the subjects who had completed study 4045-101, as well as subjects enrolled in studies 4045-301 and 4045-302 as of the data cut-off date (5/31/19). In the majority of section 8 of this review, the focus will be upon the safety database that includes these subjects, all of whom have DMD amenable to exon 45 skipping. There will also be a brief description of safety and tolerability of casimersen in the 17 healthy adults and the 16 subjects with CKD who received a single dose of the product in completed studies 4045-102 and 4045-103.

The applicant also submitted a 120-day safety update report on 9/29/20, covering the additional reporting period from 6/1/19 through 2/28/20. These more recent safety data will be reviewed separately from the original NDA safety database, in section 8.7.

8.1.2 Identified or Potential Safety Issues

The identified risk of renal toxicity is based on two factors. First, renal toxicity is listed in the Warnings and Precautions section of the Vyondys 53 Prescribing Information, and Vyondys 53 shares a similar molecular backbone with casimersen. Second, signs of renal toxicity were identified in casimersen repeat-dose toxicology studies in rodents and non-human primates.

The potential risks include the following:

1. Hypersensitivity, which is listed in the Warnings and Precautions section of the Prescribing Information for Exondys 51 and Vyondys 53, both of which share a similar molecular backbone with casimersen;
2. Four potential risks of infusion-related reactions (IRRs), infusion site reactions (ISRs), hepatotoxicity, and thrombocytopenia/coagulopathy, each of which has been reported with the infusion of other ASOs;
3. Cardiac events, which are more common in patients with DMD;
4. Rhabdomyolysis, which is more common in patients with DMD and especially following general anesthesia; and which is also of general interest for ASOs such as casimersen that are intended to target myofibers to increase the expression of dystrophin.

These identified and potential risks will be reviewed in some detail in section 8.5.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

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8.2.1.1 Three Safety Populations Defined by the Applicant

All studies conducted by the applicant for this indication defined the safety population to include any subject who was enrolled and who received at least one dose of casimersen. Using this database, the applicant has constructed three overlapping safety populations, each of which serves a different purpose for the safety analysis.

1. Population 1 is defined as all subjects in the randomized, double-blind, placebo-controlled period of study 4045-301 as of the cut-off date of 5/31/19. This population includes 57 subjects treated with casimersen and 31 subjects treated with placebo.

2. Population 2 is defined as all subjects in the randomized, double-blind, placebo-controlled periods of studies 4045-101 and 4045-301 as of the cut-off date. This population includes 65 subjects treated with casimersen (i.e., 57 subjects in the double-blind period of study 4045-301, plus 8 subjects from the double-blind period of study 3034-101); and 35 subjects treated with placebo (i.e., 31 subjects from study 4045-301 plus 4 subjects from study 4045-101).

3. Population 3 is defined as all subjects who received casimersen at any time during studies 4045-101, 4045-301, or 4045-302 as of the cut-off date. This population consists of 76 casimersen-treated subjects: 57 subjects who were still in the casimersen arm of the double-blind period of study 4045-301; 7 placebo-treated subjects from the double-blind period of 4045-301 who had rolled over into the open-label period of that study; plus the 12 subjects in study 4045-101 who entered into and completed the open-label period of that study.

The following schematic depicts the flow of subjects in each of these populations. Note that the mean number of weeks that each group received study drug (i.e., placebo or casimersen) is depicted in the appropriate box.

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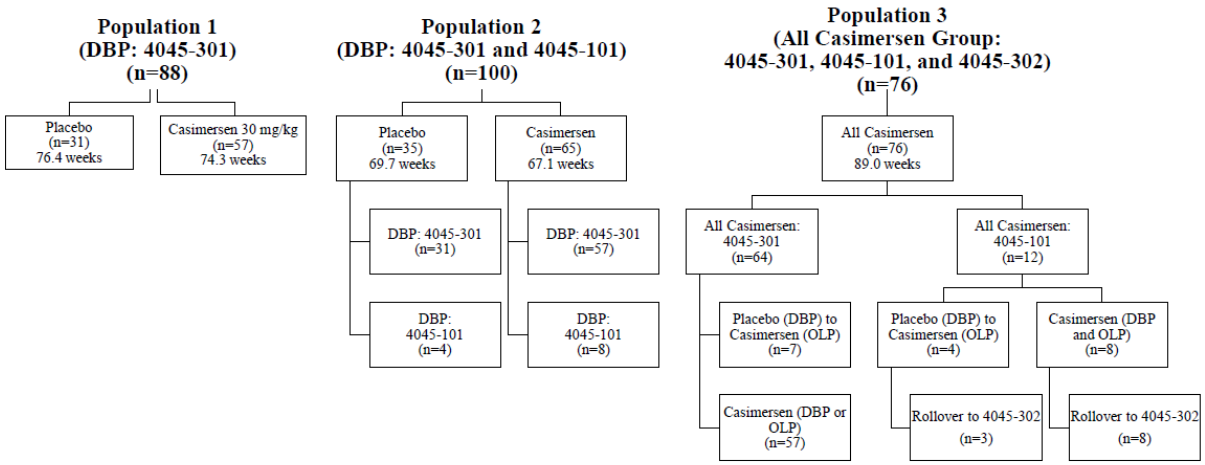
Table 29. Flow of Subjects into the Applicant's Three Safety Populations



[Source: Figure 4 from applicant's Summary of Clinical Safety, which constitutes the applicant's Integrated Summary of Safety (ISS)]

The applicant's ISS includes safety data from all three populations. Although this reviewer will evaluate safety data from the entire database of 100 subjects, population 1 (double-blind period of study 4045-301, n = 88) provides the clearest comparison of placebo-controlled data for two reasons.

First, the mean duration of double-blinded casimersen and double-blinded placebo treatment are similar (i.e., approximately 74 to 76 weeks). In contrast, the duration of double-blinded casimersen treatment or double-blinded placebo treatment during study 4045-101 is far shorter. This may cloud the interpretation of safety data when both of these double-blind periods are combined in population 2.

Second, the 8 subjects in the double-blinded casimersen arm of study 4045-101 were exposed to four ascending doses of casimersen during the planned 12-week period of that study. This design also clouds the interpretation of safety findings in the casimersen group, because it is uncertain if a finding arose from an increased dose of casimersen, or instead arose from the overall duration on casimersen irrespective of dose. In spite of these potential shortcomings of interpretation in population 2, this reviewer will refer to both populations in some situations in the following safety review.

Regarding population 3 (i.e., all-casimersen group), data from this population are useful for examining safety in subjects who, overall, had the longest duration of exposure to casimersen. The longer exposures will provide more data about long-term effects of casimersen on safety and tolerability, and hence this population should more closely reflect a real-world scenario if casimersen is granted accelerated approval. In addition, this reviewer will often compare the population 3 casimersen data to the population 2 placebo data to compare events between

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treatment groups that were exposed to study drug for the longest duration. To make certain that this comparison does not lead to the appearance of bias that would go against longer exposures to casimersen, the reviewer will also provide exposure-adjusted incidence rates (EAIRs) that permit the most accurate comparison between casimersen and placebo treatment groups. The unit of the EAIR is the number of subjects per 10 subject-years of exposure.

8.2.1.2. Overall Exposure to Casimersen and Placebo

The following table shows the overall exposure to casimersen and placebo in the safety database of 100 subjects with DMD amenable to exon 45 skipping. The table breaks down exposure by population.

Table 30. Exposure to Casimersen and Placebo in Each of the Applicant's Safety Populations

	Population 1 (Double-blind Period of Study 4045-301)		Population 2 (Double-blind Period of Studies 4045-101 and 4045-301)		Population 3 (Casimersen Treatment Period of Studies 4045-101, 4045-301, and 4045-302)
	Placebo (N=31)	Casimersen 30 mg/kg (N=57)	Placebo (N=35)	Casimersen (N=65)	All Casimersen (N=76)
Weeks on study drug					
Mean (standard deviation)	76.4 (22.04)	74.3 (24.78)	69.7 (28.11)	67.1 (30.09)	89.0 (49.77)
Median	81.9	81.9	77.3	78.0	84.1
Minimum, maximum	20, 96	8, 96	15, 96	8, 96	2, 190
Weeks on study drug category, n (%)					
0 to <24 weeks	1 (3.2)	4 (7.0)	5 (14.3)	12 (18.5)	8 (10.5)
24 to <48 weeks	2 (6.5)	6 (10.5)	2 (5.7)	6 (9.2)	9 (11.8)
48 to <72 weeks	6 (19.4)	8 (14.0)	6 (17.1)	8 (12.3)	8 (10.5)
72 to <96 weeks	16 (51.6)	32 (56.1)	16 (45.7)	32 (49.2)	25 (32.9)
96 to <120 weeks	6 (19.4)	7 (12.3)	6 (17.1)	7 (10.8)	7 (9.2)
120 to <144 weeks	not applicable	not applicable	not applicable	not applicable	8 (10.5)
≥144 weeks	not applicable	not applicable	not applicable	not applicable	11 (14.5)
Number of infusions received					
Mean (standard deviation)	75.0 (21.46)	72.5 (24.46)	68.5 (27.42)	65.6 (29.54)	87.4 (49.49)
Median	78.0	79.0	77.0	75.0	81.0
Minimum, maximum	20, 96	8, 96	15, 96	8, 96	2, 190
Patient-years of study drug exposure					
Mean (standard deviation)	1.464 (0.4224)	1.423 (0.4749)	1.335 (0.5388)	1.287 (0.5768)	1.706 (0.9539)
Median	1.569	1.569	1.481	1.495	1.611
Minimum, maximum	0.38, 1.85	0.16, 1.85	0.29, 1.85	0.16, 1.85	0.04, 3.65
Sum	45.383	81.131	46.727	83.647	129.645

[Source: Table 12 of Summary of Clinical Safety]

The cumulative casimersen exposure in the overall safety database is 129.6 subject-years, as shown in the final row under population 3. The duration of exposure in all casimersen-treated subjects ranges from < 24 weeks (n = 8; 10.5%) to >/= 144 weeks (n = 11; 14.5%). The median casimersen exposure in the group of all casimersen-treated subjects is 84.1 weeks (1.6 years).

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Note that the exposure to casimersen and to placebo in populations 1 and 2 are similar. In population 1, the median exposure to either casimersen or to placebo is approximately 1.6 years. In population 2, the median exposure in either group is approximately 1.5 years. The reason for the slightly decreased median exposure in the 100 subjects in population 2 is that the double-blind period of study 4045-101 was planned to be 12 weeks in duration, in contrast to the much longer period of time that the 88 subjects in study 4045-301 were in the double-blind period of that study (median time of 78 to 79 weeks).

8.2.2. Relevant characteristics of the safety population

8.2.2.1. The Disposition, Demographic Characteristics, Extent of Diversity, and Disease Characteristics of Subjects in Study 4045-301

The Disposition of Subjects in Study 4045-301

The eligibility criteria for study 4045-301 included requirements that subjects: had DMD amenable to exon 45 skipping; were between 7 and 13 years of age; and had a 6-minute walk distance (6MWD) between 300 and 450 meters at both Screening and Baseline visits. These criteria defined the intended treatment population of patients with DMD amenable to exon 45 skipping, but they do not represent the full spectrum of that population. Patients with DMD commonly live into their twenties, and therefore the specified age range in this study accounts for a rather small percentage of the intended patient population. The study also enrolled an ambulatory population who had a 6MWD of at least 300 meters at Baseline. The majority of this study population would be expected to remain ambulatory during a longer study, as reported by McDonald and colleagues (2013) when they evaluated the status of subjects with DMD who received placebo (n = 57) during a 48-week phase 2b clinical trial.

The following table shows subject disposition for the 96-week randomized double-blind period of study 4045-301. All subjects denoted in the casimersen column received 30mg/kg by IV infusion once weekly.

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Table 31. Subject Disposition During 96-week Double-blind Period of Study 4045-301

	Placebo (N = 31) n (%)	Casimersen (N = 57) n (%)
Number of subjects who: [n, %]		
Completed 96-week period	7 (23%)	14 (25%)
Discontinued study	0	3 (5%)
Ongoing in 96-week period	24 (77%)	40 (70%)
Reasons for discontinuation		
Adverse event	0	0
Lost to follow-up	0	0
Protocol violation	0	0
Withdrawal by subject	0	2 (4%)
Withdrawal by investigator	0	0
Death	0	1 (2%)
Other reason	0	0
Weeks Exposed in 96-week Period		
n	31	57
Mean (SD)	75.6 (22.1)	73.7 (24.5)
Median	81.0	81.0
Min, Max	19.1, 96.0	7.4, 95.4

[Source: ISS Table 1.1.1]

Details about the fatal case will be provided further below.

<u>Demographic Characteristics and Ethnic Diversity of Subjects in Study 4045-301</u>
Demographic characteristics of the 88 subjects who were in the 96-week double-blind period of study 4045-301 are tabulated below. Casimersen was administered weekly by IV infusion at a dose of 30mg/kg.

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Table 32. Demographic Characteristics of Subjects in Study 4045-301

	Placebo (N = 31) n (%)	Casimersen (N = 57) n (%)
Gender		
Male	31 (100%)	57 (100%)
Female	0	0
Age (years)		
Mean (SD)	9.0 (1.9)	8.9 (2.0)
Min, Max	7, 13	7, 13
6 to < 9 years	15 (48%)	29 (51%)
9 to < 12 years	12 (39%)	19 (33%)
12 + years	4 (13%)	9 (16%)
White	27 (87%)	51 (90%)
Black / African-American	0	0
Asian	0	5 (9%)
American Indian / Alaskan	0	0
Native Hawaiian / Pacific Islander	0	1 (2%)
Other / Missing	4 (13%)	0
Ethnicity		
Hispanic or Latino	3 (10%)	2 (4%)
Not Hispanic or Latino	26 (84%)	53 (93%)
Not reported / Unknown / Missing	2 (6%)	2 (4%)

[Source: ISS, Table 2.1]

Clinical Reviewer's Comments

Regarding race and ethnicity, subjects were approximately 88% white, and their ethnicity was approximately 90% not of Hispanic or Latino origin. This suggests an imbalance of the subjects enrolled in this study in comparison to the anticipated wider demographics of treated patients in the marketplace if the product is approved. However, this potential imbalance is likely to be of no clinical consequence, because the mechanism of action of casimersen is to promote skipping of exon 45, and this mechanism should be independent of race or ethnicity. Given these considerations, there appears to be no demographic imbalance that would impact the results of study assessments.

Regarding this study's restricted age range and ambulatory status, it is possible that the potential clinical effects of casimersen and the rate of drug-associated adverse events may be different in the younger, ambulatory subjects of this study population versus an older, less ambulatory or non-ambulatory population. However, this possibility is not being tested in the interim analysis of dystrophin expression in the study. This possibility can be examined in PSURs that are submitted by the applicant if the product is approved.

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Baseline Disease Characteristics of DMD and its Treatment During Study 4045-301

Below is depicted a series of features regarding DMD and its treatment in the 88 subjects who were in the 96-week randomized, double-blind, placebo-controlled period of study.

Table 33. Baseline Characteristics of DMD and its Treatment in Study 4045-301

	Placebo (N = 31) n (%)	Casimersen (N = 57) n (%)
Time since DMD Diagnosis (months)		
Mean (SD)	64.0 (30.4)	61.9 (34.6)
Median	53.4	59.6
Min, Max	5.8, 141.8	2.2, 152.5
Corticosteroid Type		
Deflazacort	24 (77%)	35 (61%)
Prednisone	6 (19%)	20 (35%)
None	1 (3%)	2 (4%)
Corticosteroid Frequency		
Daily	28 (90%)	46 (81%)
Intermittent	2 (7%)	9 (16%)
None	1 (3%)	2 (4%)

[Source: ISS, Table 2.1]

Clinical Reviewer's Comment
The time from diagnosis of DMD until study enrollment and the proportion of subjects with daily corticosteroid use are similar. The minor differences should not affect the results of efficacy or safety measure.

8.2.2.2 Treatment Compliance, Concomitant Medications, and Rescue Medication Use

As can be anticipated for a lengthy study of subjects with DMD, a wide variety of concomitant medications were used. The following table lists concomitant medications that potentially improve cardiac or muscle function in subjects with DMD. Per inclusion criterion 6 for study 4045-301, study participants who took these particular medications must have been on a stable dose for at least 12 weeks prior to study entry, and the dose was expected to remain constant during the study.

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Table 34. Concomitant Medications that Potentially Improve Cardiac or Muscle Function in Subjects with DMD

Drug Class or Agent	Placebo (N = 31) n (%)	Casimersen (N = 57) n (%)
ACE Inhibitors	14 (45%)	24 (42%)
Angiotensin Receptor Blockers (ARBs)	0	3 (4%)
Beta-adrenergic Receptor Blockers	2 (%)	3 (5%)
Aldosterone Receptor Antagonists	4 (13%)	4 (7%)
Oral Potassium	0	0
Coenzyme Q	0	0
Systemic Aminoglycosides	1 (3%)	0
Somatotropin	0	1 (2%)

[Source: ISS, Table 2.2]

Clinical Reviewer's Comments

The distribution of these concomitant medications across the two treatment groups is roughly the same. For that reason, the potential ability of these agents to affect cardiac or muscle function should also be roughly the same in the two groups. Although these comments apply to a greater extent in evaluating the clinical efficacy of casimersen in a confirmatory study, they also apply to the evaluation of safety, below.

8.2.2.3. Effect of Renal Impairment on Casimersen's PK Profile

Other ASOs with a similar molecular backbone to casimersen (i.e., Exondys 51 and Vyondys 53) are eliminated primarily renally. The applicant has conducted a renal impairment study (4045-103) of casimersen in adult subjects with stage 2 and stage 3 CKD compared to adult subjects with normal renal function. The mean geometric ratio of C_{max} was similar in subjects with stage 2 CKD and in subjects with normal renal function; there was an increased mean geometric ratio of C_{max} in subjects with stage 3 CKD compared to those with normal renal function (1.24 X). The mean geometric ratio of AUC_{0-t} was increased in subjects with stage 2 CKD (1.22 X) and in subjects with stage 3 CKD (1.79 X) when compared to subjects with normal renal function.

Clinical Reviewer's Comments

These results suggest that renal clearance of casimersen is reduced in otherwise healthy adults who have renal impairment based on estimated creatinine. However, because of the effect of reduced skeletal muscle mass on creatinine measurements in patients with DMD, it is difficult to make recommendations for specific dosage adjustments of casimersen, should it be approved, in patients who have both DMD amenable to exon 45 skipping and renal impairment.

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8.2.3. Adequacy of the safety database

The size of the safety database for casimersen is similar to or larger than the safety databases of other ASOs that have been deemed adequate for accelerated approval in specific populations of patients with DMD. In the pre-NDA meeting of 6/5/19, FDA agreed in principle about the adequacy of the applicant's proposed size of the safety database, which was similar in size to the database that was submitted in this NDA.

Clinical Reviewer's Comment
This reviewer judges that the safety database submitted in this NDA is adequate in size for this purpose.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The data integrity of the submission appears to be adequate and acceptable. As one example of data integrity, treatment-emergent adverse events (TEAEs) were reported for subjects from each of the sites in study 4045-101.

It is not possible to evaluate the site reporting rate of TEAEs in the sites in ongoing study 4045-301, because all sites have been de-identified by using a single site ID (i.e., site 999) for every site in that study, and every subject has been de-identified as well. This de-identification procedure was used in order to prevent un-blinding of the applicant's study team members, because some sites had few enrolled subjects. The procedure was agreed by FDA at the pre-NDA meeting on 6/5/19. Nevertheless, TEAEs are listed in ADAE.xpt for 85 subjects out of the total number of 88 subjects who were enrolled as of the cut-off date in population 1, which consists of the randomized, double-blind, placebo-controlled period of study 4045-301. This number of subjects with reported TEAEs provides an indirect way to surmise site reporting rates for this study.

Clinical Reviewer's Comments
The quality of the applicant's submission is adequate and acceptable. The contents are organized per standard eCTD specifications, and all items that were agreed during the pre-NDA meeting have been included. Few Information Requests have been needed in order to obtain unsubmitted materials, or to find and to interpret submitted materials.

8.3.2. Categorization of Adverse Events

8.3.2.1 Definitions, Coding, Capture, and Follow-up for Non-serious and Serious TEAEs in

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Studies 4045-101 and 4045-301

In the adverse events section of each study protocol, non-serious and serious adverse events were defined in accordance with ICH Topic E2a, 1995 and with FDA's 2012 guidance, *Safety Reporting Requirements for INDs and BA/BE Studies*. TEAEs were "defined as an AE that started or worsened or became serious on or after the start of first infusion of study treatment and occurred within 28 days after last infusion [section 8.1.1, SAP]." Events were coded per MedDRA version 17.1, and in general the event terms were split rather than lumped. This reviewer judges that the verbatim terms were coded correctly.

The relationship of each event to the investigational product, or to a study procedure, or to the underlying condition of DMD was graded by the investigator as unrelated, possibly/probably related, or definitely related. The severity of each event was graded per the following definitions:

1. Mild: The event does not interfere with the subject's usual activities.
2. Moderate: The event interferes with the subject's usual activities.
3. Severe: The event prevents the subject from undertaking their usual activities and requires therapeutic intervention or cessation of the study treatment.

Note that the Common Terminology Criteria for adverse Events (CTCAE) were not used to grade adverse event severity.

All adverse events were captured between the time that each subject signed the informed consent until the subject completes the last follow-up visit of the study, or until 28 days after the last study drug infusion for subjects who discontinued before the end of the study. Adverse events were also captured at any time after the end of the study if the investigator became aware of an event that was possibly, probably, or definitely related to the drug product. TEAEs were defined as either new events that arose during the capture period, or as events that were present at Baseline but that worsened during the capture period. Adverse events for each subject were followed until the earliest of: resolution of the event; the subject's completion of the study; or the termination of the study.

8.3.2.2 Analyses and Summary of Adverse Events

The applicant used MedDRA SMQs to evaluate the identified and potential risks that are listed in section 8.1. Summaries of non-serious and serious adverse events were displayed as the event frequency per subject; multiple events of the same type in an individual subject were summarized only once for that subject.

The applicant calculated an exposure-adjusted incidence rate (EAIR) to account for the

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exposure to study drug in the subjects who experienced TEAEs.

Clinical Reviewer's Comments
The applicant's capture, coding, follow-up, and analyses of non-serious and serious adverse events and the applicant's methods of their analysis are adequate and acceptable. Although the severity of adverse events was not graded using CTCAE criteria, the above-cited definitions for the three grades of severity (i.e., mild, moderate, and severe) are similar to those for CTCAE grades 1, 2, and 3, respectively.

8.3.3. Routine Clinical Tests

See the Schedules of Events for each period of study 4045-301 in Section 6.1.1 (subsection on Trial Design). During the 96-week randomized, double-blind, placebo-controlled period, lab assessments were made weekly through Week 8; at Week 12; then every 8 weeks through Week 48; and then every 12 weeks through Week 96. During the subsequent 48-week open-label period, lab assessments were made weekly through Week 8; at Week 12; and then every 12 weeks through week 48.

The safety labs assessed clinical analytes, hematological parameters, coagulation, and urine parameters. The specific assessments are shown below.

Table 35. Safety Lab Assessments During Study 4045-301

Chemistry:	Sodium, chloride, potassium, calcium, glucose, creatinine, blood urea nitrogen (BUN), albumin, uric acid, total bilirubin, alkaline phosphatase, amylase, ALT, AST, gamma-glutamyl transferase (GGT), LDH, C-reactive protein (CRP), CK, and serum cystatin C
Hematology:	Red blood cells (RBCs), total white blood cells (WBCs), hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and abnormal cells
Coagulation Screen:	Prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time (aPTT)
Urinalysis:	pH, specific gravity, protein, glucose, ketones, cytology, hemoglobin, and KIM-1

[Source: Protocol for Study 4045-301, section 10.4.3]

In the table above, KIM-1 is the abbreviation for Kidney Injury Molecule 1. KIM-1 is a transmembrane protein that is found in the renal tubule. Kim-1 protein is elevated in the presence of renal tubule injury, and it is a biomarker for kidney injury (Han et al., 2002). This

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biomarker of renal tubule injury and other urine parameters are assessed much more frequently in study 4045-301 than in many studies in other therapeutic indications, for two reasons. First, renal injury is an identified risk for other ASOs used to treat targeted patient populations within DMD (e.g., Vyondys 53); and second, "scattered multifocal renal tubule degeneration" was identified by microscopic observation in toxicology studies of casimersen-treated rats.

Serum cystatin-C is a less commonly used assessment in many studies. Assessment of this molecule provides a way to detect early declines in renal function in both children and adults, and the presence of this marker is not influenced by serum creatinine (Grubb, 2017). This latter factor makes this marker particularly useful in the assessment of renal function in patients with DMD, in whom creatinine measurements provide less reliable assessments of renal function due to decreased skeletal muscle mass.

All safety lab assessments are made by a central laboratory [redacted] (b) (4) The criteria used to define abnormal values of the labs shown in the table above are provided in Appendix Tables 1 – 3 in the applicant's Statistical Analysis Plan (section 15). They will not be reproduced in this document.

When abnormal laboratory values are identified, each site investigator judges them as Clinically Significant (CS) or Not Clinically Significant (NCS). Clinical significance is defined by any lab abnormality that requires a change in medical management. Any lab abnormality that meets clinical significance is followed until that abnormality returns to normal levels, or to the Baseline value for that subject.

Vital Signs, ECGs, and Echocardiography (ECHO) parameters were also assessed during the study. The Schedule of Assessments show the visits at which these assessments were made. PCSA values for each parameter were pre-specified in the SAP.

Clinical Reviewer's Comments

The frequency and types of safety lab assessments are adequate and acceptable. In particular, the frequent assessment of serum cystatin C, urine KIM-1, and other urine parameters helps to ensure that potential renal injury and/or decline in renal function can be identified early in their clinical course.

The defined criteria for lab abnormalities are acceptable to this reviewer in their entirety. Of particular note, the definition for abnormal urine protein is any protein > 1+. This threshold for abnormality is also acceptable. The definitions of a clinically significant abnormal lab value and the procedure used by site investigators to follow lab abnormalities for each subject are also acceptable.

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8.4. Safety Results

Sections 8.4.1 through 8.6 will evaluate safety findings from the database that was submitted on 1/10/20, with a reporting cut-off date of 5/31/19. Section 8.7 will evaluate additional findings from the 120-day safety update report, which covers the period from 6/1/19 through 2/28/20.

8.4.1. Deaths

There was a single death in study 4045-301 and no deaths in other studies.

Subject 4045-301. (b) (6) died during study 4045-301, with SAEs of cardiac arrest, hyperkalemia, and rhabdomyolysis. This 10-year-old male subject enrolled into the study in January 2018 and he was assigned to casimersen treatment. In addition to DMD, current conditions included hypertension, contractures, and a Cushingoid appearance. Concomitant medications included deflazacort, omeprazole, zinc, and several vitamins. On Day 400 he underwent surgical placement of a central venous port under sevoflurane general anesthesia, with additional IV fentanyl and propofol. Soon after extubation following surgery, he complained of severe muscle pain, and within minutes he developed cardiac arrest with asystole. He was resuscitated after approximately 15 minutes. A few minutes later he developed ventricular fibrillation, from which he was also resuscitated. During the resuscitation efforts he was hyperkalemic, with the highest recorded value of 9.1 mM (reference range 3.4 – 5.4 mM). Following resuscitation he was noted to have chromaturia, and the hyperkalemia was attributed to rhabdomyolysis. He had fixed dilated pupils following the resuscitation, and four days later brain death was confirmed. No autopsy was performed. The investigator attributed the three SAEs to the subject's study procedure and to his underlying condition of DMD.

Clinical Reviewer's Comments
Rhabdomyolysis is known to be more common in patients with DMD after general anesthesia, including anesthesia using sevoflurane. Rhabdomyolysis has also been reported following administration of fentanyl or propofol. Hyperkalemia is a cardinal feature of rhabdomyolysis, and the profound hyperkalemia that was identified in this subject likely contributed to cardiac arrest. The length of time needed to resuscitate the subject from cardiac arrest (described as at least 15 minutes) caused central ischemia/hypoxia and brain death. This reviewer agrees that the three SAEs were a complication of the surgical procedure, in combination with the underlying condition of DMD.

8.4.2. Serious Adverse Events

8.4.2.1 Display of Treatment-emergent SAEs by Populations and Treatment Groups in Studies

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4045-101, 4045-301, and 4045-302

All treatment-emergent serious adverse events in studies 4045-101, 4045-301, and 4045-302 were reviewed by using JMP Clinical 7.1 and the applicant's ADAE.xpt file. This reviewer verified all data contained in the applicant's overall summary of these SAEs (ISS Table 10.1), which is organized by MedDRA hierarchy (version 17.1). Individual subject narratives were also reviewed.

Because the applicant's ISS table 10.1 has been verified, this table of SAEs is presented below.

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Table 36. Treatment-emergent SAEs in Studies 4045-101, 4045-301, and 4045-302

	POP1 (Double-Blind Period of 4045-301)		POP2 (Double-Blind Period of 4045-101 & 4045-301)		POP3 (Casimersen Treatment Period of 4045-101, 4045-301 & 4045-302)
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=31)	Casimersen 30 mg/kg (N=57)	Placebo (N=35)	Casimersen (N=65)	All Casimersen (N=76)
Number of Patients with at Least One Treatment-Emergent Serious Adverse Event	6 (19.4%)	12 (21.1%)	6 (17.1%)	13 (20.0%)	17 (22.4%)
CARDIAC DISORDERS	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Cardiac arrest	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Hydrocele	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
EYE DISORDERS	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Papilloedema	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
GASTROINTESTINAL DISORDERS	1 (3.2%)	0	1 (2.9%)	0	1 (1.3%)
Hiatus hernia	0	0	0	0	1 (1.3%)
Oesophageal food impaction	1 (3.2%)	0	1 (2.9%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3.2%)	0	1 (2.9%)	0	1 (1.3%)
Chest pain	0	0	0	0	1 (1.3%)
Non-cardiac chest pain	1 (3.2%)	0	1 (2.9%)	0	0
INFECTIONS AND INFESTATIONS	1 (3.2%)	4 (7.0%)	1 (2.9%)	5 (7.7%)	5 (6.6%)
Bacteraemia	0	0	0	1 (1.5%)	1 (1.3%)
Gastrointestinal viral infection	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Influenza	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Otitis media chronic	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Pneumonia	1 (3.2%)	0	1 (2.9%)	0	0
Septic embolus	0	0	0	1 (1.5%)	1 (1.3%)
Viral infection	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (9.7%)	2 (3.5%)	3 (8.6%)	2 (3.1%)	4 (5.3%)
Fall	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Femur fracture	0	2 (3.5%)	0	2 (3.1%)	3 (3.9%)
Hand fracture	1 (3.2%)	0	1 (2.9%)	0	0
Lower limb fracture	1 (3.2%)	0	1 (2.9%)	0	0
Lumbar vertebral fracture	1 (3.2%)	0	1 (2.9%)	0	0
Tibia fracture	0	0	0	0	1 (1.3%)
INVESTIGATIONS	1 (3.2%)	2 (3.5%)	1 (2.9%)	2 (3.1%)	2 (2.6%)
Intraocular pressure increased	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Troponin T increased	1 (3.2%)	0	1 (2.9%)	0	0
Urine protein/creatinine ratio increased	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
METABOLISM AND NUTRITION DISORDERS	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Hyperkalaemia	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (3.2%)	4 (7.0%)	1 (2.9%)	4 (6.2%)	4 (5.3%)
Rhabdomyolysis	1 (3.2%)	4 (7.0%)	1 (2.9%)	4 (6.2%)	4 (5.3%)
VASCULAR DISORDERS	0	0	0	1 (1.5%)	1 (1.3%)
Vena cava thrombosis	0	0	0	1 (1.5%)	1 (1.3%)

Data Cutoff: 31-May-2019, 4045-101 Data Extraction: 10-Dec-2018, 4045-301 Data Extraction: 09-Jul-2019, 4045-302 Data Extraction: 05-Jul-2019.
Note: Adverse Events are coded using MedDRA dictionary version 17.1. Adverse events are attributed to the treatment received at the start of the adverse event. Treatment-emergent adverse events are those starting during or after the first infusion of study drug or within 28 days after the last infusion. Patients who experienced a coded event more than once are only counted once per treatment received.
Note: For POP1 and POP2, only events that occurred during the double-blind period of the studies are included.

[Source: ISS Table 10.1]

A brief inspection of this table shows that the overall proportion of subjects with SAEs in the

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casimersen and placebo treatment groups are similar. In the all-placebo group of population 2 (n = 35), 17% of subjects had at least one reported SAE. To provide a comparable comparison group, 20% of casimersen-treated subjects in population 2 (n = 65) had at least one reported SAE. In the largest all-casimersen group (n = 76), 22% of subjects had at least one reported SAE. In-depth analyses of SAEs are presented below, first by individual subjects, then by treatment groups, and finally by this clinical reviewer's judgement about the relatedness of these events.

8.4.2.2 Individual Subjects with the Most Clinically Noteworthy SAEs

All SAEs are clinically noteworthy events. However, when one compares the table above to a listing of SAEs by subject, a number of subjects stand out as having the most clinically noteworthy events.

1. The first subject is 4045-301. (b) (6), who had ultimately fatal SAEs of rhabdomyolysis, hyperkalemia, and cardiac arrest. His case is discussed in the section above.

2. The second subject is 4045-101 (b) (6), who had SAEs of bacteremia, septic embolus, and vena cava thrombosis. The narrative of this case is as follows.

   This 10-year-old subject was enrolled in (b) (6) and he was assigned to casimersen treatment. In addition to DMD, current conditions included GERD, obesity, steroid-induced aggression, and a Cushingoid habitus. Concomitant medications included deflazacort, CoQ10, metformin, fish oil, TUMS, fluoxetine, Vitamin D, Vitamin C, and multivitamins. He had an elevated WBC before randomization, and at multiple assessments before onset of the reported SAEs. A central venous port was surgically placed on Day 39. On Day 52 he developed an upper respiratory infection, and on Day 57 he was treated in an emergency room setting for bacteremia. On Day 58 he was hospitalized with a septic embolus to the lungs. An ECHO showed a superior vena cava thrombosis. The central port was removed. After treatment with a variety of antibiotics and alteplase, all events resolved. The investigator judged that the SAEs were not related to study drug.

   Clinical Reviewer's Comment
   In this reviewer's judgment, these SAEs were likely associated with the presence of a central venous port. An alternative possibility is that the elevated WBC that persisted from Screening through the onset of the SAEs may have heralded a bacteremia that was already present before port placement and before the reported onset of these events. At any rate, this reviewer agrees that the SAEs in this case are not related to casimersen treatment.

3. Five other subjects with rhabdomyolysis will be discussed in section 8.5.

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4. Other subjects with potential cardiac-associated events (two separate cases of chest pain and of non-cardiac chest pain / increased troponin T), and with potential nephrotoxicity (urine protein/creatinine ratio increased) will also be discussed in section 8.5.

8.4.2.3. Higher-level Analyses of SAEs by Treatment Groups and by Subgroups

Turning now to a higher-level analysis of SAEs by treatment groups, the proportion of subjects with reported SAEs in each treatment group of population 1 (i.e., the 96-week randomized, placebo-controlled period of study 4045-301) and in population 3 (i.e., all casimersen-treated subjects) is shown in the table below. The number of SAEs by population and by treatment group is also shown; note that some subjects experienced more than 1 SAE.

Table 37. Proportion of Subjects with SAEs and Numbers of SAEs by Treatment Group

	Population 1		Population 3
Treatment Group	Placebo (N = 31)	Casimersen (N = 57)	Casimersen (N = 76)
Proportion of subjects with SAEs n (%)	6 (19%)	12 (21%)	17 (22%)
Number of SAEs n (%)	8 (26%)	17 (30%)	24 (32%)

[Source: Clinical Reviewer's cross-reference between applicant's ISS Table 10.1 and analyses using JMP Clinical 7.1 with applicant's ADAE.xpt file]

Note that the proportion of subjects with SAEs is similar across treatment groups. However, note also the number of SAEs. This SAE rate appears to increase across treatment groups: from 26% in the population 1 placebo group; to 30% in the population 1 casimersen group; and then to 32% in the population 3casimersen group.

Clinical Reviewer's Comments
This apparent increase in the number of SAEs across groups is artifactual when one considers the following data for each treatment group.

1. *In the population 1 placebo group, there is a subject who had two SAEs that occurred at the same time and are interconnected (non-cardiac chest pain and troponin T increased). If one treated these interconnected events as one event, then the population 1 placebo group would have 7 SAEs (23%).*

2. *In the population 1 casimersen group, there were two subjects with SAEs that occurred*

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at the same time. One subject had simultaneous events of papilledema and increased intraocular pressure; and one subject had simultaneous and ultimately fatal events of rhabdomyolysis, hyperkalemia, and cardiac arrest (described further in the section above). If one treated the interconnected events for each subject as one event per subject, then the population 1 casimersen group would have 14 SAEs (25%).

3. *The population 3 all-casimersen group includes the two casimersen-treated subjects from population 1, each of whom had with simultaneous events (cited in point 2, above). Population 3 also includes a casimersen-treated subject with three simultaneous events from population 2 (bacteremia, septic embolus, and vena cava thrombosis). If one treated the interconnected events for each subject as one event per subject, then population 3 would have 19 SAEs (25%).*

8.4.2.4. Evaluation of SAEs by SOCs and by Subgroups in Studies 4045-101, 4045-301, and 4045-302

Evaluation of the SOCs with SAEs provides a useful start to the between-groups comparison of SAEs. The following table depicts these SOCs by treatment group and by the numbers of SAEs within each SOC. Note that the reviewer's strategy is to use the population 2 placebo group, because it contains the entire placebo dataset from the studies (n = 35); and for a similar reason, to use the population 3 casimersen group, because it contains the entire casimersen dataset from the studies (n = 76).

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Table 38. Proportion of Subjects with SAEs within Each Treatment Group by SOC

Every SOC with SAEs n (%)	Population 2 Placebo Group N = 35	Population 3 Casimersen Group N = 76
Cardiac	0	1 (1%)
Congenital / Familial Genetic	0	1 (1%)
Eye	0	1 (1%)
Gastrointestinal	1 (3%)	1 (1%)
General Disorders/ Administration Site Conditions	1 (3%)	1 (1%)
Infections / Infestations	1 (3%)	5 (7%)
Injury / Poisoning / Procedures	3 (10) Comment: all fractures	4 (5%) Comment: all fractures)
Investigations	1 (3%)	2 (3%)
Metabolism/Nutrition		1 (1%)
Musculoskeletal	1 (3%) Comment: rhabdomyolysis	4 (5%) Comment: all rhabdomyolysis
Vascular	0	1 (1%)

[Source: Clinical reviewer's use of ISS Table 10.1]

Clinical Reviewer's Comments

The numbers and percentages of SAEs in each SOC are small, and in most SOCs a between-groups comparison does not appear to show a risk that is greater for casimersen-treated subjects than for placebo-treated subjects. Two SOCs may warrant a closer inspection: Musculoskeletal Disorders; and Infections and Infestations.

Rhabdomyolysis was the only SAE in the Musculoskeletal SOC, and approximately twice the proportion of subjects with rhabdomyolysis were in casimersen-treated subjects when compared to placebo-treated subjects. This apparent increase in the casimersen group is somewhat reduced by additional data from non-serious treatment-emergent adverse events. There was one additional non-serious case of rhabdomyolysis in a placebo-treated subject, but no non-serious cases in the casimersen group. Rhabdomyolysis will be evaluated in greater detail in section 8.5.

In the infections and Infestations SOC, 5 subjects (7%) in the casimersen group and 1 subject (3%) in the placebo group had an SAE associated with infection. However, 1 of the subjects in the casimersen group, subject 4045-101 (b) (6) *, had two concurrent SAEs of bacteremia and septic embolus in this SOC, and a third concurrent SAE of vena cava thrombosis in the Vascular Disorders SOC. This case is discussed above. These SAEs occurred after surgical placement of a central venous port, and therefore they are port-related events and do not represent the*

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development of idiopathic infections. If this subject is omitted from the casimersen group to examine only subjects with idiopathic infections, then 4 casimersen-treated subjects (5%) had SAEs of infections, vs. 3% of placebo-treated subjects. The possibility that casimersen-treated subjects may have a higher risk of infections than placebo-treated subjects is discussed further below.

8.4.2.5. Analysis of Potential Relatedness of the SAEs in Studies 4045-101, 4045-301, and 4045-302

The following assessments by this reviewer of relatedness are segregated into a brief discussion of potential relatedness to study drug, to study procedures, and to the underlying condition of DMD.

1. Potentially Related to Study Drug
   There are no reported SAEs in placebo-treated subjects that appear to this reviewer to be related to study drug. However, there is one SAE in casimersen-treated subjects that may be related to casimersen. Subject 4045-301 (b) (6) had a reported SAE of urine protein/creatinine ratio increased. In view of the identified risk of kidney injury in subjects treated with Vyondys 53, which shares a similar molecular backbone with casimersen, and in keeping with the renal findings in casimersen-treated rats in nonclinical studies, this SAE may be related to casimersen.

2. Potentially Related to Study Procedures
   There are no reported SAEs in placebo-treated subjects that appear to be related to study procedures. One subject has three interconnected SAEs that appear to be related to a surgical port placement. Following this surgical procedure, subject 4045-101. (b) (6) developed SAEs of bacteremia, septic embolus, and vena cava thrombosis. This subject will be discussed in greater detail in the next section.

3. Underlying DMD
   There are a number of SAEs in both treatment groups that appear to be related to the underlying condition of DMD. In the placebo group, these include three subjects with fractures, a subject with pneumonia, a subject with esophageal food impaction (i.e., a possible result of swallowing dysfunction, which is common in DMD), and a subject with rhabdomyolysis. In the casimersen group, there were four subjects with SAEs of fractures, four with SAEs of rhabdomyolysis, and three subjects with SAEs of infection.

   Clinical Reviewer's Comment
   There does not appear to be an imbalance in potential relatedness of the reported SAEs to study drug. However, and as could be anticipated, there are a number of SAEs in each treatment group that appear to be related to study procedures or to the subjects'

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underlying condition of DMD.

8.4.2.6. Studies 4045-102 and 4045-103 in Healthy Adults and in Adults with CKD but without DMD

There were no SAEs in either study.

Clinical Reviewer's Overall Comments about SAEs in the Total Safety Database
On face, the distribution of SAEs across treatment groups in subjects with DMD appears to be similar. There are a few SAEs that may appear to be unbalanced (e.g., rhabdomyolysis in five subjects, four of whom are in the casimersen treatment group). These cases will be discussed in section 8.5.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

8.4.3.1 Discontinuations due to Adverse Events

As of the cut-off date of 5/31/19, there were no discontinuations due to adverse events in studies 4045-101, 4045-301, or 4045-302, which evaluated subjects with DMD. There were no discontinuations due to adverse events in studies 4045-102 or 4045-103, which evaluated healthy adults and participants with CKD.

8.4.3.2. Drug Discontinuations

In the Summary of Clinical Safety (i.e., the ISS report for this submission), four subject discontinuations from the safety populations of studies 4045-101, 4045-301, and 4045-302 are shown in Table 11. These withdrawals are listed briefly below.

1. Subject 4045-101. (b) (6) discontinued while receiving casimersen during the 132-week open-label period of study 4045-101. The reason given is "withdrawal by subject." There were no TEAEs within two years of the subject's withdrawal.

2. Subject 4045-301. (b) (6) discontinued while receiving casimersen during the 96-week randomized, double-blind period of study 4045-301. The reason given is "withdrawal by subject." There were no TEAEs within four months of the subject's withdrawal.

3. Subject 4045-301. (b) (6) discontinued while receiving casimersen during the 96-week randomized, double-blind period of study 4045-301. The reason given is "withdrawal by subject." There were two TEAEs with a PT of cough, the first such event approximately

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four months before the subject's withdrawal, and the second such event approximately two months before withdrawal.

4. Subject 4045-301. (b) (6) died following the three nearly simultaneous SAEs of rhabdomyolysis, hyperkalemia, and cardiac arrest. The narrative for this subject is located above in section 8.4.1.

There were no discontinuations for any reason in studies 4045-102 or 4045-103.

Clinical Reviewer's Comments

Although it is possible that there were no discontinuations due to AEs as shown for studies 4045-101, 4045-301, or 4045-302, there were three subjects who discontinued due to "withdrawal by subject," and a fourth subject who discontinued due to death. All of these subjects were in the casimersen treatment arm during the randomized, double-blind part of study 4045-301. Considering the subject who died, the three SAEs that led to the fatality were judged by the investigator and by this clinical reviewer to be related to study procedure and underlying condition rather than to casimersen. Nevertheless, the subject was in the casimersen arm. Considering the three withdrawals by subject, the last reported TEAEs for each of these subjects were four months or more before withdrawal (for subjects 4045-101. (b) (6) and 4045-301. (b) (6)), or of minor clinical significance (i.e., two events of cough at four months and at two months before withdrawal) for subject 4045-301. (b) (6) It therefore appears that these subjects withdrew for reasons other than TEAEs.

For a worst-case analysis, this clinical reviewer evaluated the possibility that the three subject withdrawals were due to unrecognized TEAEs, and therefore that all four of the withdrawals were in some manner associated with casimersen treatment. The table below shows the use of Fisher's Exact Test to test the null hypothesis of no difference in the distribution of these four subjects with "TEAEs" across the total number of subjects treated in each group (i.e., casimersen, n = 76 treated; and placebo, n = 35 treated), using a 2 X 2 contingency table and a two-tailed alpha of 0.05. There was no reason to reject the null hypothesis (two-tailed p = 0.31).

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[Fisher's Exact Test 2x2]

	WITHDRAWALS YES	NO
CAS	4	72
PBO	0	35

Two-tailed: p = 0.3060
One-tailed: p = 0.2142

_/_/_/ Analyzed by JavaScript-STAR _/_/_/

[Source: clinical reviewer's use of a Fisher's Exact Test calculator for a 2 X 2 contingency table, located on the following website: http://www.kisnet.or.jp/nappa/software/star-e/freq/2x2.htm]

The total number of withdrawals was very small. Irrespective of how the withdrawals are analyzed, and even assuming the worst case that all withdrawals were associated with casimersen treatment, there are insufficient reasons to conclude that the potential imbalance is clinically noteworthy.

8.4.4. Other Significant Adverse Events

In this section, severe TEAEs will be presented first, and then those TEAEs which required study drug interruption but did not result in subject withdrawal.

There were no severe TEAEs and no other significant events in studies 4045-102 or 4045-103. The remainder of this section discusses these types of events for the three studies that enrolled subjects with DMD amenable to exon 45 skipping.

8.4.4.1. Severe Adverse Events in Studies 4045-101, 4045-301, and 4045-302

The following table shows all severe adverse events across the three studies.

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Table 39. Severe Adverse Events in Studies 4045-101, 4045-301, and 4045-302

System Organ Class Preferred Term	Population 1 (Double-Blind Period of Study 4045-301)		Population 2 (Double-Blind Period of Studies 4045-101 and 4045-301)		Population 3 (Casimersen Treatment Period of Studies 4045-101, 4045-301, and 4045-302)
	Placebo (N=31) n (%)	Casimersen 30 mg/kg (N=57) n (%)	Placebo (N=35) n (%)	Casimersen (N=65) n (%)	All Casimersen (N=76) n (%)
Number of patients with at least 1 severe treatment-emergent adverse event	3 (9.7)	4 (7.0)	3 (8.6)	5 (7.7)	6 (7.9)
Cardiac Disorders	**0**	**1 (1.8)**	**0**	**1 (1.5)**	**1 (1.3)**
Cardiac arrest	0	1 (1.8)	0	1 (1.5)	1 (1.3)
Gastrointestinal Disorders	**1 (3.2)**	**0**	**1 (2.9)**	**0**	**0**
Oesophageal food impaction	1 (3.2)	0	1 (2.9)	0	0
General Disorders and Administration Site Conditions	**0**	**1 (1.8)**	**0**	**1 (1.5)**	**2 (2.6)**
Chest pain	0	0	0	0	1 (1.3)
Device issue[a]	0	1 (1.8)	0	1 (1.5)	1 (1.3)
Infections and Infestations	**1 (3.2)**	**1 (1.8)**	**1 (2.9)**	**2 (3.1)**	**2 (2.6)**
Gastrointestinal viral infection	0	1 (1.8)	0	1 (1.5)	1 (1.3)
Pneumonia	1 (3.2)	0	1 (2.9)	0	0
Septic embolus	0	0	0	1 (1.5)	1 (1.3)
Injury, Poisoning and Procedural Complications	**1 (3.2)**	**1 (1.8)**	**1 (2.9)**	**1 (1.5)**	**1 (1.3)**
Femur fracture	0	1 (1.8)	0	1 (1.5)	1 (1.3)
Lower limb fracture	1 (3.2)	0	1 (2.9)	0	0
Metabolism and Nutrition Disorders	**0**	**1 (1.8)**	**0**	**1 (1.5)**	**1 (1.3)**
Hyperkalaemia	0	1 (1.8)	0	1 (1.5)	1 (1.3)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (1.8)**	**0**	**1 (1.5)**	**1 (1.3)**
Rhabdomyolysis	0	1 (1.8)	0	1 (1.5)	1 (1.3)
Psychiatric Disorders	**0**	**1 (1.8)**	**0**	**1 (1.5)**	**1 (1.3)**
Dysphemia	0	1 (1.8)	0	1 (1.5)	1 (1.3)
Vascular Disorders	**0**	**0**	**0**	**1 (1.5)**	**1 (1.3)**
Vena cava thrombosis	0	0	0	1 (1.5)	1 (1.3)

[a] Verbatim term is "Port Malfunction".

[Source: ISS Table 7.2]

The proportion of subjects with severe TEAEs is similar between the placebo and casimersen groups: 3 subjects (9%) out of all subjects treated with placebo (population 2); and 6 subjects (8%) out of all subjects treated with casimersen (population 3). All of the severe TEAEs were also SAEs, with the exception of two events of dysphemia and device issue.

A perusal of these severe events reveals the following events that, to this clinical reviewer, are the most clinically noteworthy.

1. Cardiac arrest, hyperkalemia and rhabdomyolysis, which were ultimately fatal in subject 4045-301. (b) (6) (narrative in section 8.4.1)

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2. Septic embolus and vena cava thrombosis in subject 4045-101 (b) (6) (narrative in section 8.4.2)

Clinical Reviewer's Comments
All but two of the severe TEAEs were also SAEs, and these events have either been discussed in sections 8.4.1 or 8.4.2, or they will be discussed in section 8.5. The proportion of subjects with severe TEAEs is approximately evenly distributed across the treatment groups.

8.4.4.2. Drug Interruptions

This clinical reviewer used the applicant's ADAE.xpt file to generate the following table of 15 subjects who had interruptions of study drug in studies 4045-101, 4045.301, or 4045.302. Although these subjects were derived from the xpt file that lists TEAEs, this xpt file includes all subjects who had a study drug interruption for any reason, whether a clinical TEAE, or a TEAE that was reported following a significant lab abnormality.

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Table 40. Subjects with Drug Interruptions in Studies 4045-101, 4045-301, or 4045-302

Subject ID	Treatment Group	Event by Preferred Term (number of weekly doses before event onset)	SAE: Yes / No
4045-101 (b) (6)	casimersen	Bacteremia / septic embolus / vena cava thrombosis (50 doses)	Yes
4045-301 (b) (6)	placebo	Influenza (12 doses)	No
4045-301 (b) (6)	casimersen	Viral infection (130 doses)	No
4045-301 (b) (6)	casimersen	Influenza (12 doses)	No
4045-301 (b) (6)	casimersen	Rhabdomyolysis (55 doses)	Yes
4045-301 (b) (6)	casimersen	Rhabdomyolysis (12 doses); Gastrointestinal infection (56 doses)	Yes; No
4045-301 (b) (6)	casimersen	Tachycardia (63 doses)	No
4045-301 (b) (6)	placebo	Noncardiac chest pain / increased troponin-T (60 doses)	Yes
4045-301 (b) (6)	casimersen	Urine protein/creatinine ratio increased (63 doses)	Yes
4045-301 (b) (6)	casimersen	Fall (37 doses); Femur fracture (73 doses)	Yes Yes
4045-301 (b) (6)	casimersen	Influenza (24 doses)	Yes
4045-301 (b) (6)	casimersen	Cough / fever (77 doses)	No
4045-301 (b) (6)	placebo	Rhabdomyolysis (88 doses)	Yes
4045-301 (b) (6)	casimersen	Otitis media, chronic (75 doses)	Yes
4045-301 (b) (6)	casimersen	Rhabdomyolysis (25 doses); Gastrointestinal infection (64 doses)	Yes; No
4045-301 (b) (6)	casimersen	Pyrexia (79 doses); Gastroenteritis (82 doses)	No; No
4045-301 (b) (6)	placebo	Rhabdomyolysis (35 doses)	No

[Source: clinical reviewer's use of ADAE.xpt]

Of the 17 subjects with drug interruptions, 4 of these subjects were in the placebo group and they constitute 11% of all placebo-treated subjects, and 13 were in the casimersen group and they constitute 17% of all subjects in that group. Half of the events that caused drug interruptions in the casimersen group were also SAEs, and these are discussed elsewhere.

Of the non-serious events in the casimersen group, none occurred before 12 weekly doses of casimersen had been administered, and nearly all occurred after 50 or more doses had been administered. Each drug interruption was followed within several weeks by resumption of study drug administration without recurrence of the event that precipitated the interruption.

Clinical Reviewer's Comments

Although the proportion of subjects with TEAEs that caused drug interruptions in the casimersen

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group (17%) is higher than that of the placebo group (11%), the events were primarily short-lived and they occurred well after the beginning of casimersen dosing. Moreover, the events did not return after casimersen dosing was re-started. These data appear to suggest that the events were not associated with prolonged exposure to casimersen, because otherwise a recurrence could be anticipated after resumption of treatment.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

This section will provide a description and interpretation of all non-serious and serious TEAEs in the safety populations of studies 4045-101, 4045-301, and 4045-302. First a broad summary of these events will be presented, followed by an evaluation of events by SOC, then the rate of exposure-adjusted TEAEs of significant clinical interest, and concluding with the Adverse Reactions Table that will be used in the Prescribing Information if casimersen is granted accelerated approval.

The reasons for omitting from further discussion the two single-dose studies 4045-102 (AME study in healthy adults) and 4045-103 (PK in healthy adults vs. CKD stages 2 and 3 are as follows. In study 4045-102, there were 8 non-serious TEAEs and no serious TEAEs. Of the 8 non-serious TEAEs, none occurred in more than 1 subject, and none was clinically noteworthy in the judgment of this clinical reviewer. In single-dose study 4045-103, there were no non-serious or serious TEAEs.

8.4.5.1. High-level Summary of TEAEs in Studies 4045-101, 4045-301, and 4045-302

The following table summarizes all TEAEs by treatment group in the safely populations of these studies, including their severity, relatedness, and seriousness, as well as events leading to discontinuation or death. Note that this table displays numbers of events, and not the proportion of subjects who experienced these events.

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Table 41. High-Level Summary of all TEAEs in Studies 4045-101, 4045-301, and 4045-302

	POP1 (Double-Blind Period of 4045-301)		POP2 (Double-Blind Period of 4045-101 & 4045-301)		POP3 (Casimersen Treatment Period of 4045-101, 4045-301 & 4045-302)
	Placebo (N=31)	Casimersen 30 mg/kg (N=57)	Placebo (N=35)	Casimersen (N=65)	All Casimersen (N=76)
Total Number of Treatment-Emergent Adverse Events	393	859	404	912	1124
Mild	358	772	369	819	1011
Moderate	32	80	32	84	103
Severe	3	7	3	9	10
Number of Patients with at Least One, n (%):					
Treatment-Emergent Adverse Event	30 (96.8%)	55 (96.5%)	34 (97.1%)	63 (96.9%)	71 (93.4%)
Severe Treatment-Emergent Adverse Event	3 (9.7%)	4 (7.0%)	3 (8.6%)	5 (7.7%)	6 (7.9%)
Treatment-Related Treatment-Emergent Adverse Event	9 (29.0%)	18 (31.6%)	10 (28.6%)	20 (30.8%)	22 (28.9%)
Treatment-Emergent Serious Adverse Event	6 (19.4%)	12 (21.1%)	6 (17.1%)	13 (20.0%)	17 (22.4%)
Treatment-Related Treatment-Emergent Serious Adverse Event	0	3 (5.3%)	0	3 (4.6%)	3 (3.9%)
Treatment-Emergent Adverse Event Leading to Discontinuation of Study Drug	0	0	0	0	0
Treatment-Emergent Adverse Event Leading to Death	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)

[Source: ISS Table 4.1]

At least one TEAE was reported in 97% of placebo-treated subjects (population 2)and in 93% of casimersen-treated subjects (population 3). The degree of severity of TEAEs was highly similar between the placebo and casimersen groups. The table below shows the degree of severity of these events, expressed as a percentage of the total number of events.

Table 42. Severity of TEAEs in Studies 4045-101, 4045-301, and 4045-302

Severity	Placebo Group (n = 35)	Casimersen Group (n = 76)
Mild	91%	90%
Moderate	8%	9%
Severe	1%	1%

[Source: Clinical Reviewer's use of ISS Table 4.1]

Clinical Reviewer's Comments
The degree of event severity is nearly identical across treatment groups.

8.4.5.2. TEAEs within each MedDRA SOC in Studies 4045-101, 4045-301, and 4045-302

The table below shows the proportion of subjects with non-serious and serious TEAEs within each MedDRA SOC. For combined terms (e.g., GI infections), the proportions are those for unique subjects within that set of combined terms. For SOCs in which the proportion of

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subjects was at least 3% greater in the casimersen (CAS) group than in the placebo (PBO) group, additional comments are made about the types of events in the casimersen-treated group that accounted for the difference. Other comments are made if warranted. All proportions shown in the table below include a single digit after the decimal report, as listed in ISS Table 5.1. However, in the discussion that follows, these proportions will be rounded down if the final digit is ≤ 4, and rounded up if the final digit is ≥ 5.

Table 43. Subjects with at Least One TEAE in each MedDRA SOC for Studies 4045-101, 4045-301, and 4045-302

MedDRA SOC	Proportion (%) in Placebo Group (N = 35)	Proportion (%) in Casimersen Group (N = 76)	Comments
Blood and Lymphatic System	2.9%	1.3%	
Cardiac Disorders	5.7%	10.5%	No event was reported in more than 1 subject
Congenital, Familial, and Genetic	0	2.6%	
Ear and Labyrinth Disorders	5.7%	10.5%	Ear pain: 2.9% PBO vs. 7.9% CAS
Endocrine	2.9%	5.3%	
Eye	2.9%	13.2%	Cataract: 0 PBO vs. 5.3% CAS
Gastrointestinal	54.3%	59.2%	Abdominal Pain Upper[1]: 8.6% PBO vs. 15.8% CAS
General Disorders and Administration Site Conditions	37.1%	50.0%	CAS ≥ 3% more than PBO in these events: Abasia: 0 PBO vs. 3.9% CAS Fatigue: 2.9% vs. 6.6% Malaise: 0 vs. 3.9% Pyrexia: 20.0% vs. 31.6%
Immune System	8.6%	7.9%	
Infections and Infestations	74.3%	81.6%	CAS ≥ 3% more than PBO in these events: Bronchitis: 2.9% vs. 6.6% Ear Infec. / Ear Infec. viral: 2.9% vs. 9.2% GI Infections[2]: 14.3% vs. 19.7%

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			Upper respiratory tract infection (URTI) / viral URTI: 11.4% vs. 26.3% Viral infection: 0 vs. 5.3%
Injury, Poisoning, and Procedural Complications	62.9%	61.8%	
Investigations	8.6%	19.7%	Only two events with > 2-subject difference: Neutrophil count increased: 0 PBO vs. 2.6% CAS White Blood Cell Count Increased: 0 PBO vs. 2.6% CAS
Metabolism and Nutrition	2.9%	7.9%	Only one event with > 2-subject difference: Decreased appetite: 0 PBO vs. 2.6% CAS
Musculoskeletal	54.3%	52.6%	For other sections, note: Rhabdomyolysis: 5.7% PBO vs. 5.3% CAS Back pain: 22.9% PBO vs. 22.4% CAS Arthralgia: 8.6% PBO vs. 17.1% CAS
Neoplasms Benign, Malignant, Unspecified	5.7%	5.3%	Only term: skin papilloma
Nervous System	22.9%	44.7%	Headache/Cluster/Migraine: 17.1% PBO vs. 32.9% CAS Dizziness: 5.7% PBO vs. 13.2% CAS
Psychiatric	11.4%	13.2%	
Renal and Urinary	8.6%	11.8%	Proteinuria / Protein Urine Present [latter from Investigations SOC]: 0 PBO vs. 6.6% CAS
Respiratory, Thoracic, and Mediastinal	54.3%	56.6%	For other sections, note: Cough: 22.9% PBO vs. 32.9% CAS
	37.1%	32.9%	For other sections, note:

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Skin and Subcutaneous			Rash/rash generalized/rash pruritic: 14.3% PBO vs. 9.2% CAS
Social Circumstances	0	1.3%	
Surgical and Medical Procedures	2.9%	1.3%	
Vascular	2.9%	10.5%	Hematoma: 0 PBO vs. 3.9% CAS Flushing: 2.9% PBO vs. 5.3% CAS

[1] Abdominal pain upper is the only event term that is higher in casimersen-treated than placebo-treated subjects in the grouping of abdominal pain, abdominal discomfort, and abdominal pain upper

[2] The grouping termed GI Infections contains 5 event terms of: enterobiasis, gastroenteritis, gastrointestinal viral, gastrointestinal infection, and gastrointestinal viral infection.

[Source: Reviewer's use of ISS Table 5.1]

There are several observations to note from this table.

1. In the General Disorders and Administration Site Conditions SOC, pyrexia was reported in 20% of subjects in the placebo group and in 32% of subjects in the casimersen group. In comparing the higher rate of pyrexia in the casimersen group to the rate of infections in the casimersen group, three events of infection occur at higher proportions in the casimersen group: the sum of GI infection terms (14%, placebo vs. 20%, casimersen)[2]; upper respiratory tract infections (11%, placebo vs. 26%, casimersen); ear infections (3%, placebo vs. 9%, casimersen), and viral infections (0, placebo vs. 5%, casimersen). These infections are commonly associated with pyrexia.

   Clinical Reviewer's Comment
   These infections bear further scrutiny as additional safety data are submitted from ongoing studies 4045-301 and 4045-302.

2. In the Neurology Disorders SOC, dizziness (6%, placebo vs. 13%, casimersen) and headache/cluster/migraine (17%, placebo vs. 33%, casimersen) were reported at higher rates in the casimersen group in the Neurology SOC.

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Clinical Reviewer's Comment
Although headaches are common in any population, this event and the event of dizziness bear further scrutiny as additional safety data are submitted from ongoing studies 4045-301 and 4045-302.

3. In the Renal Disorders SOC, the event terms of proteinuria or protein urine increased were not reported in any subject in the placebo group, but in 7% of subjects in the casimersen group. Laboratory findings of increased urine protein are described in section 8.4.5. TEAEs and lab findings that may suggest a potential for renal injury are discussed in section 8.5.

   Clinical Reviewer's Comment
   Because renal injury is an identified risk for other ASOs, and because renal findings were observed in casimersen-treated rodents and non-human primates in repeat-dose toxicology studies, kidney injury will be listed in the Warnings and Precautions section of the Prescribing Information if casimersen is granted accelerated approval.

4. In the Musculoskeletal Disorders SOC, it is noted that two events were *not* reported in a higher proportion of casimersen-treated subjects: rhabdomyolysis (6%, placebo vs. 5%, casimersen); and back pain (23% placebo, vs. 22%, casimersen).

   Clinical Reviewer's Comment
   Regarding rhabdomyolysis, the between-group similarity in the proportion with this event suggests that rhabdomyolysis may not be a safety concern for casimersen. Rhabdomyolysis will be discussed further in section 8.5.

8.4.5.3. Rate of Exposure-adjusted TEAEs of Significant Clinical Interest

The above table provides a broad view of TEAEs across all MedDRA SOCs in the all-casimersen group (n = 76) and in the placebo group in the randomized, double-blind periods of studies 4045-101 and 4045-301 (n = 35). However, this broad view is somewhat biased in favor of the placebo group, because subjects in that group had either 12 weeks of exposure to placebo (study 4045-101; n = 4), or at most 96 weeks of exposure to placebo in study 4045-301. In contrast, some subjects in the all-casimersen group had exposures > 132 weeks.

In order to adjust for the duration of exposure in the casimersen and placebo groups, exposure-adjusted incident rates (EAIRs) for all TEAEs in each treatment group were calculated by the applicant. EAIRs are expressed as the number of subjects with a specific TEAE per 10 subject-years. For the TEAEs that were reported in ≥ 3% more subjects in the casimersen group than

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the placebo group (as shown in the table above), the calculated EAIRs for those TEAEs are shown in the table below. To maintain consistency with the populations that were represented in the table above, the EAIRs for these events are shown for the same placebo-treated subjects in the 4045-101 and 4045-301 studies (n = 35), and for all casimersen-treated subjects in those studies plus the 4045-302 study (n = 76).

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Table 44. Exposure-adjusted Incidence Rates for Selected TEAEs

Event	EAIRs (Number of subjects with each TEAE per 10 subject-years)	
	Placebo (n = 35)	Casimersen (n = 76)
Ear Pain	0.22	0.20
Abdominal pain upper	0.67	1.02
Abasia	0	0.24
Fatigue	0.22	0.41
Malaise	0	0.24
Pyrexia	1.77	2.37
Bronchitis	0.22	0.42
Ear infections	0.22	0.58
GI infections (5 events; unique subjects only)	1.15	1.30
Upper respiratory tract infection (URTI) /viral URTI (unique subjects only)	0.93	1.92
Viral infections	0	0.32
Neutrophil count increased	0	0.16
White blood cell count increased	0	0.16
Decreased appetite	0	0.16
Arthralgia	0.71	1.11
Headache/migraine/cluster (unique subjects only)	1.51	2.68
Dizziness	0.46	0.85
Proteinuria / protein urine increased	0	0.41
Cough	1.99	2.49
Rash /rash generalized / rash pruritic (unique subjects only)	0.91	0.69
Hematoma	0	0.24
Flushing	0.22	0.33

[Source: Clinical reviewer's use of ISS Table 13.1]

It is instructive to compare events in this table of EAIRs to the corresponding proportions of TEAEs that were at least 3% greater in the casimersen group. There are several events with noticeably higher EAIRs in the casimersen group. For example, the EAIR for pyrexia is approximately 1.4 times greater in the casimersen group. The EAIRs for URTI and for bronchitis in the casimersen group are approximately two-fold greater than in the placebo group, and the

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EAIR for ear infections is approximately 2.6 times greater in the casimersen group. Finally, the EAIRs for dizziness and headache are approximately 1.8 to 1.9 times higher in the casimersen group.

Conversely, Ear pain had a higher proportion in the casimersen group (7.9%) than in the placebo group (2.9%), but the corresponding EAIRs were less in the casimersen group (0.20) than in the placebo group (0.22).

Clinical Reviewer's Comments
The rates of respiratory and other infections will be monitored closely as new clinical data are submitted for evaluation. Additionally, the rates of headaches and dizziness will also be examined with new data. The possibility of a relationship between pyrexia and infections will be evaluated further below. The overall potential for hypersensitivity will be scrutinized in the future even if rash does not currently appear to be over-represented in the casimersen group.

8.4.5.4. Recommended Adverse Reactions Table for Prescribing Information if Casimersen is Granted Accelerated Approval

FDA's 2006 guidance, *"Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products-Content and Format,"* includes principles that were used in constructing an Adverse Reactions Table to be included in the Prescribing Information section if casimersen is granted accelerated approval. Staff within FDA's Safety group in Division of Neurology (Drs. Rui Li and Sally Yasuda) provided invaluable assistance in this endeavor. The principles used are as follows.

For an accurate comparison of event rates between casimersen-treated subjects and placebo-treated subjects, two features are important. First, study drug exposures should be approximately identical in each treatment group; longer exposures in one group than in the other group may result in higher rates of events in the group with the longer exposure. Second, the size of the safety database in the treatment groups with equal exposure should be as large as possible; a smaller-sized safety database would reduce the numbers of and/or accurate comparisons of adverse reactions.

Using these considerations, the table below was constructed using data from the 96-week randomized, double-blind period of study 4045-301 (placebo, n = 31; casimersen, n = 57) to show adverse reactions that occurred in at least 20% of casimersen-treated subjects and at a rate at least 5% greater than placebo.

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Table 45. Treatment-Emergent Adverse Reactions Reported in at Least 20%[1] of Subjects Treated with Casimersen and at a Rate at Least 5% More than Placebo (Study 4045-301)

Adverse Reaction	Casimersen (n = 57)	Placebo (n = 31)
Upper Respiratory Tract Infections[2]	65%	55%
Cough	33%	26%
Pyrexia	33%	23%
Headache	32%	19%
Arthralgia	21%	10%
Oropharyngeal Pain	21%	7%

[1] Other adverse reactions that occurred in at least 10% of casimersen-treated subjects, and that were reported at a rate that was 5% greater in the casimersen group than in the placebo group, were [presented based on alphabetical order of the SOC]: ear pain, nausea, ear infection, post-traumatic pain, and dizziness and light-headedness (a grouping of the two terms of dizziness and light-headedness).

[2] Respiratory tract infections is a combined grouping that consists of the five individual terms of upper respiratory infection, nasopharyngitis, pharyngitis, rhinitis, and upper respiratory tract infection.

[Source: Clinical reviewer's use of ISS Table 5.1, and ADAE.xpt file]

Clinical Reviewer's Comment
The construction of this Adverse Reactions table adheres to the methods used in constructing similar tables for the Prescribing Information of approved ASOs used to treat DMD.

8.4.6. Laboratory Findings

This clinical reviewer used ADLB.xpt and the applicant's lab shift tables (ISS Tables 14.3.1, 14.3.2, and 14.3.3) to evaluate all lab assessments. The majority of assessments of chemistry, hematology, coagulation, and urine parameters revealed no findings that were clinically noteworthy in either treatment group. Nevertheless, nine lab assessments are of interest in the context of the identified or potential risks of casimersen, as discussed in greater detail in section 8.5. These include abnormal increases in: C-reactive protein (CRP), creatinine, cystatin C, Kidney Injury Molecule 1 (KIM-1), prothrombin time (PT), the International Normalized Ratio (INR), activated partial thromboplastin time (APTT), and urine protein; and abnormally decreased platelet count.

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The proportion of subjects with abnormalities in these lab assessments will be presented below, using two methods of comparison. First, the placebo group from population 2 (i.e., the randomized, double-blind placebo-controlled periods of studies 4045-101 and 4045-301 [placebo, n = 35]) will be compared to the all-casimersen group (i.e., population 3 [casimersen, n = 76]). Second, the two treatment groups in population 2 will be compared (placebo, n = 35 vs. casimersen, n = 65). These methods of comparison offer reciprocal advantages and disadvantages. The first method provides a view of all lab data, but a comparison across its treatment groups may be biased due to the longer duration of drug exposure in the all-casimersen group (n = 76, with more than 132 weeks of exposure for some subjects) as compared to the population 2 placebo group (n = 35, with at most 96 weeks of exposure for all subjects). Population 2 provides a more balanced comparison across treatment groups because of the approximately equal duration of study drug exposure, but the lab data from casimersen-treated subjects during the open-label portion of study 4045-301 and during study 4045-302 are not included. It is important to view the lab data using both methods.

The methods used to ascertain the abnormal lab values of interest to include in the table below were as follows. When any of the nine chosen lab assessments met the criteria for potentially significant clinical abnormalities (PCSAs) as defined by the SAP (Appendix Tables 1, 2 and 3), then the proportion of subjects meeting these PCSA criteria are shown in the table. For lab assessments with no pre-defined PCSA criteria, then the table shows the proportion of subjects who had laboratory shifts from normal values at baseline to either abnormally high or abnormally low at any subsequent visit. The exception is APTT, which shows the sum of lab shifts from low or normal values to high values. Finally, for KIM-1, there is no established reference range in pediatric subjects, and therefore the adult reference range was used by the applicant. The applicant assigned a criterion of > ULN to denote an abnormal value. The table below shows the results using that threshold for abnormal.

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Table 46. Laboratory Assessments of Relevance to Identified and Potential Risks of Casimersen in Studies 4045-101, 4045-301, and 4045-302

Lab Parameter As denoted below, PCSA criteria if available; or shift from Baseline normal to abnormally high/low	RDBPC Periods of 4035-101 and 4045-301 (Population 2)		All-casimersen group including open-label (Population 3)
	Placebo (N = 35)	Casimersen (N = 65)	Casimersen (N = 76)
Normal to Abnormally High serum cystatin C (by PCSA criteria)	3%	5%	5%
Normal to Abnormally High urine protein (by PCSA criteria)	0	12%	12%
Normal to Abnormally High urine KIM-1 (using the adult criteria for ULN)	0	0	1%
Normal to Abnormally High serum creatinine (by PCSA criteria)	0	0	0
Normal to Abnormally High plasma prothrombin time (PT) (shift tables)	11%	15%	15%
Normal to Abnormally High plasma INR (shift tables)	6%	11%	9%
Low / Normal to Abnormally High plasma activated partial thromboplastin time (APTT) (shift tables)	23%	25%	33%
Normal to Abnormally Low platelet count (by PCSA criteria)	6%	9%	8%
Normal to Abnormally High plasma C-reactive protein (CRP) (shift tables)	6%	14%	17%

[Sources: Reviewer's use of: ISS Table 14.2.1 for proportions meeting PCSA criteria; ISS Tables 14.3.2 and 14.3.3 for proportions with lab shifts from baseline normal to abnormal at any time; and Summary of Clinical Safety section 2.1.8.2.3.3 for KIM-1]

Note that shifts from normal to abnormal values of alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT) are not included in the table. All values of

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AST and ALT were high in all subjects throughout the studies, and all values of alkaline phosphatase were normal or low throughout the studies.

The lab parameters in the table may be grouped into two categories.

1. Renal parameters include measurements of serum creatinine, cystatin C, urine KIM-1, and urine protein.

2. Coagulopathy/platelet parameters include measurements of PT, INR, APTT, and platelet count.

Regarding the renal parameters, serum creatinine was not increased in either treatment group. This could be anticipated due to decreased skeletal muscle mass in subjects with DMD. However, in the casimersen group compared to placebo, there was an increased proportion of subjects with abnormally high cystatin C or abnormally high urine protein. There was a single subject who had abnormally high KIM-1, and he was in the casimersen group. These data will be discussed in section 8.5.

Regarding the coagulopathy/platelet parameters, the proportions of subjects with abnormally high PT, abnormally high INR, abnormally high APTT or thrombocytopenia were greater in the casimersen group compared to the placebo group.

Clinical Reviewer's Comments
The renal parameters suggest an increased potential for renal injury in casimersen-treated subjects. This risk will be discussed further in section 8.5. The coagulopathy/platelet parameters may suggest an increased potential for coagulopathy / thrombocytopenia in casimersen-treated subjects, as reflected by a greater proportion of subjects with abnormally high PT, INR, and APTT and with abnormally low platelet count. This potential risk will also be discussed further in section 8.5.

8.4.7. Vital Signs

8.4.7.1. Summary of Vital Signs by Treatment Group

The clinical reviewer evaluated all vital signs (VS) parameters in all populations, but the following VS parameters were evaluated more closely: systolic blood pressure (SYSBP), diastolic blood pressure (DIABP), heart rate (HR), respiratory rate (RESP), and temperature (TEMP). It is helpful to first examine a box-and-whiskers plot that shows a summary of the change from baseline (CFB) to all successive values for each parameter and in each treatment group in order to gain a sense of their distributions. In this reviewer's opinion, a plot of CFB to every visit provides a more comprehensive view of CFB because any large excursion at any visit will be

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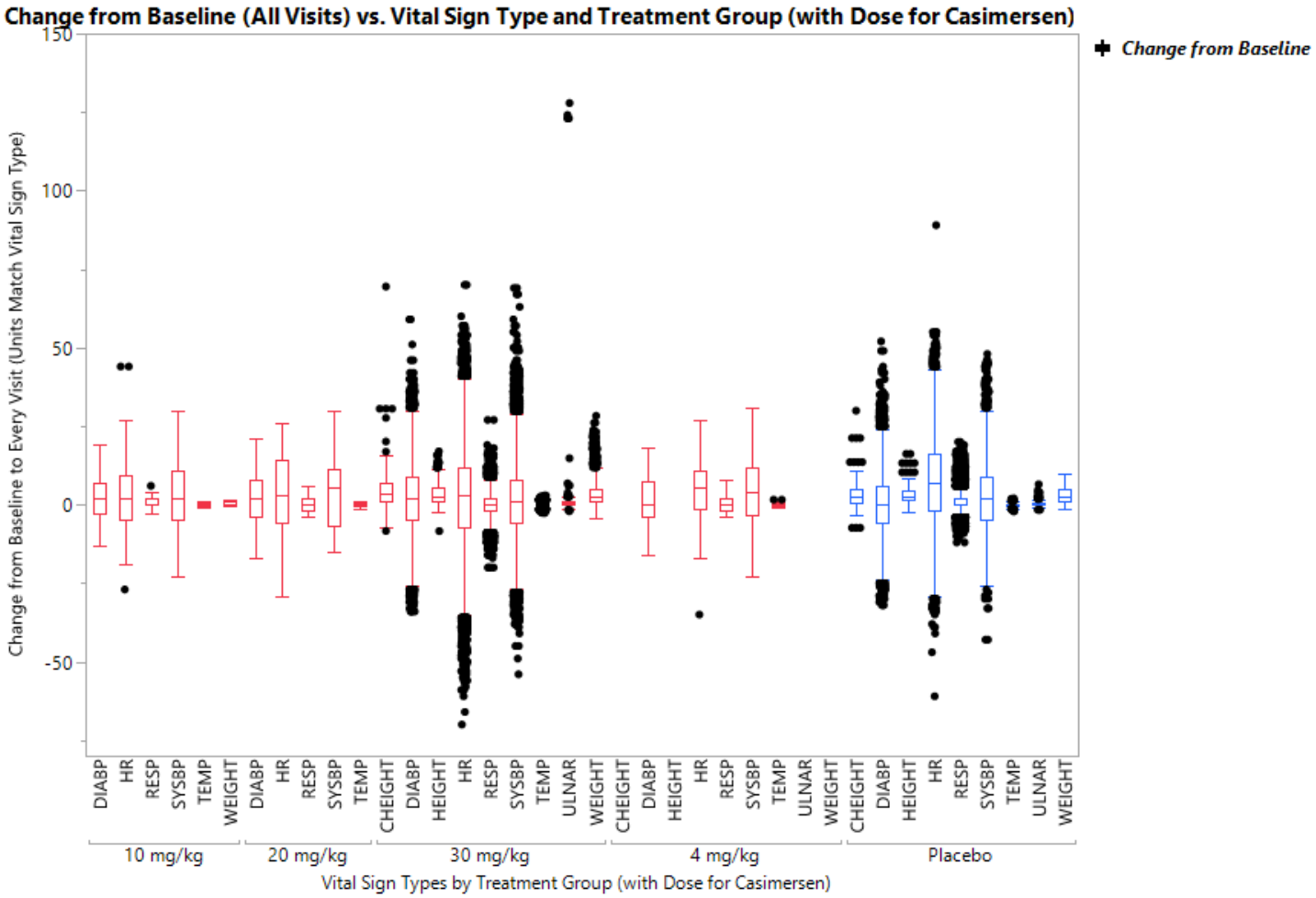
included. To put this into perspective, subjects in the placebo group had at most 96 weekly visits during which VS measurements were obtained. Subjects in the 30mg/kg casimersen group include 11 subjects who entered the extension study 4501-302, and consequently some subjects in this group had more than 144 weekly visits during which measurements were made. Therefore, by plotting a far smaller subset of CFB to a particular visit (e.g., to Week 48), there will be fewer opportunities to identify a large excursion.

These summary box-and-whiskers plots are shown below.

Table 47. Summary Box-and-Whiskers Plots[1] of Change from Baseline to All Successive Visits for Each Vital Sign Parameter[2] in the Placebo Group (Blue) and Casimersen Dose Groups (Red)



[1]In each box-and-whiskers plot, the horizontal median line separates the second from the third quartile. Outlier measurements are shown by black dots. Casimersen plots are in red, and

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placebo plots are in blue.

[2] In the table, CHEIGHT is the calculated height when a standing height could not be obtained. This was calculated using a formula that included the length of the ulna (the ULNAR parameter in the table).

[Source: clinical reviewer's use of the applicant's ADVS.xpt file and JMP Clinical 7.1].

The VS parameters in the 4mg/kg, 10mg/kg, and 20mg/kg casimersen groups have few outliers because these doses were administered only in study 4045-101, and each dose was planned to be administered only twice in each of 8 subjects. The comparison groups that are most informative are the 30mg/kg casimersen group and the placebo group.

For each VS parameter, the median CFB is approximately the same in the 30mg/kg all-casimersen and placebo treatment groups. There appears to be a greater number of outlier measurements in SYSBP in the 30mg/kg casimersen group than in the placebo group. Outlier numbers appear to be similar between groups for DIABP, HR, RESP, and TEMP.

8.4.7.2. Potentially Clinically Significant Abnormalities in Vital Signs

In order to evaluate the possibility of greater excursions in SYSBP in the 30mg/kg all-casimersen group, the table below depicts the proportion of subjects in each treatment group who have VS measurements that fall below or above a Potentially Clinically Significant Abnormality (PCSA) as pre-specified in the SAP.

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Table 48. Proportions of Subjects with Potentially Clinically Significant Abnormalities in Vital Signs in Studies 4045-101, 4045-301, and 4045-302

	POP1 (Double-Blind Period of 4045-301)		POP2 (Double-Blind Period of 4045-101 & 4045-301)		POP3 (Casimersen Treatment Period of 4045-101, 4045-301 & 4045-302)
	Placebo (N=31)	Casimersen 30 mg/kg (N=57)	Placebo (N=35)	Casimersen (N=65)	All Casimersen (N=76)
Number of Patients with Any Potentially Clinically Significant Abnormalities	30 (96.8%)	55 (96.5%)	34 (97.1%)	63 (96.9%)	74 (97.4%)
Systolic Blood Pressure (mmHg)					
Value < 90 mmHg	24 (77.4%)	38 (66.7%)	26 (74.3%)	40 (61.5%)	50 (65.8%)
Value > 140 mmHg	3 (9.7%)	11 (19.3%)	4 (11.4%)	11 (16.9%)	17 (22.4%)
Value > 160 mmHg	0	4 (7.0%)	0	4 (6.2%)	4 (5.3%)
Diastolic Blood Pressure (mmHg)					
Value < 50 mmHg	24 (77.4%)	38 (66.7%)	26 (74.3%)	42 (64.6%)	50 (65.8%)
Value > 90 mmHg	10 (32.3%)	22 (38.6%)	10 (28.6%)	22 (33.8%)	34 (44.7%)
Value > 100 mmHg	2 (6.5%)	5 (8.8%)	2 (5.7%)	5 (7.7%)	9 (11.8%)
Heart Rate (beats/min)					
Value < 60 Beats/min	0	4 (7.0%)	1 (2.9%)	4 (6.2%)	6 (7.9%)
Value > 120 Beats/min	22 (71.0%)	41 (71.9%)	25 (71.4%)	48 (73.8%)	54 (71.1%)
Respiratory Rate (breaths/min)					
Value < 12 Breaths/min	0	2 (3.5%)	0	2 (3.1%)	2 (2.6%)
Value > 20 Breaths/min	29 (93.5%)	54 (94.7%)	33 (94.3%)	61 (93.8%)	73 (96.1%)
Temperature (°C)					
Value < 36.0 °C	14 (45.2%)	35 (61.4%)	14 (40.0%)	40 (61.5%)	47 (61.8%)
Value > 38.0 °C	5 (16.1%)	5 (8.8%)	5 (14.3%)	6 (9.2%)	11 (14.5%)

[Source: Applicant's ISS Table 15.2]

The proportion of subjects with SYSBP < 90mmHg at any time is greater in the placebo group (74%) than in the all-casimersen group (66%). The proportion of subjects with SYSBP > 160mmHg is larger in the all-casimersen group (n = 4; 5%) than in the placebo group (0%). The four subjects with a SYSBP > 160mmHg were the following.

1. Subject 4045-301. (b) (6) had a single SYSBP > 160mmHg. The value was 162mmHg, and his Baseline SYSBP was 132mmHg.

2. Subject 4045-301. (b) (6) had a single SYSBP > 160mgHg. The value was 168mmHg, and the Baseline SYSBP was 145mmHg.

3. Subject 4045-301. (b) (6) had a single SYSBP > 160mmHg. The value was 161mmHg, and the Baseline SYSBP was 161mmHg.

4. Subject 4045-301. (b) (6) had a single SYSBP > 160mmHg. The value was 167mmHg, and his Baseline SYSBP was 98mmHg.

Each of these subjects was in the casimersen group in the 96-week double-blind treatment period in study 4045-301. To put into perspective the single SYSBP value that was > 160mmHg in each subject, these subjects had up to 96 weeks of visits during which SYSBP was obtained. A single SYSBP measurement above 160mmHg in 4 subjects with hundreds of site visits does not

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appear to this clinical reviewer to be noteworthy. Moreover, two of the four subjects were hypertensive at Baseline, and one was pre-hypertensive.

Clinical Reviewer's Comment
Casimersen does not appear to have any clinically noteworthy effect on any VS parameter, when compared to placebo.

8.4.8. Electrocardiograms (ECGs) and Echocardiography (ECHO)

8.4.8.1. ECGs

This clinical reviewer evaluated the ECG parameters that were obtained in each population. These parameters included the PR conduction interval, the QRS conduction interval, the QT conduction interval, and the QTcF conduction interval. ISS Table 16.2 shows that there were no subjects in any population with conduction interval values that were above or below thresholds that were pre-specified in the SAP to represent a Potentially Clinically Significant Abnormality (PCSA). Because the QTcF conduction interval is of particular clinical interest, a summary table showing those data is below.

Table 49. Proportion of Subjects with Potentially Clinically Significant Abnormalities in Studies 4045-101, 4045-301, and 4045-302

	POP1 (Double-Blind Period of 4045-301)		POP2 (Double-Blind Period of 4045-101 & 4045-301)		POP3 (Casimersen Treatment Period of 4045-101, 4045-301 & 4045-302)
	Placebo (N=31)	Casimersen 30 mg/kg (N=57)	Placebo (N=35)	Casimersen (N=65)	All Casimersen (N=76)
QTcF Interval (msec)					
Value < 320 msec	0	0	0	0	0
Value > 480 msec (Age < 12 Years) or Value > 500 msec (Age >= 12 Years)	0	0	0	0	0
Value > 450 msec	0	0	0	0	0
Value > 480 msec	0	0	0	0	0
Value > 500 msec	0	0	0	0	0
Increase of 60 or more	0	0	0	0	0

[Source: Applicant's ISS Table 16.2]

As summarized above, there was no subject in any population with an absolute QTcF values > 450 msec, and no subject with a CFB to any subsequent time point ≥ 60msec.

ISS Table 16.1 shows that the treatment group mean CFB to the Final Observation for QTcF are virtually identical: + 1.1msec for placebo (n = 35); + 1.0msec for casimersen (n = 65); and +0.9msec for the all-casimersen group (n = 76).

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Clinical Reviewer's Comments
There does not appear to be any noteworthy effect of casimersen, compared to placebo, on any ECG conduction interval measurement. The lack of effect of casimersen on the group mean CFB to Final Observation, and the lack of any PCSA values in this treatment group may be significant from a regulatory perspective. During the pre-NDA meeting of 6/5/19, FDA provided the following comment when asked by the applicant if a thorough QT study waiver could be issued "if the ECG data from clinical studies excludes large mean increases (i.e., 20 ms) in QTc" (Question 6):

> *"FDA stated that if the ECG data from clinical studies excludes a large mean effect, and if a review of the nonclinical cardiac safety data supports a large safety margin, FDA would not request a separate thorough QT study in healthy subjects [from Meeting Minutes issued 6/27/19]."*

8.4.8.2. ECHO

Two ECHO parameters were obtained during the studies: Left Ventricular Ejection Fraction (LVEF); and Fractional Shortening (FS). Fractional shortening measures the shortening in the left ventricular cavity length during systole, and it is stable as children age (Sutton et al., 1982). LVEF tends to diminish slightly as a function of age (Cain et al., 2009). The PCSA values for these parameters are < 55% and < 29%, respectively.

ISS Table 17.2 shows that there were no subjects in either the placebo group (N = 35) or the casimersen group (N = 76) who had LVEF measurements that were below PCSA values during the three studies.

Regarding FS, ISS Table 17.2 shows that 9% (n = 3) of subjects in the placebo group and 13% (n = 10) of subjects in the all-casimersen group had FS values below the PCSA during the studies. However, listings 29.1.1 and 29.1.3 show that 1 of the 3 subjects with FS shortening in the placebo group had FS values that met PCSA criteria at Screening/Baseline. Likewise, 5 of the 10 subjects with FS shortening in the casimersen group also had FS values that met PCSA criteria at Screening/Baseline. It provides no meaningful information to include these subjects in a measurement of the proportion of subjects who met PCSA criteria during the studies. For that reason, the actual proportion of subjects who did not meet these criteria before study drug administration and then met these criteria at a later time, was 6% (2/35) in the placebo group and 7% (5/76) in the casimersen group.

Clinical Reviewer's Comment
There appears to be no difference between casimersen and placebo in the proportion of subjects with clinically significant changes in LVEF or in FS during the studies.

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8.4.9. QT

No thorough QT clinical trial has been conducted. If casimersen is approved under the accelerated approval pathway, a post-marketing requirement will be issued for the applicant to submit ECG data from Study 4045-301 to support a waiver for a thorough QT study. If these data do not support a TQT study waiver, the applicant will need to evaluate the effect of golodirsen on the QTc interval in a dedicated study as per the ICH E14 guideline.

8.4.10. Immunogenicity

Potential immunogenicity may occur from antibodies that target truncated dystrophin that was formed by casimersen-induced exon-skipping. This possibility was examined by the applicant by using blood samples obtained during the 144-week study 4045-101. The 12 subjects enrolled in this study provided samples to be used for immunogenicity testing at Screening, Baseline/Week 1, Week 12, Week 36, Week 60, Week 84, Week 108, and Week 132. Each sample was assayed for the development of anti-dystrophin IgG, IgE, or IgM antibodies.

The results of these assessments are shown in ISS Tables 14.2.4.1.1 (for IgG), 14.2.4.2.1 (for IgE), and 14.2.4.3.1 (for IgM). There was no positive sample in any subject at any sampling time for IgG, IgE, or IgM anti-dystrophin antibodies.

Clinical Reviewer's Comments
Based upon the submitted data, there does not appear to be evidence for immunogenicity directed against dystrophin in these subjects. It is possible that the OBP group may recommend a post-marketing requirement (PMR) for an in silico analysis to identify neoepitopes that may be formed as a result of exon-skipping in truncated dystrophin.

8.5. Analysis of Submission-Specific Safety Issues

The identified risk of renal injury and of seven other potential risks will be discussed below. In each subsection, the basis for its status as a potential risk will be presented. Evaluations of each potential risk will follow.

8.5.1. Identified Risk of Renal Injury

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Renal toxicity is an identified risk for another ASO that shares a similar molecular backbone with casimersen (i.e., Vyondys 53). Renal toxicity was also identified in non-clinical toxicology studies in casimersen-treated rodents and non-human primates.

Three methods were used to evaluate the risk of potential renal injury. The first method was an inspection of MedDRA tables of non-serious and serious TEAEs, of severe TEAEs, and of TEAEs leading to study drug interruption. The second method was use of the broad SMQ for acute renal failure. The third method was a search for laboratory measurements of markers of renal injury that reached an abnormally high value or that reached the level of a PCSA.

8.5.1.1. Inspection of MedDRA Tables for SAEs Potentially Associated with Renal Injury

An SAE of urine protein/creatinine ratio increased was reported for casimersen-treated subject 4045-301. (b) (6) This 13-year-old male had no recorded medical history other than DMD at study enrollment. His concomitant medications as the time of study enrollment included deflazacort, testosterone isocaproate, perindopril, risedronate, vitamin D, and cod liver oil. He experienced dizziness and a fall on Day 504 of the 96-week double-blind period of study 4045-301. Several urine dipsticks following the adverse event of dizziness showed 2+ or 3+ blood and 1+ protein. He had a normal renal ultrasound on Day 513. On Day 541 he had a urine protein/creatinine ratio of 186 mg/mmol (ref range: 0.1 – 130 mg/mmol), and an SAE of urine protein/creatinine ratio increase was reported. Fourteen days after this SAE, the urine protein/creatinine ratio was further elevated at 1118 mg/mmol; and 21 days after the event, the urine protein/creatinine ratio was normal at 18mg/mmol. A pediatric nephrologist subsequently noted that the increased urine protein/creatinine ratio was transient, and that the subject also had an increased urine calcium/creatinine ratio, another cause of hematuria. It is instructive to inspect other abnormal renal laboratory values for subject 4045-301. (b) (6) using the applicant's ADLB.xpt file.

1. Urine dipsticks for blood were 1+ at Baseline (Day 1), and they were also positive at all subsequent visits except twice before data cut-off (2 values of negative, 4 values of trace, 8 values of 1+, and one value of 2+). Apparently the ADLB.xpt file does not include some of the dipstick results of 2+ or 3+ blood, which are cited in the applicant's narrative for this subject.

2. Urine dipstick for protein was trace at Baseline, and it was also positive (predominantly trace) at 8 subsequent visits including the final visit before data cut-off.

3. Urine KIM-1 was negative at every visit from Baseline through the final visit before data cut-off. The Screening value was 1.6ug/L, and the highest value was 2.7 ug/L at Day 583. It is worth noting that the applicant states that there is no established reference

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range for urine KIM-1 values in the pediatric age range, and therefore the adult reference range [redacted] (b) (4) was used (0.16 to 5.33 ug/L). However, published literature appears to suggest alternative values for the upper limit of normal (ULN) of urine KIM-1. The ULN for urine KIM-1 in a healthy adult population ranges from 1 ug/L to 2.15 ug/L (Chaturvedi et al., 2009; [redacted] (b) (4)). Moreover, there are several published reference ranges for healthy children (Huang et al., 2019; McWilliam et al., 2014, and Bennett et al., 2015). Bennett and colleagues (2015) reported that the upper 95th percentile cut-off for urine KIM-1 in male children ranged from 1.16 ug/L (10 to < 15-year-old group) to 1.28 ug/L (5 to < 10-year-old group). If one uses the latter values, then this subject's urine KIM-1 value at Screening and at most subsequent visits was abnormally high.

4. Urine microscopic analyses were positive at Day 1 and at every subsequent visit except for one through data cut-off. The abnormal findings included high RBCs per high-power field (hpf) or high WBCs/hpf, and the presence of calcium oxalate crystals or hyaline casts. Calcium oxalate crystals can be causally associated with renal injury (Ermer et al., 2017).

5. Serum creatinine and serum cystatin C were either low or low to normal, respectively, at every visit. Indeed, no subject in any of the three studies had an elevated creatinine, likely due to decreased skeletal muscle mass; and only 5 subjects had an elevated cystatin C at any time during the three studies.

Clinical Reviewer's Comments
This subject had abnormal renal parameters at Screening or Baseline, and many parameters were periodically abnormal throughout the study. In this reviewer's opinion, it is likely that this subject had pre-existing renal injury prior to study enrollment.

8.5.1.2. Inspection of MedDRA Tables for Non-serious TEAEs Potentially Associated with Renal Injury

Per the applicant's ADAE.xpt file, five casimersen-treated subjects had reports of non-serious TEAEs that may be consistent with renal injury. No placebo-treated subject had such an event. Four of the five casimersen-treated subjects were subjects 4045-301 [redacted] (b) (6) [redacted] (b) (6) The TEAEs were determined based on urine dipstick (2 patients measured trace, 2 patients measured 1+). The events were generally transient and without other renal findings (except 1 patient with mild blood in the urine on the same day as the protein finding). One of these subjects had a reported event of proteinuria at Screening and then at two later study visits [redacted] (b) (6). The other three subjects had reported events of proteinuria at later visits in the study, and in two of the three subjects [redacted] (b) (6) the events resolved while casimersen continued to be administered. One subject had an

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unresolved event of proteinuria at data cut-off (b) (6). The fifth casimersen-treated subject had a reported non-serious event of protein urine present; this was subject 4045-301. (b) (6) who also had the reported SAE of urine protein/creatinine ratio increased.

There were no severe TEAEs that may be consistent with renal injury. The only subject with an interruption of casimersen administration following a non-serious or serious TEAE potentially associated with renal injury was subject 4045-301 (b) (6) who had the SAE of urine protein/creatinine ratio increased. No subject withdrew from the study due to any TEAE.

Clinical Reviewer's Comment
Although there may be mitigating factors that could explain some non-serious TEAEs of proteinuria or of protein urine present, the nonclinical findings of renal toxicity may have a clinical correlate with the observation that only casimersen-treated subjects had these events.

8.5.1.3. Broad SMQ of Acute Renal Failure

This reviewer used the broad SMQ of acute renal failure to search the applicant's ADAE.xpt file. The only events that were identified were those which have been described above (i.e., proteinuria and protein urine present).

8.5.1.4. Laboratory Findings Potentially Suggestive of Renal Injury

Laboratory parameters that may reveal renal injury include serum cystatin C and serum creatine, urine KIM-1, and proteinuria. Per ISS Tables 14.3.2 and 14.3.3, shifts from normal lab measurements of cystatin-C at Baseline to abnormally high measurements at any subsequent time revealed 5 subjects: one placebo-treated subject (3%) and four casimersen-treated subjects (5%). As described above, no subject in the study had a high serum creatinine at any visit in the studies. In addition, given the uncertainty in the reference range for urine KIM-1, it is not possible to determine shifts from normal at Baseline to abnormally high values of urine KIM-1 during the study.

Regarding proteinuria, a dipstick urine protein above 1+ is defined as a PCSA per the applicant's SAP. The applicant's ISS Table 14.2.1, which summarizes the number of all subjects with any PCSA lab values, lists 9 subjects in the casimersen group (n = 76) with PCSA values for dipstick urine protein, but no subjects in the placebo group (n = 35). This reviewer used the applicant's ISS listings 26.1.1 through 26.1.4 and the ADLB.xpt file to identify the 9 casimersen-treated subjects (12%). Each had a dipstick urine protein that was 2+ at least once during the studies. The 9 casimersen-treated subjects include 4045-301. (b) (6) (from ISS listing 26.1.3); and (b) (6). (from ISS listing 26.1.4).

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A lower threshold for abnormality can also be used to examine elevated dipstick urine protein. ISS Table 14.3.1 to 14.3.3 summarize the proportions of subjects with a lab shift from normal dipstick urine protein at Baseline to any higher value at the final observation (e.g., trace, 1+, 2+). Per these tables, 9% of placebo-treated subjects and 22% of casimersen-treated subjects had such a shift in the randomized double-blind periods of studies 4045-101 and 4045-301.

Clinical Reviewer's Comments about the Potential for Renal Injury.
A review of serious and nonserious TEAEs, study drug interruptions due to TEAEs, and laboratory findings that suggest the presence of renal injury appear to indicate that casimersen-treated subjects had a greater rate of such TEAEs or lab measurements. Although there are mitigating factors for a few of the identified abnormalities in casimersen-treated subjects, the preponderance of data suggests a potential risk of casimersen-induced renal injury. These clinical data may align with the non-clinical findings of casimersen-induced toxicity in toxicology studies in rodents and in non-human primates.

Taken together, the nonclinical and clinical data support that a risk of casimersen-induced renal injury should be included in the Warnings and Precautions section of the casimersen Prescribing Information if the drug is granted accelerated approval.

8.5.2. Potential Risk of Hypersensitivity

Hypersensitivity is a potential risk of many ASOs, including Exondys 51 and Vyondys 53, each of which shares a similar molecular backbone with casimersen. The potential of hypersensitivity in casimersen-treated subjects will be evaluated by using a similar strategy to that used to evaluate the potential risk of renal injury (section 8.5.1).

8.5.2.1. Inspection of MedDRA Table [ISS 11.2.1] for Serious and Non-serious TEAEs Potentially Associated with Hypersensitivity

In the three studies, there were no SAEs, severe non-serious TEAEs, or interruptions in study drug administration due to events that would suggest the development or presence of hypersensitivity per the hypersensitivity SMQ. When subjects with pyrexia were also included (see below), one subject with pyrexia had a drug interruption (subject 4045-301 (b) (6)). Pyrexia is not included in the hypersensitivity SMQ.

8.5.2.2. Evaluation of Events Identified Using the Hypersensitivity SMQ

ISS Table 11.2.1 presents the proportion of subjects with events that were identified using the hypersensitivity SMQ. In the overall placebo group (N = 35), 51% of unique subjects were

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identified as having one or more terms. In the overall casimersen group (N = 76), 37% of unique subjects were identified.

To evaluate these data in greater depth, this reviewer used the broad hypersensitivity SMQ with the applicant's ADAE.xpt file to derive data that were used to construct the table below, which shows the proportion of subjects with TEAEs that may represent hypersensitivity. Some terms that were split have now been combined, as shown in the table. Note that pyrexia is not a term contained in the hypersensitivity SMQ. Using ISS Table 5.1, the reviewer included subjects with pyrexia in the table below, because fever is a common albeit nonspecific accompaniment of drug hypersensitivity. Note also that the reviewer inspected each subject with each term, and then omitted the inclusion of subjects who had clear causes for the event other than potential hypersensitivity. The reasons for these omissions are footnoted below the table.

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Table 50. Proportion of Subjects with One or More TEAEs that May Herald Hypersensitivity[1]

TEAE (preferred term)	Placebo (N = 35) (%)	Casimersen (N = 76) (%)
Asthma	3%	0
Bronchospasm	3%	1%
Conjunctivitis (all: conjunctivitis, conjunctivitis allergic)	11%	3%
Dermatitis (all: dermatitis, dermatitis contact, infusion site dermatitis)	9%	5%
Eczema	3%	3%
Erythema	6%	4%
Eyelid edema	0	1%
Flushing	3%	5%
Pruritis	0	3%
Pyrexia	20%	32%
Rash (all: rash, rash generalized, rash pruritic, catheter site rash)	14%	13%
Skin exfoliation	3%	0
Urticaria	6%	1%

[1]Subjects were omitted if causes of their events clearly did not represent drug hypersensitivity. For nearly all of these terms, more placebo-treated subjects were omitted than casimersen-treated subjects.

- Dermatitis caused by adhesive tape, or skin reaction caused by a topical skin lotion
- Wheezing in a subject with pre-existing asthma and restrictive lung disease
- Allergic cough due to “hay fever” in the verbatim term
- Rhinitis allergic and seasonal allergy
- Photosensitivity reaction (phytophotodermatitis) in a subject exposed to wild parsnips (a common cause)
- Hypersensitivity that occurred from contact with a balloon
- Choking on food

[Sources: ADAE.xpt, ADMH.xpt, ISS Listings 24.1.1 and 24.1.2]

The overall proportion of unique subjects who had events in the placebo group was 51%, versus 50% in the all-casimersen group in spite of the longer exposures in that group. Unique subjects are defined as those who are only counted in this calculation once, even if they experienced events classified using more than one of the preferred terms in the table.

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A further inspection of this table reveals three events in which the proportion of casimersen-treated subjects was more than placebo-treated subjects:

1. Flushing (casimersen, n = 4 [5%] vs. placebo, n = 1 [3%])

2. Pruritis (casimersen, n = 2 [3%] vs. placebo, n = 0)

3. Pyrexia (casimersen, n = 24 [32%] vs. placebo, n = 7 (20%])

Use of ISS Table 11.4.1 reveals that more casimersen-treated subjects had these events within 24 hours of study drug infusion than did placebo-treated subjects (flushing: 5% casimersen vs. 3% placebo; pruritis: 3% vs. 0; and pyrexia: 9% vs. 3%). The emergence of these events at times close to study drug infusion may increase the likelihood that these events were associated with treatment using casimersen.

However, the EAIR (number of subjects per 10 subject-years of exposure) for two of these three event terms is less in casimersen-treated subjects than in placebo-treated subjects.

1. For flushing, the EAIR in the placebo group was 0.223 vs. 0.165 in the casimersen group.
2. For pyrexia, the EAIR in the placebo group was 0.669 vs. 0.484 in the casimersen group.
3. For pruritis, the EAIR in the placebo group was 0 vs. 0.078 in the casimersen group.

Clinical Reviewer's Comments

This reviewer recognizes that some people may consider events of rhinitis allergic and seasonal allergy to be potential harbingers of hypersensitivity. This reviewer strongly disagrees. Nevertheless, for the sake of completion:

- *The proportion of subjects with rhinitis allergic was 6% in the placebo group out of 35 (EAIR = 0.44) and 3% in the casimersen group out of 76 (EAIR = 0.16).*

- *The proportion of subjects with seasonal allergy was 6% in the placebo group (EAIR = 0.44) and 7% in the casimersen group (EAIR = 0.41).*

These data do not suggest that a higher proportion of subjects in the casimersen group has either rhinitis allergic or seasonal allergy than in the placebo group, and the EAIRs suggest that the opposite is true [Sources: ISS Tables 5.1, 11.2.1, and 13.1].

Drug hypersensitivity is commonly associated with events of pyrexia, flushing, and pruritis, each of which was reported in a higher proportion of casimersen-treated subjects. However, using the EAIR to further examine these events, the rates of pyrexia and flushing were actually greater in the placebo group. Only pruritis demonstrated a higher proportion in the casimersen group (3% [n = 2 subjects]). Conversely, a higher proportion of placebo-treated subjects had other events commonly associated with drug hypersensitivity (e.g., conjunctivitis [11%, placebo vs.

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3%, casimersen]; dermatitis of all types [9%, placebo vs. 5%, casimersen]; rash of all types [14%, placebo vs. 11%, casimersen]; and urticaria [6%, placebo vs. 1%, casimersen]). Given the imbalances that are greater in the placebo group for all but one of the events that are potentially associated with hypersensitivity, the overall profile of these events suggests that hypersensitivity reactions are not associated with casimersen treatment.

8.5.2.3. Laboratory Findings Potentially Suggestive of Hypersensitivity

Among the lab assessments that were obtained across the three studies, there are no assessments that specifically herald a drug hypersensitivity reaction. As non-specific assessments that may be associated with drug hypersensitivity, eosinophil counts, basophil counts, and C-reactive protein (CRP) levels were evaluated using the following methods. First, subjects who had shifts from normal to abnormally high eosinophil counts, basophil counts, or CRP levels at any time were identified. Second, subjects who met the criteria for PCSAs in eosinophil counts (i.e., > 1.5X ULN) or basophil counts (i.e., > ULN) at any time were also identified. There was no pre-specified criterion to define a PCSA for CRP. The table below shows the findings as a function of the proportion of subjects who met each criterion. For consistency with the table of TEAEs (above), this table of abnormal lab parameters will also compare proportions of all placebo-treated subjects (n = 35) to those of all casimersen-treated subjects (n = 76).

Table 51. Proportion of Subjects with Abnormalities in Laboratory Parameters Possibly Associated with Hypersensitivity

Lab Parameter	Shift from Normal to Abnormal		PCSA	
	PBO (N = 35) (%)	CAS (N = 76) (%)	PBO (N = 35) (%)	CAS (N = 76) (%)
Eosinophil Count[1]	29%	20%	9%	13%
Basophil Count[2]	11%	13%	11%	13%
CRP Level	6%	17%	not defined	not defined

[1]The definition of an abnormally high eosinophil count (> ULN) is at a lower threshold than the criterion for a PCSA in eosinophil count (> 1.5X ULN)

[2]The definition of an abnormally high basophil count (> ULN) is the same as the criterion for a PCSA in basophil count (> ULN).
[Sources: ISS Tables 14.3.2, 14.3.3, and 14.2.1]

Clinical Reviewer's Comment about Lab Assessments
In the casimersen group, the rates are greater for shifts to abnormally high values for basophil counts and for CRP levels than in the placebo group; but the rate for a shift to abnormally high

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eosinophil counts is greater in the placebo group. The proportion of subjects who have PCSA eosinophil and basophil counts is higher in the casimersen group, but not substantially higher.

Clinical Reviewer's Overall Assessment about the Potential Risk of Hypersensitivity
TEAEs that may herald hypersensitivity are not imbalanced in a way that suggests hypersensitivity reactions occur to a greater degree in the casimersen group than the placebo group; in fact, the opposite is true. Likewise, there are no laboratory assessments that clearly demonstrate casimersen-induced hypersensitivity. Among the three lab parameters examined, only a shift to abnormally high CRP levels appears to be over-represented in the casimersen group, and CRP is nonspecific as a marker for hypersensitivity. Taken together, there is no conclusive evidence that casimersen causes drug hypersensitivity. This reviewer recommends that this potential risk does not need to be included in the Warnings and Risk section of casimersen's Prescribing Information if the drug is granted accelerated approval. This potential risk will continue to be examined as additional clinical data are submitted.

8.5.3. Potential Risk of Infusion-related Reactions (IRRs) and Catheter-associated Infusion Site Reactions (ISRs)

IRRs and ISRs are a consequence of the IV infusion of many drugs, and ASOs are among them. IRRs were identified by the applicant by seeking reported TEAEs that occurred within 24 hours of an infusion of study drug.

ISRs that occur following catheter infusion and within 24 hours of study drug infusion are also IRRs, but there is an additional group of catheter-associated ISRs that occur later than 24 hours after study drug infusion. To prepare a complete list of these ISRs even if not occurring within 24 hours after infusion, this reviewer identified all ISRs by searching the ADAE.xpt file using the search terms "catheter" or "site" or "infusion" or "injection." This search strategy yielded events associated with either intravenous catheter infusions or with infusions made through a central venous port. Any port-related events were omitted from further evaluation in this section, because these events are evaluated in section 8.5.7. Only ISRs associated with the use of catheter infusions are discussed in this section.

8.5.3.1. Inspection of MedDRA Tables for Serious and Non-serious TEAEs that Represent IRRs

There were no serious IRRs. Likewise, there were no non-serious IRRs that were rated as severe, and none that led to drug interruption or discontinuation.

ISS Table 11.4.1 was inspected to identify IRRs that occurred in at least 3% of casimersen-treated subjects in Population 3, and that occurred at a higher rate that in placebo-treated

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subjects from Population 2. This threshold was used because the number of subjects who constitute at least 3% of subjects in the all-casimersen group (n = 76) is three or more subjects. The following table displays the proportion of subjects with events that met the above criteria in the three studies. For the combined terms of abdominal pain and abdominal pain upper, only unique subjects were included in this row.

Table 52. IRRs that Occurred in at Least 3% of Casimersen-treated Subjects and at a Greater Rate than Placebo

IRR (preferred term)	Placebo (N = 35) (% of Subjects)	Casimersen (N = 76) (% of Subjects)
Headache	6%	15%
Pyrexia	3%	9%
Abdominal Pain & Abdominal Pain Upper	6%	8%
Upper Respiratory Tract Infection	0	7%
Nausea	0	7%
Flushing	3%	5%
Scoliosis	0	5%
Cough	0	4%
Nasopharyngitis	3%	4%
Rhinitis	0	4%
Proteinuria	0	4%

[Source: ISS Table 11.4.1]

Clinical Reviewer's Comments
Among the IRRS shown above, those that appear to this reviewer to be noteworthy and also more common in casimersen-treated subjects are headache, pyrexia, abdominal pain (both terms), and upper respiratory tract infection. Although not shown in this table, noteworthy events that were more common in placebo-treated subjects were diarrhea (placebo, 11% vs. casimersen, 7%) and vomiting (placebo, 11%, vs. casimersen, 9%). On face, there appears to be a somewhat greater number of noteworthy IRRs that occur in the casimersen group.

8.5.3.2. Evaluation of IRRs Using the Applicant's Customized Query for IRRs with Onset Within 24 Hours of Infusion

In order to cross-check the results from the IRR table above with results obtained in another fashion, this reviewer identified subjects by applying the applicant's custom query for IRRs to the ADAE.xpt file. Subjects were omitted from further evaluation if they met either of two criteria. First, if the identified events occurred in fewer than 3% of casimersen-treated subjects, these subjects were omitted from further evaluation in order to be consistent with the table above. Second, subjects who had localized events at the site of catheter-administered study

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drug were omitted because they are captured in the table below, which shows catheter-associated ISRs. After accounting for these omissions, the subjects identified with this customized query matched those represented in the IRR table above.

8.5.3.3. Inspection of MedDRA Tables for Serious and Non-serious TEAEs that Represent Catheter-associated ISRs

There were no serious catheter-associated ISRs. Likewise, there were no non-serious ISRs that led to drug interruption or drug discontinuation, and no ISRs that were rated as severe.

The following table displays the proportion of subjects with catheter-associated ISRs that occurred at any time during the three studies, irrespective of the relationship between event onset and the time of last study drug infusion. Port-related events are not included because they are described in section 8.5.7.

Table 53. Catheter-associated ISRs that Occurred at Any Time during Studies 4045-101, 4045-301, and 4045-302

ISR (Preferred Term)	Placebo (N = 35) (%)	Casimersen (N = 76) (%)
Infusion site dermatitis	3%	0
Injection site pain	3%	0
Device occlusion	0	1%
Catheter site hematoma	0	1%
Infusion site pruritis	0	1%

[Source: use of ADAE.xpt file]

Clinical Reviewer's Comments
There is no clear imbalance in catheter-associated ISRs between the casimersen and placebo groups. Note that this table does not include port-related events, which are discussed in section 8.5.7.

Clinical Reviewer's Comments about IRRs and Catheter-associated ISRs
There does not appear to be a noteworthy between-groups imbalance in either IRRs or in ISRs that are associated with venous catheter administration, with the exception of the events of headache, pyrexia, abdominal pain, and upper respiratory tract infections. These events will be included in the Adverse Reactions section of the Prescribing Information for casimersen, if it is granted accelerated approval. At this moment the clinical reviewer concludes that there is no reason to include these events as identified risks in the Prescribing Information. Nevertheless, these potential risks should continue to be evaluated.

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8.5.4. Potential Risk of Hepatotoxicity

Hepatotoxicity has been identified during treatment with other ASO infusions, although not with ASOs that share a molecular backbone with casimersen. This potential risk is evaluated below.

8.5.4.1. TEAEs that may Represent Hepatotoxicity

ISS Table 12.2.1, treatment-emergent hepatic events, was derived by searching for preferred terms in any of the following SMQs: cholestasis and jaundice of hepatic origin SMQ; hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions SMQ; hepatitis, noninfectious SMQ; liver neoplasms, benign [including cysts and polyps] SMQ; liver malignant tumors SMQ; liver-related investigations, signs and symptoms SMQ; and liver-related coagulation and bleeding disturbances SMQ. No serious or non-serious TEAEs that could be associated with hepatic injury were identified in any of the three studies. There were no drug interruptions due to a hepatic event.

This reviewer used the applicant's customized query for drug-induced hepatic toxicity to search the ADAE.xpt file. No subjects were identified. Consequently, there are no hepatotoxicity-associated SAEs, severe serious or non-serious TEAEs, or TEAEs during which study drug was interrupted.

8.5.4.2. Laboratory Assessments that May Represent Hepatotoxicity

There are a variety of laboratory assessments that can suggest the presence of drug-induced liver injury (DILI). These include abnormal elevations in ALT, AST, total bilirubin, GGT, APTT, INR, or PT; and abnormal reductions in serum albumin.

As a means to identify clinically significant and potentially fatal cases of DILI, subjects who meet the criteria for Hy's Law can be identified. The criteria that are typically used to define subjects who represent possible Hy's Law cases are the presence of all of the following (FDA, 2009):

1. ALT or AST > 3X ULN;
2. alkaline phosphatase < 2X ULN;
3. an increase in bilirubin ≥ 2X ULN;
4. and not explainable by ongoing events that are clearly not drug-induced, such as viral hepatitis.

The applicant used a modified definition of Hy's Law, as follows: the presence of either ALT or AST ≥ 2X Baseline, and/or total bilirubin > 2X ULN. Per this modified definition, an elevated

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total bilirubin is not required to meet the threshold for Hy's Law if transaminase values are ≥ 2X Baseline.

ISS Table 14.2.2 displays the proportion of subjects who met Hy's Law criteria in any of the three studies. Per that table, the Hy's law criteria were met by 49% of all placebo-treated subjects (N = 35) and by 28% of all casimersen-treated subjects (N = 76). However, this table also shows that no subject in any of the three trials had an elevated bilirubin > 2X ULN at any time. For this reason, what ISS Table 14.2.2 actually shows is that 49% of placebo-treated subjects and 28% of casimersen-treated subjects had at least one ALT and/or one AST post-baseline measurement that was ≥ 2X Baseline. To put these proportions into context, no subject in either treatment group in any trial had a normal ALT level at Baseline; all were high [Source: ISS Tables 14.3.1, 14.3.2, and 14.3.3]. Likewise, only one subject (placebo group) had a normal AST level at Baseline; the remainder of subjects in both treatment groups had high AST levels at Baseline. Because all subjects except for this placebo-treated subject began their trial with high ALT and high AST levels, no subject had a lab shift from normal at Baseline to high during the study, except for the single placebo-treated subject. He shifted from normal to high during study 4045-101.

In short, there were no Hy's Law cases in these studies. Instead, the high ALT and/or AST levels in every subject at Baseline represent the anticipated release of transaminases from degenerating skeletal muscle as a consequence of DMD.

The following table shows the proportion of subjects with shifts from normal to high levels of total bilirubin, GGT, APTT, INR, or PT at any time during the studies; and the proportion with shifts from normal to low measurements of serum albumin. In principle these abnormalities could herald hepatotoxicity.

Table 54. Proportion of Subjects with Laboratory Shifts from Normal to Abnormal as a Potential Reflection of DILI

Laboratory Parameter	Placebo (N = 35) (%)	Casimersen (N = 76) (%)
Total Bilirubin, Normal to High	6%	1%
GGT, Normal to High	3%	5%
APTT, Low/Normal to High	23%	33%
INR, Normal to High	6%	9%
PT, Normal to High	11%	15%
Albumin, Normal to Low	0	1%

[Source: ISS Tables 14.3.2 and 14.3.3]

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Clinical Reviewer's Assessment of the Potential Risk of Casimersen-Induced Hepatotoxicity
Four of the six laboratory parameters that are potentially related to hepatic injury shifted from normal to abnormal in a higher proportion of casimersen-treated subjects. Two of the six parameters shifted from normal to abnormal in a higher proportion of placebo-treated subjects. The differences in the proportion of subjects with abnormal shifts in each lab parameter was at most 5% between groups. This reviewer concludes that there is no noteworthy or imbalanced lab shift that would suggest the presence of casimersen-induced hepatotoxicity. This conclusion is supported by the lack of any hepatic-associated TEAEs in either treatment group. For these reasons, this reviewer does not believe that hepatotoxicity should be included as a potential risk in the Prescribing Information for the drug if it is granted accelerated approval.

8.5.5. Potential Risk of Cardiac Events

Cardiac findings, especially cardiomyopathy, are relatively common in subjects with DMD. For that reason, these types of events are evaluated below.

8.5.5.1. Cardiac-associated SAEs Reported During the Three Studies

Three SAEs were reported during the studies.

1. Subject 4045-301. (b) (6) was treated with placebo, and he had an SAE with preferred terms of non-cardiac chest pain and Troponin T increased. These events also led to interruption in study drug administration.

2. Subject 4045-301. (b) (6) was treated with casimersen, and he had an SAE with a preferred term of chest pain. This event was also judged as severe.

3. Subject 4045-301. (b) (6) was treated with casimersen, and he had ultimately fatal SAEs of rhabdomyolysis, hyperkalemia, and cardiac arrest. These events occurred in quick succession after he received sevoflurane general anesthesia for a port placement. His narrative is in section 8.4.1.

There were no other cardiac-associated events that were rated as severe, or that caused drug interruptions.

8.5.5.2. Cardiac-associated Non-serious TEAEs Reported During the Three Studies

To identify all cardiac-associated TEAEs, the applicant constructed ISS Table 12.3.1 by using the following SMQs: the cardiomyopathy SMQ; the cardiac failure SMQ; and the arrhythmia related investigations, signs and symptoms SMQ. The table below shows the identified cardiac events.

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Table 55. Cardiac Events Identified with Cardiac-associated SMQs in the Three Studies

	POP1 (Double-Blind Period of 4045-301)		POP2 (Double-Blind Period of 4045-101 & 4045-301)		POP3 (Casimersen Treatment Period of 4045-101, 4045-301 & 4045-302)
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=31)	Casimersen 30 mg/kg (N=57)	Placebo (N=35)	Casimersen (N=65)	All Casimersen (N=76)
Number of Patients with at Least One Treatment-Emergent Cardiac Event	4 (12.9%)	6 (10.5%)	4 (11.4%)	6 (9.2%)	8 (10.5%)
CARDIAC DISORDERS	2 (6.5%)	4 (7.0%)	2 (5.7%)	4 (6.2%)	5 (6.6%)
Arrhythmia	1 (3.2%)	0	1 (2.9%)	0	0
Cardiac arrest	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Cardiomyopathy	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Left ventricular dysfunction	0	0	0	0	1 (1.3%)
Tachycardia	1 (3.2%)	1 (1.8%)	1 (2.9%)	1 (1.5%)	1 (1.3%)
Ventricular hypertrophy	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3.2%)	2 (3.5%)	1 (2.9%)	2 (3.1%)	4 (5.3%)
Chest pain	1 (3.2%)	2 (3.5%)	1 (2.9%)	2 (3.1%)	4 (5.3%)
INVESTIGATIONS	1 (3.2%)	0	1 (2.9%)	0	0
Heart rate increased	1 (3.2%)	0	1 (2.9%)	0	0
RENAL AND URINARY DISORDERS	1 (3.2%)	0	1 (2.9%)	0	0
Myoglobinuria	1 (3.2%)	0	1 (2.9%)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)
Nocturnal dyspnoea	0	1 (1.8%)	0	1 (1.5%)	1 (1.3%)

[Source: ISS Table 12.3.1]

In both treatment groups (placebo, N= 35; casimersen, N = 76), approximately 11% of subjects were identified by the applicant to have had a cardiac event. The only event that was identified in more than 1 subject in either treatment group was chest pain (placebo, 1 subject; vs. casimersen, 4 subjects).

In order to gain more information about events of chest pain as identified by SMQs that searched for this preferred term among others, this reviewer used the words "chest pain" to search ADAE.xpt. This search term identified subjects with not only preferred terms of "chest pain," but also verbatim terms that included the words "chest pain" within a longer term. The table below shows the results of the search.

Table 56. Subjects in the Three Studies with Preferred or Verbatim Terms of Chest Pain in ADAE.xpt

Placebo Group (N = 35) Subject ID and Terms	Casimersen Group (N = 76) Subject ID and Terms
4045-101. (b) (6) • Preferred Term: procedural pain • Verbatim Term: "chest pain from port placement"	**4045-101.** (b) (6) **Event 1** • Preferred Term: procedural pain

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	• Verbatim Term: "non-cardiac chest pain after port removal" **Event 2** • Preferred Term: procedural pain • Verbatim Term: "non-cardiac chest pain after port placement"
4045-301. (b) (6) • Preferred Term: chest pain • Verbatim Term: "chest pain"	**4045-301.** (b) (6) • Preferred Term: chest pain • Verbatim Term: "chest pain"
4045-301. (b) (6) • Preferred Term: non-cardiac chest pain • Verbatim Term: "chest pain most probably not cardiac"	**4045-301.** (b) (6) **Event 1** • Preferred Term: chest pain • Verbatim Term: "chest pain, etiology unknown" **Event 2** • Preferred Term: musculoskeletal chest pain • Verbatim Term: "chest pain, musculoskeletal"
4045-301. (b) (6) **Event 1** • Preferred Term: non-cardiac chest pain • Verbatim Term: "chest pain (right side) (reflux)" **Event 2** • Preferred Term: myalgia • Verbatim Term: "chest pain (muscle)"	**4045-301.** (b) (6) • Preferred Term: chest pain • Verbatim Term: "chest pain, NOS"
	4045-301. (b) (6) **Event 1** • Preferred Term: chest pain • Verbatim Term: "chest pain (possible heartburn per mother, patient stated pain was 7 out of 10)" **Event 2** • Preferred Term: non-cardiac chest pain

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	• Verbatim Term: "non-cardiac chest pain" Event 3 • Preferred Term: non-cardiac chest pain • Verbatim Term: "non-cardiac chest pain"

[Source: use of ADAE.xpt]

Using this search of ADAE.xpt, 4 subjects were identified in the placebo group. Only 1 of these 4 subjects (404-301. (b) (6)) had a preferred term of chest pain, hence the capture of only that subject by the applicant's SMQs. The other 3 subjects in the placebo group had the words "chest pain" in the verbatim terms for their events, but none of the descriptions in these verbatim terms appears to invoke chest pain of cardiac origin. For these reasons, the reviewer concludes that there was indeed only a single subject in the placebo group with a valid preferred term of chest pain. This single subject in the 35 subjects of the total placebo group (N = 35) amounts to a proportion of 3%.

In the casimersen group, 5 subjects were identified. Four of these 5 subjects (4045-301 (b) (6)) had chest pain as the preferred term, and by this means they were identified via the applicant's SMQ searches. None of the verbatim terms describe a source of chest that is conclusively non-cardiac, with the possible exception of the event in subject 4045-301. (b) (6), in which the subject's chest pain is attributed by the mother to "possible heartburn." However, this attribution is insufficient to conclude that the preferred term is not cardiac in origin. The fifth subject (4045-101 (b) (6)) had preferred terms of "procedural pain" for two separate events; neither of these events would be captured by the applicant's search strategy. The verbatim terms for these two events included the words "chest pain," but the language in the verbatim terms also indicated that the chest pain was caused by procedural events associated with port placement or port removal. These events of chest pain are clearly not of cardiac origin. The reviewer concludes that there were indeed 4 subjects in the casimersen group with valid preferred terms of chest pain. These 4 subjects out of 76 subjects in the all-casimersen group amount to a proportion of 5%.

Clinical Reviewer's Comments

The ultimately fatal SAE that is cited above and described elsewhere was judged by the investigator as being related to the use of sevoflurane anesthesia, which has been reported as a risk in patients with DMD. The other two SAEs that are cited above involved chest pain, with one event occurring in each treatment group. This reviewer does not believe that these SAEs represent an imbalance between treatment groups.

There was not a difference in the overall proportion of subjects with cardiac events between treatment groups, nor a substantial difference in the proportion of subjects with the most

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common preferred term of chest pain. This judgment is bolstered by the ECG and ECHO data discussed in a previous section. The latter data showed no substantial difference between treatment groups in the proportion of subjects with a PCSA in any ECG or ECHO parameters across the three studies. Based upon these clinical and objective data, the reviewer concludes that the cardiac events were caused not by casimersen, but rather by the underlying condition of DMD in these subjects.

8.5.6. Potential Risk of Coagulopathy/Thrombocytopenia

Coagulopathy and/or thrombocytopenia have been identified as risks after infusion of other ASOs, albeit not with ASOs that share a molecular backbone with casimersen. These potential risks will be evaluated together in this section.

8.5.6.1. SAEs Associated with Coagulopathy or Thrombocytopenia During the Three Studies

One subject (4045-101 (b) (6)) who was treated with casimersen developed sequential SAEs of bacteremia, septic embolus, and vena cava thrombosis following a port placement. The narrative for this series of SAEs is in section 8.4.2.

Two of the three SAEs reported for this subject were also severe events (septic embolus and vena cava thrombosis). In addition, the three SAEs caused a drug interruption. There were no other TEAEs potentially associated with coagulopathy or thrombocytopenia that resulted in drug interruptions.

8.5.6.2. Non-serious TEAEs Associated with Coagulopathy or Thrombocytopenia During the Three Studies

This reviewer used the hematopoietic thrombocytopenia SMQ to search ADAE.xpt. No events were identified using this strategy. The identical result was obtained by the applicant's use of this SMQ, as shown in ISS Table 12.4.1.

The reviewer used ISS Table 5.1 to identify any TEAEs that are potentially associated with either coagulopathy or thrombocytopenia. The following table lists these events.

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Table 57. Proportion of Subjects with TEAEs that are Potentially Associated with Coagulopathy or Thrombocytopenia in the Three Studies

TEAE preferred term	Placebo (N = 35) (%)	Casimersen (N = 76) (%)
Epistaxis	6%	3%
Hematoma, post-procedural hematoma, or catheter site hematoma	0	7%
Coagulopathy	3%	0
Application site bruise, catheter site bruise, infusion site bruising, injection site bruising, vessel puncture site bruise, contusion, post-procedural contusion, or eye contusion	31%	20%

[Source: reviewer's use of ISS Table 5.1]

If the complete list of TEAEs in this table is assumed to be associated with coagulopathy or thrombocytopenia in each treatment group, then the proportion of unique subjects with these events in the placebo group was 40%, and in the casimersen group it was 26%. Note that the definition of unique subjects was that a subject was counted only once in the overall total, even if that subject had more than one of the preferred terms comprising the list.

The reviewer recognizes that the listed events of bruises and contusions could occur in anyone, irrespective of coagulation or platelet status. If all events of bruise or contusion (i.e., the last row in the above table) are removed, then the proportion of unique subjects with the remaining events in each treatment group would be 9% in the placebo group and 8% in the casimersen group.

Clinical Reviewer's Comments
There does not appear to be an imbalance that suggests casimersen-treated subjects have more of these events than placebo-treated subjects, whether the entire list of events is evaluated, or the subset of the list that omits bruises and contusions.

8.5.6.3. Evaluation of Lab Parameters that Indicate Coagulopathy or Thrombocytopenia

PCSAs in platelet count are pre-specified in the SAP as either of: a platelet count that is < 150 X 10^9/L; or a platelet count that is < 200 X 10^9/L and also at least 100 X 10^9/L below the platelet count at Baseline. ISS Table 14.2.1 shows that 6% of placebo-treated subjects (N = 35) and 8%

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of casimersen-treated subjects (N = 76) met PCSA criteria for low platelet count at least once during the three studies.

The proportion of subjects with shifts in the values of lab parameters from Baseline to abnormally high or abnormally low at any time during the studies is shown in ISS Tables 14.3.1, 14.3.2, and 14.3.3. The table below shows these lab shifts for platelet count, APTT, INR, and PT during the double-blind periods of studies 4045-101 and 4045-301 (i.e., population 2).

Table 58. Shifts from Baseline to Abnormal Levels of Platelets, APTT, INR, and PT in Population Two

Lab Parameter	Placebo (N = 35) (%)	Casimersen (N = 65) (%)
Platelet Count: Shift from High or Normal at Baseline to Low	3%	6%
APTT: Shift from Low or Normal at Baseline to High	23%	25%
INR: Shift from Low or Normal at Baseline to High	6%	11%
PT: Shift from Low or Normal at Baseline to High	11%	15%

[Source: ISS Table 14.3.2]

These 4 lab parameters were evaluated further by examining the mean change from Baseline to the Final Observation for each treatment group in the same population. The Table below shows these data.

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Table 59. Mean Changes from Baseline to Final Observation in Platelet Count, APTT, INR, and PT

	Placebo (N = 35)			Casimersen (N = 65)		
Lab Parameter	Mean Baseline	Mean Final Observation	Mean CFB	Mean Baseline	Mean Final Observation	Mean CFB
Platelet count (cells X 10^9/L)	312	325	+13	318	317	-2
APTT (sec)	25.3	27.4	+2.1	24.4	26.8	+2.3
INR	1.04	1.02	-0.02	1.02	1.02	0.0
PT (sec)	10.9	10.8	-0.1	10.8	10.8	+0.1

[Source: ISS Table 14.1]

Clinical Reviewer's Comments about Lab Parameters

In the table of lab shifts, a higher proportion of casimersen-treated subjects shifted to abnormal values for each of the lab parameters, as compared to placebo-treated subjects. However, the profile of these parameters in the table of mean CFB for each treatment group does not suggest any group abnormality. For each of the 4 parameters within the casimersen group, the mean final observation was within normal limits, and the mean CFB for each parameter in the casimersen group was very similar to corresponding values in the placebo group. Taken together, these lab results do not appear to show a greater potential for casimersen-treated subjects to develop a coagulopathy or thrombocytopenia than placebo-treated subjects.

Clinical Reviewer's Comments about the Overall Potential for Coagulopathy or Thrombocytopenia

The lab measurements of 4 parameters that provide an index to coagulopathy or a direct measurement (in the case of platelet count) do not suggest a potential for coagulopathy or thrombocytopenia in the casimersen group. Likewise, the relevant TEAEs do not suggest an increased potential for coagulopathy or thrombocytopenia in the casimersen group. In fact, the casimersen group had somewhat lower rates of events that could be considered indicative of coagulopathy. In view of these clinical data, this reviewer does not recommend that a potential risk of coagulopathy or thrombocytopenia should be included in the Warnings and Precautions section of the Prescribing Information should casimersen be granted accelerated approval.

8.5.7. Port-related Events

Port-related TEAEs are common during prolonged treatment with any infused drug or biological product. The evaluation below will examine whether there is a substantial difference in the proportion of subjects with these events as a function of treatment group.

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The applicant constructed ISS Table 12.5.1 by identifying subjects with port-related events by searching for preferred terms in each of the following: embolic and thrombotic events, venous SMQ; extravasation events (injections, infusions, and implants) SMQs; in High Level Terms (HLTs) of sepsis, bacteremia, viremia and fungemia NEC (not elsewhere classified); in HLTs under implant and catheter site reactions HLT; and in High Level Group Term (HLGTs) of endocardial disorders, and device issues. Verbatim terms were also sought containing: /port<, /central venous< and /central line<. Events were not included they occurred while the subject had a port inserted.

According to ISS Table 12.5.1, the number of unique subjects with TEAEs that occurred while a port was inserted was 4 out of 15 in the placebo group (27%), and 14 out of 31 in the casimersen group (45%).

This reviewer used all port-related TEAE terms captured in ISS Table 12.5.1 in order to perform an independent search for subjects with those terms. Sources included ADAE.xpt, ISS Listing 25.4.1 (port-related events), ISS Listings 22.2.1 through 22.2.5 (events related to study procedures), and subject narratives as needed. The reviewer omitted any subjects with procedural pain associated with muscle biopsies, and also any subjects with an event that was not explicitly associated with a port. Catheter site infusion reactions (i.e., reactions due to peripheral venous catheter infusions and not to infusions through a central venous port) were also omitted. These latter events are discussed above in section 8.5.3.

Via this process, the reviewer identified in the placebo group a total of six unique subjects who experienced TEAEs while a port was being inserted or in place (40%). From the casimersen group (N = 31), fifteen unique subjects experienced TEAEs while a port was being inserted or in place (48%).

Regarding significant port-related events, 3 events in the casimersen group were SAEs. These events were bacteremia, septic embolus, and vena cava thrombosis (all in subject 4045-101. (b) (6)). Three port-related TEAEs in the casimersen group were severe. These included the non-serious TEAE of device issue (subject 4045-301. (b) (6)), and two serious TEAEs of septic embolus and vena cava thrombosis (both in subject 4045-101 (b) (6)). Finally, 3 events led to drug interruption. These included the SAEs of bacteremia, septic embolus, and vena cava thrombosis (subject 4045-101. (b) (6)).

Clinical Reviewer's Comments

There is no substantial difference between treatment groups in the proportion of subjects with port-related events. Although it may appear that there are more significant serious and non-serious TEAEs in the casimersen group, note that the collection of SAEs, severe TEAEs, and TEAEs leading to drug interruption occurred in just two subjects. For these reasons, the reviewer

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concludes that port-related events do not need to be included in the Warnings and Precautions section of the Prescribing Information should casimersen be granted accelerated approval.

8.5.8. **Rhabdomyolysis**

Rhabdomyolysis occurs more commonly in patients with DMD than in the general population. Moreover, patients with DMD may experience this event after a smaller degree of physical activity than others, and general anesthetic agents such as sevoflurane may also precipitate rhabdomyolysis in these patients. In addition, this event is of interest in the context that casimersen's mechanism of action targets myofibers.

All of the events of rhabdomyolysis occurred in subjects enrolled in study 4045-301. Six serious or non-serious TEAEs of rhabdomyolysis were reported. Two subjects (6%) in the placebo group (N = 31), and 4 subjects (7%) in the casimersen group (N = 57) experienced this event. The table below shows pertinent characteristics of these events in the six subjects.

Table 60. Characteristics of the Six Events of Rhabdomyolysis in Study 4045-301[1]

Case ID	Treatment	Trigger	Myalgia (Yes/No)	Weakness/difficulty walking (Yes/No)	Discolored urine (Yes/No)	Creatinine kinase level (U/L)
4045-301 (b) (6)	Casimersen 30 mg/kg	Sevoflurane	Yes (plus pseudohypertrophy calf)	No	Yes	18,326 (B) 6,639 (-57 d) 12,851 (0 d) 41,509 (+1 d) 23,457 (+2 d)
4045-301	Casimersen 30 mg/kg	Activity	Yes	Yes	Yes	11,943 (B) 18,890 (-36 d) 41,579 (0 d) 29,201 (6 d)
4045-301	Casimersen 30 mg/kg	Sevoflurane	Yes	No	No	10,704 (B) 7,038 (-70 d) 58,660 (0 d) 264,800 (+1 d) 133,040 (+2 d) 36,140 (+3 d) Patient expired 4 d after event onset
4045-301	Casimersen 30 mg/kg	Activity	Yes	Yes	Yes	11,757 (B) 16,472 (-8 d) 75,654 (0 d) 18,476 (+6 d)
4045-301	Placebo	Activity	Yes (plus calf swelling)	No	No	12,144 (B) 12,693 (-40 d) ~41,000 (0 d) 22,662 (+1 d) 6,139 (+5 d)
4045-301	Placebo	Unknown	Unknown	Unknown	Unknown	16,193 (B) 13,630 (-77 d) 15,220 (+7 d)

B=Baseline; d=days from event onset.

[1] Note the mis-identification of the final subject's study ID. The subject's ID is actually 4045-301. (b) (6)

[Source: Summary of Clinical Safety, Table 34]

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Of the five TEAEs of rhabdomyolysis about which details are known, three events occurred after moderate to vigorous physical activity, and two events occurred after the use of sevoflurane for general anesthesia.

Five of the six events were SAEs, and one event was non-serious. In addition, one of the serious events of rhabdomyolysis caused a fatal outcome (rhabdomyolysis, hyperkalemia, and cardiac arrest in subject 4045-301. (b) (6)). The narrative of this case is in section 8.4.1.

In each of the five non-fatal cases, the event of rhabdomyolysis caused a study drug interruption. However, in each of these cases, study drug was re-initiated without a recurrence of diagnosed rhabdomyolysis. An event of chromaturia was reported approximately ten months after resolution of rhabdomyolysis in subject 4045-301 (b) (6), but the event resolved after one day without other sequelae.

Clinical Reviewer's Comments
These events of rhabdomyolysis appear to have been precipitated by physical activity or by the use of sevoflurane, both of which are known to be able to trigger rhabdomyolysis in patients with DMD. There does not appear to be an imbalance of these events between the treatment groups. The reviewer concludes that each of these events of rhabdomyolysis are consistent with the greater risk for such events in patients with DMD. This conclusion also suggests that muscle-associated events such as rhabdomyolysis are not associated with casimersen's targeted mechanism of action in myofibers.

8.6. Safety Analyses by Demographic Subgroups

All enrolled subjects in the applicant's three submitted studies in DMD were males due to the X-linked inheritance pattern of DMD. Approximately 90% of the subjects were white, and few were of Hispanic or Latino ethnicity. Hence there are no suitable subgroups for analyses using gender, race, or ethnicity.

However, two other subgroups were used by the applicant to analyze the studies for differences in safety outcomes. These subgroups were age (three subgroups of: 6 to < 9 years; 9 to < 12 years; and 12 years or older) and BMI (2 subgroups of: < median; or >/= median).

8.6.1. Evaluation of SAEs by Age and BMI Subgroups

The most meaningful safety outcome to analyze by subgroups are all subjects with reported SAEs in the double-blinded treatment periods of studies 4045-101 and 4045-301 (i.e., population 2). The table below displays SAEs by subgroup. The N values in each subgroup

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denote the number of subjects in that group. The treatment groups are from studies 4045-101 and 4045-301 (i.e., population 2). The SAE % values within each subgroup denote the proportion of subjects who have SAEs.

Table 61. Comparison of SAEs by Age and BMI Subgroups within Each Treatment Group

	Subgroup				
	Age (years)			BMI	
	6 to < 9	9 to < 12	12 and older	< median	≥ median
Placebo: N SAE % in group	15 20%	13 15%	7 14%	14 7%	19 26%
Casimersen: N SAE % in group	29 17%	21 29%	15 13%	34 18%	29 24%

[Source: ISS Tables 10.2.1, 10.2.2, and 10.2.3 for the three Age subgroups; and ISS Tables 10.4.1 and 10.4.2 for the two BMI subgroups]

The placebo subgroups may be used to define the rough variability in the proportions of SAEs, because casimersen cannot influence those data. In the discussions below, the placebo subgroups will be described first, followed by an evaluation of the proportions of SAEs in the casimersen subgroups.

8.6.1.1. Analysis of SAEs in Age Subgroups

In the three age subgroups within the placebo group, the proportion of subjects with SAEs ranged from 14% to 20%. In the same age subgroups, the proportion of casimersen-treated subjects with SAE ranged from 13% to 29%. The age subgroup that may appear to have a higher proportion of SAEs in the casimersen group than the placebo group is the subgroup from 9 to < 12 years of age. Using ISS Table 10.2.2 to examine the SAEs within this age subgroup shows that three casimersen-treated subjects reported four SAEs in the infections SOC (bacteremia, septic embolus [both in the same subject], gastrointestinal viral infection, and influenza); and that one placebo-treated subject in this age subgroup reported one SAE in the infections SOC (pneumonia). In this same age subgroup, three casimersen-treated subjects reported SAEs of rhabdomyolysis; and no placebo-treated subject reported an SAE. Of note is that all of these serious TEAEs were transient, and that all subjects received study drug after event resolution, without recurrence of the events.

Clinical Reviewer's Comments
Although the casimersen age subgroup of 9 to < 12 years had an increased number of SAEs of rhabdomyolysis and an increased number of SAEs in the infections SOC, there are several caveats to concluding a treatment group imbalance from these data. First, all numbers in each subgroup were rather small, making it difficult to draw firm conclusions. Second, no event recurred in the face of continued study drug treatment. Finally, it is not logical to this reviewer

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that a potential safety concern would be confined to the middle age subgroup, but non-existent in the younger or older subgroups. For these reasons, the reviewer concludes that there is no clear effect of age subgroups on SAE rates. Nevertheless, the possible risk of infection in casimersen-treated subjects bears close scrutiny as further safety data become available from the ongoing studies 4045-301 and 4045-302. In addition, subjects with rhabdomyolysis are discussed at greater length above, in section 8.5.8.

8.6.1.2. Analysis of SAEs in BMI Subgroups

In the subgroup of BMI < median, the SAE rate was 18% in casimersen-treated subjects and 7% in placebo-treated subjects. In the subgroup of BMI ≥ median, the SAE rate was 24% in casimersen-treated subjects and 26% in placebo-treated subjects. Using ISS Table 10.4.1 to examine reported SAEs in the subgroup of BMI < median, the only imbalance is in the Infections SOC, in which three casimersen-treated subjects reported three SAEs (influenza, otitis media chronic, and viral infection), and no placebo-treated subjects reported SAEs in this SOC.

Clinical Reviewer's Comments
Using the same reasoning for the BMI subgroup data as for the age subgroup data, it appears to this reviewer that there is no clear effect of BMI subgroups on SAE rates, perhaps with the exception of infections. If casimersen is granted accelerated approval, then caregivers and patients should be educated to report significant infections to their medical care personnel in order to obtain appropriate medical management.

8.6.2. Analysis of Non-serious TEAEs in Age Subgroups

The reviewer used ISS Tables 5.2.2.1 through 5.2.2.3 to collate a list for each age subgroup of the most frequent non-serious TEAEs that were more common in the casimersen group than the placebo group. The table below shows the proportions of subjects who experienced the five most common non-serious TEAEs in each age subgroup in population 2, to maintain consistency with the evaluation of events in this same population, as described above. The table below also shows the proportion of subjects experiencing severe non-serious TEAEs in each subgroup.

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Table 62. Five Most Common Non-serious TEAEs in the Casimersen Treatment Group of Each

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Age Subgroup[1]

AGE 6 to < 9 years		
	PBO (N = 15) % subjects	CAS (N = 29) % subjects
Proportion with Severe Events	0	3%
Non-serious TEAEs (preferred terms)		
Cough	33%	35%
Headache	13%	21%
Ear infection /Nasal congestion	7% / 13%	17% each
Rash	7%	14%
Nausea / Arthralgia / Seasonal allergy	0 / 7% / 7%	10% each
AGE 9 to < 12 years		
	PBO (N = 13) % subjects	CAS (N = 21) % subjects
Proportion with Severe Events	15%	14%
Non-serious TEAEs (preferred terms)		
Nasopharyngitis / Vomiting	31% / 31%	48% each
Pyrexia	15%	43%
Headache	15%	38%
Diarrhea / Cough	31% / 15%	33% each
Fall / Oropharyngeal pain	15% / 8%	29% each
AGE 12 years and older		
	PBO (N = 7) % subjects	CAS (N = 15) % subjects
Proportion with Severe Events	14%	7%
Non-serious TEAEs (preferred terms)		
Headache	29%	47%
Back Pain	29%	40%
Vomiting / Arthralgia / Pain in extremity	14% / 29% / 14%	33% each
Nausea / Contusion / Dizziness	0 / 14% / 14%	27% each
URTI / Muscular weakness / Oropharyngeal pain	14% / 0 / 14%	20% each

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[1]The presence of more than one TEAE in the placebo column of any row means that each of those events was experienced by an identical proportion of casimersen-treated subjects.

[Source: ISS Tables 5.2.2.1, 5.2.2.2, 5.2.2.3]

There is no noteworthy imbalance between the placebo and casimersen treatment groups in the proportion of subjects with severe events in any age subgroup. However, there appears to be an increased proportion of severe events in both treatment groups in the two older subgroups compared to the younger subgroup. It appears from the nature of the most common TEAEs in the two older subgroups that the extent of disability due to DMD is increasing compared to the younger subgroup. For example, there are no common events of weakness or back / extremity pain in the younger sub group, but one or more of these events are common in the older subgroups. Headaches, GI events, and infections are present in each age group. The most common of these events was headache. Nearly all events of headache in both treatment groups were mild, transient (i.e., resolved on date of onset), and unassociated with other events.

Clinical Reviewer's Comments
Other than an increase in the proportion of subjects with severe events in the older age subgroups, and an anticipated increase of events associated with disability as a function of older age in DMD, there appears to be no class of non-serious event that is clearly associated with age.

8.6.3. Analysis of Non-serious TEAEs in BMI Subgroups

The reviewer pursued a similar strategy in analyzing the five most common TEAEs in casimersen-treated subjects within each of the BMI subgroups in the randomized, double-blind periods of studies 4045-101 and 4045-3-1 (i.e., population 2). ISS Tables 5.2.4.1 and 5.2.4.2 were used to construct the table below.

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Table 63. Five Most Common Non-serious TEAEs in the Casimersen Treatment Group of Each BMI Subgroup[1]

BMI < MEDIAN In Randomized, Double-Blind Periods of Studies 4045-101 and 4045-301		
	PBO (N = 14) % subjects	CAS (N = 34) % subjects
Proportion with Severe Events	0	0
Non-serious TEAEs (preferred terms)		
Pyrexia / Vomiting	21% / 29%	32%
Arthralgia	14%	21%
Oropharyngeal pain	7%	18%
Rhinitis / Constipation / Back pain / Pain in Extremity	7% / 0 / 7% / 7%	15%
Ear infection	7%	12%
BMI >= MEDIAN In Randomized, Double-Blind Periods of Studies 4045-101 and 4045-301		
	PBO (N = 19) % subjects	CAS (N = 29) % subjects
Proportion with Severe Events	16%	17%
Non-serious TEAEs (preferred terms)		
Headache / Nasopharyngitis	16% / 42%	48%
Cough / Diarrhea	11% / 32%	38%
Nausea	0	35%
Pyrexia	21%	31%
Fall	26%	28%

[1]The presence of more than one TEAE in any row means that the events in that row were experienced by the same proportion of casimersen-treated subjects.

[Source: ISS Tables 5.2.4.1 and 5.2.4.2]

There is no imbalance between treatment groups in the proportion of subjects with severe events in either of the BMI subgroups. GI events and infections are among the most common events in each BMI subgroup, as is pyrexia. This reviewer concludes that the most common non-serious TEAEs are not noticeably different as a function of BMI.

The apparent imbalances between casimersen and placebo treatment groups in the proportions of subjects with events of pyrexia, GI events, and events of infection have been discussed at greater length in a number of sections above.

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Clinical Reviewer's Comments
There appears to be no class of non-serious event that is over-represented in the casimersen vs. placebo treatment group as a function of BMI.

8.7. Evaluation of Safety Data in the 120-day Safety Update Report

This section evaluates safety findings from the 120-day Safety Update Report. The Safety update Report presents data following the data cut-off (5/31/19) of the original NDA submission, for the reporting period extending from 6/1/19 through 2/28/20.

8.7.1 Overview

The 120-day Safety Update Report includes new safety data from the cut-off date of 5/31/19 (i.e., the cut-off date for the clinical submission for the NDA) through the cut-off date of 2/28/20. This duration will be termed the SU period. During the SU period, nine additional subjects were enrolled into study 4045-301 (n = 2, placebo; n = 7, casimersen). The total safety database for Population 1 as of the SU cut-off-date (2/28/20) consists of data from 97 subjects (n = 33, placebo; n = 64, casimersen). In the SU period's ISS tables and listings, safety data are presented cumulatively for each of the three safety populations.

For each section below, sources for the data presented are SU period's ISS tables for all cumulative TEAEs, cumulative SAEs, and cumulative adverse events leading to discontinuation. ISS listings were also examined if needed.

8.7.2. Cumulative SAEs

SAEs had a similar incidence rate in both treatment groups, with the exception of events of rhabdomyolysis (placebo, 3% vs. casimersen, 6%). There were no new SAEs of rhabdomyolysis during the SU period. Events of rhabdomyolysis are discussed in earlier sections of this review.

8.7.3. Cumulative Adverse Events Leading to Discontinuation

There were no new events that led to study drug discontinuation during the SU period.

8.7.4. Cumulative Non-serious TEAEs

The following table shows the proportion of casimersen-treated subjects with treatment-emergent adverse reactions at rates of at least 20% and also at least 5% greater than the rates in placebo-treated subjects.

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Table 64. Treatment-Emergent Adverse Reactions Reported in at Least 20%[1] of Subjects Treated with Casimersen and at a Rate at Least 5% More than Placebo (Study 4045-301)

Adverse Reaction	Casimersen (n = 64)	Placebo (n = 33)
Pyrexia	34%	27%
Headache	34%	21%
Procedural Pain	25%	18%
Upper Respiratory Tract Infection	25%	12%
Arthralgia	20%	15%

[1] Other adverse reactions that occurred in at least 10% of casimersen-treated subjects, and that were reported at a rate that was 5% greater in the casimersen group than in the placebo group, were [presented from higher to lower rates in the casimersen group]: rhinitis, oropharyngeal pain, nausea, post-traumatic pain, and ear pain.

Clinical Reviewer's Comment

This cumulative table of adverse reactions (i.e., original cut-off date plus SU time) is similar to the adverse reactions table in section 8.4.5 (i.e., only original cut-off date). There are several observations, however.

1. *The increased rates of upper respiratory tract infection in this cumulative table reinforces the possibility that casimersen may be associated with higher rates of certain infections. Note that the term "upper respiratory tract infection" in this table is a single event term, and not a grouping of several event terms as was provided in section 8.4.5.4.*

2. *The increased rate of proteinuria in the list of reactions that are footnoted below the cumulative table of treatment-emergent adverse reactions, above, is consistent with the increased rate of proteinuria that was identified in the original dataset (i.e., cut-off date of 5/31/19). This reinforces the possibility that casimersen may have an increased likelihood for renal injury. See also section 8.7.5.1. for additional discussion of this issue.*

8.7.5. Submission-specific Issues

In the eight subsections below, the applicant's search strategies for each Issue of Identified or Potential Risk during the SU time were identical to those used to evaluate these issues in the original safety data, which are described in section 8.5. The eight subsections below are presented in the same order as in section 8.5.

8.7.5.1. Renal Toxicity

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The SMQ for Acute Renal Failure identified no cases of new TEAEs of acute renal failure during the SU period. The cumulative total proportion of subjects with proteinuria (preferred terms of "protein urine present" and "proteinuria" was 8% in the casimersen group (N = 64) and 0 in the placebo group (N = 33).

In study 4045-301, two new casimersen-treated subjects and no new placebo-treated subjects had potentially clinically significant abnormal (PCSA) dipstick urine protein at any time during the SU period. PCSA urine dipstick protein is defined as > 1+ by the applicant's SAP. The cumulative rate of PCSA dipstick urine protein was 16% in the casimersen group and 0 in the placebo group.

In study 4045-301, two new placebo-treated subjects and no new casimersen-treated subjects had a shift from a normal baseline dipstick urine protein to any abnormal level in the SU period. The cumulative rate of a lab shift from normal to abnormal dipstick urine protein is 17% in the casimersen group and 15% in the placebo group.

Clinical Reviewer's Comment
The identified risk of renal injury in casimersen-treated subjects continues to be apparent in the cumulative safety database. This risk will be addressed in the label for the product if it is granted approval.

8.7.5.2. Hypersensitivity

The applicant's use of MedDRA's Hypersensitivity SMQ in the cumulative safety database identified a similar number of events as in the original database, with a lower proportion of such events in the casimersen group than the placebo group.

Clinical Reviewer's Comment
This result in the cumulative database is consistent with the lack of conclusive evidence in the original database that casimersen is associated with a risk for hypersensitivity.

8.7.5.3. Infusion-Related Reactions (IRRs)

The applicant used the same definition of IRRs to identify events in the SU period as was used in the original period: namely, any TEAE with onset within 24 hours following an IV infusion of placebo or of casimersen. In this cumulative database, this clinical reviewer followed the same strategy as was used in the original database, as follows. The table below shows the proportion of all TEAEs that occurred within 24 of IV infusion in the All-casimersen population (N = 101), if but only if the events occurred in this casimersen group at a rate ≥ 3% and also at a rate > in the placebo group in Population 2 (N = 37).

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Table 65. IRRs that Occurred in at Least 3% of Casimersen-treated Subjects and at a Greater Rate than Placebo

IRR (preferred term)	Placebo (N = 37) (% of Subjects)	Casimersen (N = 101) (% of Subjects)
Headache	5%	16%
Vomiting	8%	10%
Pyrexia	5%	9%
Abdominal Pain, Abdominal Pain Upper, and Abdominal Pain Lower	5%	9%
Nasopharyngitis	5%	6%
Upper Respiratory Tract Infection	3%	6%
Nausea	0	6%
Cough	0	5%
Flushing	3%	4%
Contusion	0	4%
Scoliosis	0	4%
Rhinitis	0	4%
Ligament Sprain	0	3%
Cataract	0	3%

Clinical Reviewer's Comment
The IRRs themselves and the cumulative proportion of subjects with each IRR are similar to those in the original database. Among the IRRS shown above, those that appear to this reviewer to be noteworthy and also more common in casimersen-treated subjects are headache, pyrexia, and upper respiratory tract infection. These events are discussed in greater detail in earlier subsections of section 8.

8.7.5.4. Hepatotoxicity

For this cumulative safety database, the applicant used the same search strategy to identify potential events of hepatotoxicity as was used in the original database. No events were detected. Moreover, no subject met laboratory criteria that are used to identify cases of Hy's Law, using the widely accepted criteria for Hy's Law, as discussed in section 8.5.4.2.

Clinical Reviewer's Comment
There does not appear to be a risk of hepatotoxicity in casimersen-treated subjects.

8.7.5.5. Cardiac Events

To identify cardiac events, the applicant used the same MedDRA SMQ search strategy in the cumulative safety database as in the original database. In study 4045-301, there was a greater

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proportion of treatment-emergent cardiac events in placebo-treated subjects (15%) than in casimersen-treated subjects (12%). No event occurred in more than 2 subjects in either treatment group. Turning to potentially clinically significant abnormalities (PTCAs) in cardiac conduction intervals, no subject in either treatment group in any population had PTCAs for PR, QRSA, or QTcF conduction intervals. In particular, no subject had a QTcF absolute value > 450msec, and no subject had a change from Baseline in QTcF of > 60msec.

Clinical Reviewer's Comment
There does not appear to be a risk of cardiac events that are associated with casimersen use.

8.7.5.6. Thrombocytopenia / Coagulation

The same search strategy was used to search for TEAEs of thrombocytopenia in the cumulative database as in the original database. No subject in either treatment group was identified with an event of thrombocytopenia. Laboratory shift tables were used to identify subjects in either treatment group with a shift from normal or high platelet counts at Baseline to a low platelet count at any time during study 4045-301. In casimersen-treated subjects, 5% shifted to a low platelet count, and 3% of placebo-treated subjects had such a shift. In both treatment groups, all subjects with a shift to a low platelet count had returned to a normal platelet count at the next scheduled visit.

To examine laboratory value changes that could potentially denote a coagulation issue, this clinical reviewer used the cumulative safety database to identify subjects with lab shifts from low or normal values at Baseline to abnormally high values at any time in study 4045-301 for the following parameters: activated partial thromboplastin time (APTT); International Normalized Ratio (INR); and prothrombin time (PT). The following table shows the proportion of subjects who met these criteria.

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Table 66. Shifts from Low or Normal Baseline Levels to Abnormally High Levels of APTT, INR, and PT in Study 4045-301

Lab Parameter	Placebo (N = 33) (%)	Casimersen (N = 64) (%)
APTT: Shift from Low or Normal at Baseline to High	30%	20%
INR: Shift from Low or Normal at Baseline to High	9%	11%
PT: Shift from Low or Normal at Baseline to High	15%	16%

Clinical Reviewer's Comment
Neither TEAEs nor laboratory values that can indicate issues of thrombocytopenia or coagulation appear to show an increased likelihood for these issues to occur in casimersen-treated subjects as compared to placebo-treated subjects. The results in the cumulative safety database are qualitatively similar to those in the original database.

8.7.5.7. Port-related Events

The search strategy for port-related events in the cumulative database was the same as that used in the original database. In study 4045-301, this search strategy identified port-related events in 33% of casimersen-treated subjects during port use (N = 21), and in 29% of placebo-treated subjects during port use (N = 14). None of the events was serious. Only a single identified event (i.e., procedural pain) occurred in more than one subject. Two casimersen-treated subjects had severe port-related TEAEs: device issue in one subject, and procedural pain in another.

Clinical Reviewer's Comment
There does not appear to be a noteworthy imbalance between treatment groups in the proportion of subjects with port-related TEAEs.

8.7.5.8. Rhabdomyolysis

The applicant used the same MedDRA Rhabdomyolysis SMQ to identify potential events of rhabdomyolysis in the original and the cumulative safety databases. In the cumulative safety database for study 4045-301, this strategy identified fewer TEAEs in the casimersen group (16%) than in the placebo group (24%). Many of the event terms were "myalgia" or "musculoskeletal pain."

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In the subjects with event terms of rhabdomyolysis, five subjects were in the casimersen group (8%) and two were in the placebo group 6%). In the casimersen group, four of the five subjects had serious events and one subject had an event in which seriousness was not reported. The four subjects with serious events in the casimersen group are the same as in the original database, and these subjects are discussed in section 8.5. In the placebo group, one of the two subjects had a serious event of rhabdomyolysis (3%), and one subject had a non-serious event. All but six of the eight subjects with an event of rhabdomyolysis were reported to have a causal precipitant of sevoflurane anesthesia or heightened physical activity. Two subjects did not have a reported cause for the event (one each in the casimersen and placebo groups).

Clinical Reviewer's Comment
In the cumulative safety database, there does not appear to be a noteworthy imbalance of these events between the treatment groups. Although there was a higher rate of serious events of rhabdomyolysis in the casimersen group (6%) than in the placebo group (3%), all of these events had associated causes of sevoflurane anesthesia of heightened physical activity, both of which are common causes of rhabdomyolysis in patients with DMD. The reviewer concludes that the events of rhabdomyolysis in both treatment groups are consistent with the greater risk for such events in patients with DMD.

Clinical Reviewer's Overall Interpretation of the Cumulative Information Provided by the Additional Data in the 120-day Safety Update
The cumulative safety data that cover the original NDA database (cut-off date 5/31/19) and the additional SU period (cut-off date 2/28/20) are not qualitatively different from the safety data contained in the original database. The clinical reviewer's interpretation of the cumulative safety data is similar to that for the original data. There are no new safety data from the SU period that raise new safety concerns. In conclusion, an evaluation of the eight safety-specific issues raises a potential risk for renal injury in subjects treated with casimersen. This potential risk will be included in labelling if the product is granted approval.

8.8. Specific Safety Studies/Clinical Trials

This section does not apply because no separate safety trials were conducted to evaluate a specific safety concern.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

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No nonclinical long-term carcinogenicity studies have been conducted. In the pre-NDA meeting that was held on 6/5/19, the applicant requested a deferral on 26-week mouse and 2-year rat carcinogenicity studies, which the applicant stated would be conducted as a post-marketing commitment. FDA responded that "considering the seriousness of the indication, studies to assess the carcinogenic potential of casimersen would not be needed at the time of NDA submission [Question 8, pre-NDA meeting minutes, sent 6/27/19]."

In the ISS for studies 4045-101, 4045-301, and 4045-302, the SOC of Neoplasms Benign Malignant and Unspecified includes skin papilloma as the only TEAE. This event term was reported in 6% of placebo-treated subjects (n = 35) and in 5% of casimersen-treated subjects (n = 76). It should be note that a subset of the subjects in the three studies has received weekly doses of casimersen for more than 96 weeks, without any TEAE that could be regarded as a malignancy.

Clinical Reviewer's Comment
Although the submitted clinical data do not suggest a potential for the development of tumors by casimersen, the size of the extant database is small. Nonclinical carcinogenicity studies will likely be requested as a post-marketing requirement.

8.9.2. Human Reproduction and Pregnancy

DMD is a disease that is fully expressed only in males. Individuals with the condition are affected well before the age of 10 years, and they rarely live past the age of 30 years.

Nonclinical reproductive toxicology studies showed no adverse effects on the male reproductive system in non-human primates, mouse models of DMD, or juvenile rats. No adverse effects were observed on postnatal development of male rats in the juvenile rat study, including bone growth, learning and behavior, or the immune system.

Clinical Reviewer's Comment
No adverse effects were shown on the male reproductive system in nonclinical studies. Together with the fact that human females will not be exposed to casimersen, there appears to be no issue with casimersen as regards human reproduction or pregnancy.

8.9.3. Pediatrics and Assessment of Effects on Growth

Per 505B(k) of U.S.C. 355c(k), a pediatric waiver request was submitted by the applicant on the basis that casimersen was granted orphan drug designation in the US for the treatment of DMD

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on 6/4/19 (ODD# DRU-2019-6900). In the clinical trials that enrolled the targeted patient population, the age range of enrolled subjects was 7 – 13 years of age. There was no clear distinction in the rate of adverse events as a function of BMI, although this conclusion is limited to the small size of the studies and the concurrent use of oral corticosteroids.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

8.8.4.1. Overdose

There is no information regarding overdose in the Prescribing Information for other ASOs that share a molecular backbone with casimersen (i.e., Exondys 51 and Vyondys 53). However, it might be anticipated that an overdose with casimersen could increase the likelihood of renal injury, which is an identified risk for this ASO. It is therefore instructive to analyze the four subjects who had overdoses of casimersen during studies 4045-101 and 4045-301. For each of these four subjects, the table below shows the week(s) of the study during which an overdose occurred; the magnitude of overdose in relationship to the planned dose of casimersen; and any TEAEs, changes in urine KIM-1 values, or positive dipstick urine protein that occurred around the time of the overdose.

Table 67. Subjects with Casimersen Overdoses

Subject ID	Study Week(s) at Which Overdose Occurred	Magnitude of Overdose vs. Planned Dose	Reported TEAEs (Preferred Terms) around Time of Overdose	Changes in Urine KIM-1 Values (ug/L) around Time of Overdose	Changes in Urine Protein (Dipstick) around Time of Overdose
4045-101. (b) (6) (b) (6)	Week 82	67%	Tibia fracture	No increase	No increase
4045-101.	Weeks 113 – 120	11%	none	No increase	No increase
4045-101. (b) (6)	Weeks 67 and 68	12%	URTI	No increase	No increase
4045-301. (b) (6)	Week 1	14%	none	Baseline: 1.1 Week 1: 1.4 Week 2: 1.8 Week 3: 1.2	Baseline: Neg Week 1: Neg Week 2: 1+ Week 3: Neg

[Source: Summary of Clinical Safety, Table 46; and clinical reviewer's use of ADAE.xpt, ADLB.xpt, ISS Listing 26.6.2, and the subject narrative for subject 4045-301 (b) (6)]

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An additional search of ADAE.xpt by this reviewer revealed no TEAEs that included the term "overdose" for any subject at any time.

There appears to have been no clinical consequence of overdose in the first three of the four subjects who are listed above.

1. The subject with the highest magnitude of overdose (i.e., 67% in subject 4045-101. (b) (6)) had a non-serious event of tibia fracture, which has no likely association with his overdose. He had no increase in urine KIM-1 value, and no positive dipstick urine protein.

2. The subject with the longest interval of overdosing (i.e., Weeks 113 – 120 in subject 4045-101. (b) (6)) had no TEAEs that were reported during this interval, and his urine KIM-1 values and dipstick urine protein were unchanged.

3. Subject 4045-101. (b) (6) had a non-serious event of URTI, which is unlikely to be associated with his overdose. His urine KIM-1 value did not increase, nor was his dipstick urine protein positive.

4. However, subject 4045-301 (b) (6) had an increased value of urine KIM-1 one week following the overdose, before it returned to a near-baseline value two weeks later. He also had a 1+ dipstick urine protein one week after the overdose, before it returned to negative one week later. This subject had no reported TEAE at this time.

Clinical Reviewer's Comment
It is possible that one of the four subjects who received an overdose of casimersen experienced renal-associated consequences of increased urine KIM-1 and a positive dipstick urine protein of 1+. However, this subject had only a single overdose, and the magnitude of overdose was small (14%). The other subjects, including the two with highest magnitude of overdose and longest duration of overdose, had no clinical or laboratory evidence of any consequences. Nevertheless, this potential laboratory evidence for renal injury following a casimersen overdose supports including a risk of renal injury in the Warnings and Precautions section of the Prescribing Information for casimersen, if it is granted accelerated approval.

8.8.4.2. Drug Abuse Potential

The Controlled Substances Staff (CSS) provided a consultation under IND 118086 on June 27, 2019, and concluded that casimersen does not have the profile of a drug with abuse potential because it:

1. does not produce central nervous system behaviors in either animals or humans;

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2. has a mechanism of action that is limited to effects on mRNA;

3. does not distribute into the brain after intravenous administration.

Therefore, CSS staff concluded that an abuse potential assessment for casimersen is unnecessary.

8.8.4.3. Withdrawal or Rebound

Given the apparent lack of a risk of casimersen as regards drug abuse, the risk of withdrawal of rebound symptoms might be anticipated to be unlikely. In this context, it is helpful to examine the possible occurrence of signs of withdrawal or rebound in the casimersen-treated subjects who had brief drug interruptions during management of TEAEs, as listed above in section 8.4.4. Each of these subjects resumed study drug treatment following their drug interruptions.

Aside from the TEAEs that precipitated the drug interruption, there were no other TEAEs reported at the time of casimersen interruption or immediately following resumption of casimersen administration. Of note is that subject 4045-101. (b) (6) had a TEAE with a preferred term of "drug withdrawal headache." However, the verbatim term is "headache/caffeine withdrawal."

Clinical Reviewer's Comments
Casimersen appears to have very little risk for drug abuse, or for drug withdrawal/rebound symptoms.

8.10. Safety in the Post-market Setting

8.10.1. Safety Concerns Identified in the Post-market Experience

This section is not relevant because casimersen is not marketed in any region.

8.10.2. Expectations on Safety in the Post-market Setting

If the product is approved, then casimersen will be administered via IV infusion in a clinical setting during its initial use, in order to train patients and caregivers how to administer the product in a home setting and how to avoid infections associated with infusions. The applicant

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has established a home-assistance program, SareptAssist, to provide infusion specialists for home administration. This two-pronged strategy may lower the rate of port-related events (e.g., infections) that could otherwise occur in a post-market setting. Moreover, home visits by these infusion specialists can be anticipated to increase the likelihood of identifying other adverse events such as pyrexia, the detection of which could be followed by clinical visits for appropriate evaluation and medical management.

The identified risk of renal injury is a possible outcome, which could result in proteinuria, hematuria, or other renal outcomes over time. The home infusion of casimersen by infusion specialists in a post-market setting may aid in the detection of such events. Other potential risks of hypersensitivity, hepatotoxicity, or coagulopathy/thrombocytopenia should be detectable by periodic lab monitoring at clinic visits in a post-market setting.
In the sections above, the possibility was raised that casimersen-treated subjects may have increased rates of infections and/or pyrexia. Weekly clinic visits for the IV infusion of casimersen will facilitate the detection of these events, should they occur.

Because of limitations due to the small number of subjects exposed during trials of casimersen and the more limited duration of exposure than would occur in a post-market setting, it is likely that adverse reactions not observed thus far, or not observed with greater severity, will become apparent in the post-market setting.

Clinical Reviewer's Comments
Other approved ASOs are being administered to patients with DMD, and to date no unanticipated clinical consequences have occurred. Should casimersen be approved for patients with DMD amenable to exon 45 skipping, this drug will be administered once weekly in home settings by infusion specialists. This will aid in the detection of adverse events and their subsequent medical management as appropriate.

8.10.3. Additional Safety Issues from Other Disciplines

No other disciplines have safety issues.

8.11. Integrated Assessment of Safety

Nonclinical toxicology studies of casimersen in rodents and in non-human primates revealed evidence of renal injury. Clinical data in this NDA show proportionally higher rates of TEAEs of proteinuria and higher rates of positive urine protein by dipstick in casimersen-treated subjects, compared to subjects who received placebo. There were no other adverse events or laboratory indices to indicate the presence of more severe renal injury. Proteinuria as a sign of potential

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renal injury in patients with DMD has been observed during administration of some approved ASOs, and this safety concern is monitorable by periodic urinalyses. It is recommended that a potential risk of renal injury should be included in the Warnings and Precautions section of the Prescribing Information for casimersen if it is granted accelerated approval.

Other broad safety issues of potential concern were evaluated on the basis of their occurrence with approved ASOs that are administered via IV infusion to treat DMD or other conditions. These issues included potential risks of hypersensitivity, hepatotoxicity, infusion-related reactions, infusion-site reactions, port-related events, coagulopathy/thrombocytopenia, and rhabdomyolysis. These potential risks did not materialize to a clinically significant degree in the submitted safety database for casimersen, and therefore this reviewer does not recommend that these potential risks should be included in the Warnings and Precautions section of the Prescribing Information if casimersen is granted accelerated approval. Nevertheless, these potential risks will continue to be evaluated as new clinical data are submitted by the applicant.

A final topic that is unclear is the extent to which respiratory and other infections are increased in casimersen-treated subjects, as well as events of dizziness or headache. Exposure-adjusted incidence rates (EAIRs) of upper respiratory infections, bronchitis, and ear infections were more than two-fold higher in casimersen-exposed subjects than in the placebo treatment group. The EAIR of pyrexia was also higher in the casimersen treatment group, and this finding may support an increased rate of some infections in this group. The EAIRs of dizziness and headache were nearly two-fold higher in the casimersen group. . Even though these rates may be inaccurate due to the relatively small studies of casimersen to date, patients and caregivers should be educated about these events if casimersen is granted accelerated approval.

The overall safety profile of casimersen is in keeping with other ASOs that have been approved as targeted exon-skipping treatments in DMD. There are no apparent or potential safety issues that are not monitorable or unable to be detected in a clinical setting. Through the use of home infusions specialists to administer the product once weekly by IV infusions, and through education of caregivers and patients about the potential safety concerns that have been described in this section of the review, this reviewer concludes that these potential concerns should not pose an undue risk to patients with DMD amenable to exon 45 skipping.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee is planned.

10. Labeling Recommendations

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10.1. Prescription Drug Labeling

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See the final labelling if the product is approved. There are two major recommendations of this reviewer, as follows.

1. WARNINGS AND PRECAUTIONS section

   (b) (4)

   [redacted]

2. Renal Toxicity, section 5
   Consider using the following text "Although clinically significant renal toxicity was not observed in the clinical studies with TRADENAME, higher proportions of casimersen-treated subjects developed abnormally high urine protein by dipstick than placebo-treated subjects. Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides."

10.2. Nonprescription Drug Labeling

This section is not relevant.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS is required, because the post-marketing experience with the applicant's two other approved ASOs, Exondys 51 and Vyondys 53, has thus far raised no unexpected safety concerns. Moreover, the use of home infusion specialists to administer the weekly IV infusions will both diminish the likelihood of port-related adverse events, and heighten detection of other adverse events so that they can be medically managed as appropriate.

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12. Post-marketing Requirements and Commitments

Following are the PMRs that are anticipated should casimersen be granted accelerated approval.

- In order to verify the clinical benefit of casimersen, complete Study 4045-301 (ESSENCE), A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy. The study includes a randomized, double-blind, placebo-controlled period of 96- weeks and concludes after an open label extension period to 144 weeks. The primary endpoint will be the 6-minute walk test.
- Submit ECG data from Study 4045-301 to support a request to waive a thorough QT study. If these data do not support a TQT study waiver, you will need to evaluate the effect of casimersen on the QTc interval in a dedicated study as per the ICH E14 guideline.
- A two-year carcinogenicity study of intravenously administered casimersen in rat.
- A 26-week carcinogenicity study of casimersen, administered by a clinically relevant route, in an appropriate transgenic mouse model.
- Evaluate the immunogenicity of casimersen-induced truncated dystrophin protein. Assess the immunogenicity risk of any novel epitopes that will be present in the casimersen-induced truncated dystrophin protein. This can be done using clinical data, *in silico* or *in vitro* assays. If there are novel epitopes that could increase the immunogenicity risk, evaluate the immunogenicity of casimersen-induced truncated dystrophin protein in the corresponding patients treated with casimersen in Study 4045-301 (b) (4)
- Evaluate patient immune responses, (b) (4) to dystrophin, (b) (4)
- (b) (4)
  Test samples that are positive for antibodies to casimersen for titer and neutralizing activity using fully validated assays. Until these assays have been fully validated and

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reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions to allow for retesting as needed. Determine the impact of immune responses on product pharmacokinetics and clinical efficacy and safety. The final report submission should include the final clinical study report and the 96-week immunogenicity evaluation. The Final Immunogenicity Report should include the 144-week data.

- We note a recent change in the analytical method for particulate matter characterization from USP <788> Microscopy (Method 2) to USP <788> Light Obscuration (Method 1) for release and stability testing. Submit interim particulate matter stability data using the revised analytical method (i.e., Method 1) as soon as the data are available per the proposed schedule outlined in the table entitled "Table 1: Estimated Timing for Casimersen Stability Data Using USP <788> Method 1" in the document entitled "qualinfo-amend.pdf" in Section 1.11.1 of the amendment submitted on October 06, 2020.
- The freeze/thaw and in-use stability data provided in the original submission used USP <788> Microscopy (Method 2) for particulate matter characterization. Repeat both studies using the USP <788> Light Obscuration (Method 1) and submit the results in a supplement. These repeat studies should be performed using one batch of to-be-marketed (TBM) drug product manufactured at the commercial site.
- Per the document entitled "qual-info.pdf" in the amendment submitted on September 14, 2020, (b) (4) Independently perform these (b) (4) studies using casimersen drug product as well.
- Per the submission, the leachable study was performed using Lot 94EY-DT01 after 54 months of storage in the inverted position at 5 ± 3 °C. Repeat the leachable study using one batch of to-be-marketed (TBM) drug product manufactured at the commercial site during stability, where the data is collected at multiple stability time-points per the testing frequency recommended in ICH Q1A(R2).

13. Appendices

13.1. References

Note: References are cited in the order in which they appear in the text.

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13.2. Financial Disclosure

Two of the five submitted studies can be considered covered studies. Study 4045-101 contributed a small amount of safety data to FDA's evaluation of this NDA. Study 4045-301 contributed the bulk of the safety data and all of the dystrophin efficacy data that are evaluated in consideration for accelerated approval.

Table 68. Covered Clinical Study: 4045-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements? Not applicable, no disclosable interests/arrangements	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

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minimize potential bias provided? Not applicable		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3 of 3		
Is an attachment provided with the reason? Not applicable. All certifications provided.	Yes ☐	No ☐ (Request explanation from Applicant)

Table 69. Covered Clinical Study: 4045-301 (for sites that contributed clinical data in the NDA submission, as identified through BIMO)

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 44		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: Two investigators received (b) (6) payments from the applicant many years ag (b) (6) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from Applicant)

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Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☒ Explanation provided in clinical review as to why it would be impossible for bias to occur in the muscle biopsy assessments that were submitted in this NDA for accelerated approval. These assessments were made by outside vendors.
Number of investigators with certification of due diligence (Form FDA 3454, box 3) all		
Is an attachment provided with the reason? Not Applicable; all certifications provided	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

DAVID HOSFORD
02/24/2021 09:35:19 AM

THOMAS G BIEL
02/24/2021 02:14:41 PM

ASHUTOSH V RAO
02/24/2021 02:20:02 PM

XIANG LING
02/24/2021 02:23:12 PM

KUN JIN
02/25/2021 09:07:25 AM
I concur with the statistical review.

HSIEN MING J HUNG
02/25/2021 09:20:09 AM

TERESA J BURACCHIO
02/25/2021 09:36:32 AM