CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Memorandum

Date	February 18, 2021
From	Teresa Buracchio, M.D. Deputy Director, Division of Neurology 1 Eric Bastings, M.D. Deputy Director, Office of Neuroscience
Subject	Summary Memorandum
NDA/BLA # and Supplement#	213026
Applicant	Sarepta
Date of Submission	June 25, 2020
PDUFA Goal Date	February 25, 2021
Proprietary Name	Amondys 45
Established or Proper Name	Casimersen
Dosage Form	Intravenous solution
Applicant Proposed Indication/ Population	Treatment of Duchenne muscular dystrophy (DMD) in [redacted] (b) (4) patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.
Applicant Proposed Dosing Regimen	30 mg/week
Regulatory Action	Approval
Approved Indication/ Population	Treatment of Duchenne muscular dystrophy (DMD) in [redacted] (b) (4) patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.
Approved Dosing Regimen	30 mg/week

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Duchenne muscular dystrophy (DMD) is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years.

Casimersen is an antisense oligonucleotide (ASO) of the phosphorodiamidate morpholino oligomer (PMO) subclass that was designed to target premessenger ribonucleic acid (mRNA) in the nucleus of a cell to alter the splicing process that creates a mature mRNA. Casimersen targets a region in exon 45 to restore the mRNA reading frame and induce the production of de novo truncated dystrophin protein. Casimersen has been developed as once-weekly intravenous (IV) infusions at a dose of 30 mg/kg infused over 35-60 minutes.

There are four FDA-approved treatments for DMD. Deflazacort (Emflaza) is a glucocorticoid approved for treatment of DMD in patients 2 years of age and older. Deflazacort is purported to have anti-inflammatory and immunosuppressive properties, and has been shown to improve muscle strength in DMD patients. Eteplirsen (Exondys 51) received a biomarker-based accelerated approval in 2016, for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 51 skipping. Golodirsen (Vyondys 53, approved 2019) and viltolarsen (Viltepso, approved 2020) received biomarker-based accelerated approvals for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 53 skipping. Eteplirsen, golodirsen, and viltolarsen were approved based on the demonstration of increases in truncated dystrophin protein; the clinical benefit of these dystrophin changes are being evaluated in confirmatory studies.

This submission contains biomarker and safety data from the casimersen arm of Study 4045-301, a double-blind, placebo-controlled, multicenter clinical trial with an open-label extension study to assess the efficacy and safety of casimersen and golodirsen in patients with DMD. The study consists of a 96-week randomized, double-blind, placebo-controlled period, followed by a 48-week open-label period. The primary clinical endpoint of the study is the change from baseline in the six-minute walk test (6MWT) at Week 96. Although the assessment of dystrophin protein expression (in biceps muscle biopsy samples) determined by western blot at Week 48 is listed as a secondary endpoint in the protocol, this served as the primary biological endpoint in the interim analysis to support accelerated approval for casimersen in this submission. The applicant submitted dystrophin data from 43 evaluable patients (27 casimersen, 16 placebo) with mutations amenable to exon 45 skipping.

A statistically significant increase in dystrophin was observed with once-weekly IV casimersen compared to placebo. Increases in dystrophin levels were observed from baseline in both the placebo and casimersen group; however, the casimersen group had a statistically significantly greater increase in dystrophin protein levels from Baseline to Week 48 compared to the placebo group (mean difference of 0.594%; p = 0.004). The change in dystrophin level, albeit small, has a high level of statistical persuasiveness.

The dystrophin biomarker data are proposed by the applicant as a surrogate endpoint that is reasonably likely to predict a clinical benefit, in support of the approval of casimersen under the accelerated approval pathway. The accelerated approval pathway is appropriate for casimersen because DMD is clearly a serious and life-threatening disease, and casimersen has the potential to address an unmet medical need and provide an advantage over available therapy (deflazacort) in some patients. Deflazacort has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile. Casimersen has a novel mechanism of action that has a well-understood relationship to the disease pathophysiology, and is the first drug that has been shown to increase dystrophin levels in DMD patients with a genetic mutation amenable to exon 45 skipping, thereby potentially improving muscle function. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for casimersen is similar in size to other approved ASO's, such as eteplirsen and golodirsen, that have received accelerated approval based on a conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. Based on these precedents, and barring any evidence to suggest otherwise, the statistically significant increase in de novo (truncated) dystrophin protein demonstrated in Study 4045-301 supports accelerated approval of casimersen for the treatment of DMD in patients with a genetic mutation amenable to exon 45 skipping. Study 4045-301 is ongoing, and the clinical outcomes from the study will serve to assess the clinical benefits of the observed increases in dystrophin.

Although limited in size, the safety database is adequate to support the safety of casimersen for a rare condition such as DMD. Overall, the most frequent adverse events observed with casimersen were mild, and included upper respiratory tract infections, cough, pyrexia, headache. Kidney is a well-known target organ for ASOs, and casimersen is primarily distributed to the kidney. Renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for renal toxicity in humans. No serious renal adverse reaction was reported in casimersen clinical studies. The seriousness of the indication along with the unmet medical need make the risk for renal toxicity acceptable, and manageable through labeling and enhanced pharmacovigilance. PMRs will be issued for assessments of QT prolongation (see Section 5) and immunogenicity.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• DMD is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. • The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years.	DMD is a serious and life-threatening disease. The loss of muscle strength in DMD is progressive, leading to loss of ambulation in the teens, followed by decline in respiratory and cardiac function, resulting in death typically in the third decade.
Current Treatment Options	• Emflaza (deflazacort) is a glucocorticoid approved for treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older. • Exondys 51 is approved 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. • Vyondys 53 and Viltepso are approved 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.	Deflazacort, the only drug with full approval for the treatment of DMD, has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile. There are no therapies targeted to mutations amenable to exon-45 skipping.
Benefit	• Truncated dystrophin quantification by western blot showed a mean change in dystrophin levels from 0.9% of normal at Baseline to 1.7% of normal at Week 48 in the casimersen group, compared to a mean change from 0.5% of normal at Baseline to 0.8% of normal at Week 48 in the placebo group. The casimersen group had a statistically significantly greater increase in dystrophin protein levels from Baseline to Week 48 compared to the placebo group (mean difference of 0.594%; $p = 0.004$). • Exon 45 skipping was confirmed by measurement and sequence verification of exon 45 skipped mRNA. 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; $p < 0.001$).	The applicant has demonstrated a small, but statistically significant increase in de novo (truncated) dystrophin protein with casimersen compared to placebo in DMD patients with a genetic mutation amenable to exon 45 skipping. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for casimersen is similar in size to that established for eteplirsen and golodirsen, drugs that received accelerated approval based on a conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit.
Risk and Risk	•At the time of the NDA submission, there were 76 patients exposed to	Overall, the most frequent adverse events

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Management	casimersen, with 59 patients with >48 weeks of exposure, and 19 patients with >120 weeks of exposure. • The most common adverse reactions (incidence ≥20% and 5% higher than placebo) were upper respiratory tract infections, cough, pyrexia, headache, arthralgia and oropharyngeal pain. • Renal toxicity was the primary toxicity observed in nonclinical studies. No serious renal adverse reactions or events of acute renal toxicity were observed in the clinical studies. Compared to patients on placebo, more patients who received casimersen had increases in urine protein > 1+. The potential for kidney toxicity will be described in the Warnings and Precautions section of labeling. • There is also a risk of infection and other complications related to the indwelling catheters that may be used to administer casimersen, but this risk is not specific to casimersen. • There is inadequate data to assess the potential for QT prolongation and immunogenicity.	observed with casimersen were mild; none caused substantial or permanent harm to patients. Upper respiratory tract infections, cough, pyrexia, headache are the most common adverse events. Nonclinical studies indicate a potential for renal toxicity in humans, but no serious renal adverse reaction have been observed in clinical studies. The seriousness of the indication, along with the unmet medical need, make the risk for serious renal toxicity acceptable. It will be important to inform patients and prescribers about the risk, and a warning regarding the potential for kidney toxicity will be included in labeling. Additional pharmacovigilance for kidney toxicity will also be requested. Because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting. Risk management can be achieved through clear product labeling and routine postmarketing surveillance, plus additional pharmacovigilance for kidney toxicity. The applicant will be required to assess the immunogenicity of casimersen, and evaluate the potential for QT prolongation as post-marketing requirements.

2. Background

This application provides dystrophin biomarker data proposed as a surrogate endpoint that is reasonably likely to predict clinical benefit in support of the accelerated approval of casimersen for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed DMD mutation amenable to exon 45 skipping. Casimersen is a new molecular entity (NME), and has not previously been the subject of any marketing application.

Casimersen (also referred to as SRP-4045 in this memorandum) is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass that was designed to target premessenger ribonucleic acid (mRNA) in the nucleus of a cell, to alter the splicing process that creates a mature mRNA. Casimersen targets a region in exon 45 to restore the mRNA reading frame and induce the production of de novo truncated dystrophin protein. Casimersen has been developed as once-weekly intravenous (IV) infusions at a dose of 30 mg/kg infused over 35-60 minutes.

There are four FDA-approved treatments for DMD. Deflazacort (Emflaza) received full approval in February 2017 for the treatment of DMD. Deflazacort is a glucocorticoid, a member of the corticosteroid class of medications, that is purported to have anti-inflammatory and immunosuppressive properties, and has been shown to improve muscle strength in DMD patients. Eteplirsen (Exondys 51) received a biomarker-based accelerated approval in September 2016 for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 51 skipping. Golodirsen (Vyondys 53, approved 2019) and viltolarsen (Viltepso, approved 2020) received biomarker-based accelerated approvals for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 53 skipping. Eteplirsen, golodirsen, and viltolarsen were approved based on the demonstration of increases in truncated dystrophin protein; the clinical benefit of these dystrophin changes is being evaluated in confirmatory studies.

DMD is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years.[1]

This submission contains biomarker and safety data from the casimersen arm of Study 4045-301. Study 4045-301 is a double-blind, placebo-controlled, multicenter clinical trial, with an open-label extension, and is intended to assess the efficacy and safety of casimersen and

[1] Romitti et al. Pediatrics. 2015; 135. https://pediatrics.aappublications.org/content/135/3/513

golodirsen in patients with DMD. Additional safety data are provided from other Phase 1 studies in the casimersen clinical development program.
A detailed summary of the regulatory history of casimersen is provided in the combined clinical and statistical review.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application.

Casimersen injection 50 mg/mL is a sterile, isotonic, phosphate-buffered solution for intravenous (IV) infusion. It is supplied as single-dose vials containing 100 mg casimersen per 2 mL phosphate-buffered saline. The proposed dose of casimersen is 30 mg/kg administered by IV infusion once per week. The product must be diluted in saline prior to use.

Drug Substance.
The OPQ team has determined that the casimersen drug substance is adequately characterized. The analytical procedures are adequately validated and suitable for their intended use. Process impurities are adequately characterized, and their limits in the drug substance specifications are qualified in nonclinical studies. The specification is sufficient to control the identity, purity, strength, and quality of the drug substance. Clinical, nonclinical, and registration batch analyses are provided and are within specifications.

Drug Product.
The proposed to-be-marketed (TBM) formulation contains excipients (b) (4) all excipients are of USP/NF grade and within IIG limits. Per the applicant, casimersen is amphiphilic in nature and has the potential to adsorb to hydrophobic interfaces and subsequently form subvisible particles and visible particles-like proteins. The applicant has proposed an in-line 0.2 µm dosing filter to be used during administration; adequate instructions have been included in the label. The applicant has performed an in-use stability study to demonstrate that the drug product remains stable during preparation and administration using the IV bag system.

The presence of visible particles in a product intended for intravenous (IV) administration is considered an outstanding product quality concern. The OPQ review note that:

> "The presence of visible particles in a product intended for intravenous (IV) administration would normally preclude an approval recommendation for the application. However, the Division of Neurology 1 (DN1) clinical team 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 recommendation is subject to post-marketing requirements (PMRs) as delineated below. Product Quality PMRs are deemed necessary because the

applicant has not fully characterized the mechanism of particle formation and factors that could promote particle formation, or conclusively established that corrective actions to prevent particle formation are not feasible."

In addition to the PMRs, the Office of Testing and Research (OTR) will also investigate the particulate matter observed in casimersen injection vials, with the goal to understand the mechanism of particle formation, and fully characterize the composition and physicochemical properties of the particles. The applicant has agreed to cooperate with the investigation and provide samples for testing.

A (b) (4) month retest date is granted for the drug substance when stored at (b) (4) C, and a 24-month expiration dating period is granted for the drug product when stored refrigerated (5°C ± 3°C) in the commercial packaging.

The manufacturing process and in-process controls are adequately described and deemed suitable for commercial production.

All manufacturing facilities for this product were found to be acceptable. OPQ recommends approval of this NDA, with post-marketing requirements (PMRs) to more fully characterize the mechanism of particle formation, factors that could promote particle formation, and the feasibility of formulation modifications to prevent particles formation. Please refer to the OPQ review for details of the product quality assessment.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Barbara Wilcox, with Dr. Lois Freed performing a secondary review.

Following are the key findings from the nonclinical studies:

Kidney was the primary target organ in all nonclinical studies. Specifically, kidney toxicity was observed in studies in male mice and rats. In male mice, casimersen was administered weekly for 12 weeks (0, 12, 120, or 960 mg/kg) or 22 weeks (0, 300, 960, or 2000 mg/kg) by intravenous injection, or for 26 weeks by subcutaneous injection (0, 300, 600, or 960 mg/kg). Renal findings consisted of tubular basophilia and microvacuolation at the highest dose tested in the 12-week study, which progressed to tubular degeneration/regeneration at all doses in the 22- and 26-week studies. A no-effect dose for adverse effects on kidney was not identified.

Dr. Freed notes that nonclinical findings of renal toxicity have also been observed with the sponsor's other PMOs, golodirsen and eteplirsen; however, a direct comparison cannot be made across the studies. Juvenile toxicology studies allow the closest comparison: eteplirsen, golodirsen, and casimersen were all tested in juvenile Sprague Dawley rat at IV doses of 0, 100, 300, and 900 mg/kg/week from PND 14 to PND77. Although exposures were similar across the studies, only the golodirsen study had drug-related deaths due to primary renal impairment and/or renal failure. The adverse effects on bone mineral content and density

observed with eteplirsen (all doses) and golodirsen (high dose only) in juvenile rat (high dose only) were not detected with casimersen.

Intravenous administration of casimersen (0, 100, 300, and 900 mg/kg) to juvenile male rats once weekly for 10 weeks (postnatal days 14 to 77) resulted in renal tubular degeneration or necrosis at the highest dose tested. All findings were minimal, except for mild vacuolation in the majority of high-dose animals. No effects were observed on the male reproductive system, neurobehavioral development, or immune function.

Reproductive and developmental toxicology studies were not required because of the intended patient population (extremely rare in females).

Casimersen was negative in a standard battery of in vitro (bacterial reverse mutation assay and chromosomal aberration assay in CHO cells) and in vivo (mouse bone marrow micronucleus) genetic toxicology assays.

Dr. Wilcox and Dr. Freed conclude that the nonclinical data support approval of casimersen for the intended indication, with appropriate labeling and postmarketing commitments for carcinogenicity studies in mouse and rat. The nonclinical studies suggest that renal toxicity may occur with chronic exposure to casimersen; however, renal toxicity can be monitored in humans. As previously agreed to by the division, carcinogenicity studies in two species may be conducted as PMRs, based on the seriousness of the indication.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Drs. Yifei Zhang (the primary reviewer), Bilal AbuAsal (the clinical pharmacology team lead), Hobart Rogers, Atul Bhattaram, Christian Grimstein, and Sreedharan Sabarinath. The final signatory for the OCP review was Dr. Mehul Mehta.

Table 1 below summarizes the key findings of the OCP review with respect to the pharmacologic and clinical pharmacokinetic (PK) properties of casimersen.

Table 1: Summary of OCP Review Findings

Mechanism of Action	Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. Exon skipping is intended to allow for production of an internally truncated but functional dystrophin protein.
Absorption	Casimersen is administered intravenously and bioavailability is assumed to be 100%. Median Tmax was approximately 1 hour (end of infusion).

Distribution	The mean casimersen steady-state volume of distribution was 367 mL/kg at a dose of 30 mg/kg. Casimersen plasma protein binding ranged from 8.4% to 31.6%, and is not concentration dependent.
Metabolism and Elimination	Casimersen is metabolically stable when incubated with hepatic microsomes from mouse, rat, monkey, and human. No metabolites were detected in plasma or urine of human after IV administration. The plasma clearance (CL) of casimersen was 180 mL/hr/kg at the 30 mg/kg dose. The elimination half-life (t1/2) was 3.5 hours (SD 0.4 hours). Casimersen is predominantly renally eliminated, with more than 90% excreted unchanged in urine.
Renal Impairment	In non-DMD subjects with Stage 2 CKD (eGFR ≥60 mL/min/1.73 m2 and <90 mL/min/1.73 m2), casimersen C_{max} was similar to that in matched healthy subjects (eGFR ≥90 mL/min/1.73 m2), and AUC approximately 1.2-fold higher. In subjects with Stage 3 CKD (eGFR ≥30 mL/min/1.73 m2 and <60 mL/min/1.73 m2), the C_{max} and AUC were increased approximately 1.2-fold and 1.8-fold, respectively. The effect of Stage 4 or Stage 5 CKD on casimersen exposure was not studied. Creatinine clearance is not considered as a reliable metric to characterize renal function in the DMD population because the disease affects muscle tissue. Therefore, no dose-adjustment recommendations based on creatinine clearance can be provided for casimersen. However, patients with known renal function impairment should be closely monitored during treatment with casimersen.
Hepatic Impairment	Casimersen is primarily excreted in urine unchanged. Hepatic metabolism is not expected to affect the exposure of casimersen. Therefore, no dose adjustment is needed in patients with hepatic impairment.
Drug Interactions	In vitro assessments suggest that casimersen has a low potential for drug-drug interactions with CYP enzymes and drug transporters.

Dosing Regimen:
The recommended dose of casimersen is 30 milligrams per kg of body weight administered by IV infusion once weekly over 35 to 60 minutes via an in-line 0.2-micron filter.

Genetic mutations:
The following is copied from the OCP review:

> "There were seven different DMD deletion mutations represented in the registration trial of casimersen (44, 46, 46-47, 46-48, 46-49, 46-51, and 46-55). Additional DMD deletion mutations (e.g., 46-53, 46-57) may be amenable to exon 45 skipping based on the mechanism of action. Although casimersen was not studied in all DMD deletion mutations amenable to exon 45 skipping, it is reasonable to extrapolate efficacy to ultra-rare populations (i.e., mutations with only one or two known subjects), given the

inherent variability in disease, and our understanding of the mechanism of action in restoring the reading frame. In addition, the safety of casimersen is not expected to be different in these ultra-rare populations of patients. In summary, given the challenges of studying these ultra-rare populations of disease, coupled with the lack of any unique safety concerns, the review team recommends extending the approval to all DMD mutations amenable to exon-45 skipping."

QT prolongation:
No thorough QT clinical trial has been conducted, and the applicant did not submit a request for a QT waiver. A post-marketing requirement will be issued to submit ECG data from Study 4045-301 in support of a possible 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 casimersen on the QTc interval in a dedicated study, as per the ICH E14 guideline.

OCP recommends approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

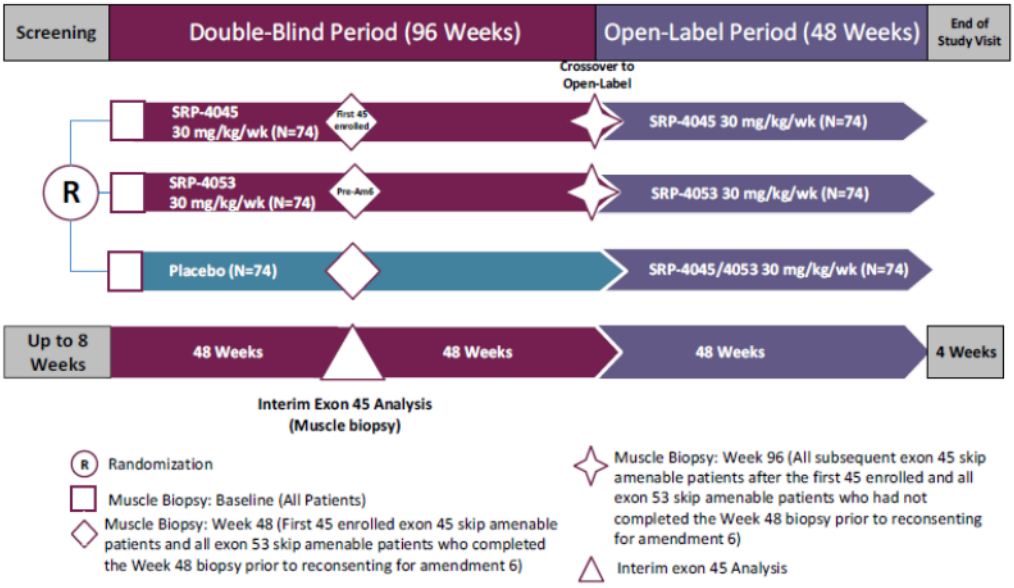
Dr. David Hosford was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead. Dr. Baikuntha Aryal and Dr. Ashutosh Rao (lead) from the Office of Biotechnology Products (OBP) reviewed the dystrophin assays.

The efficacy of casimersen for this application was based on an interim analysis of the change from baseline to Week 48 dystrophin protein expression in biopsied muscle tissue, as measured by western blot, in patients with a diagnosis of DMD amenable to exon 53 skipping from the casimersen arm of Study 4045-301. This interim analysis was previously agreed with the Division at meetings on February 15, 2018, August 23, 2018, and June 27, 2019 (see Dr. Hosford's review for a detailed discussion of the regulatory history). It was also agreed at those meetings that data from clinical functional endpoints would not need to be submitted for the application in order to maintain the integrity of the blinded clinical data from Study 4045-301, which is ongoing.

Study 4045-301 is a double-blind, placebo-controlled, multicenter clinical trial, intended to assess the efficacy and safety of casimersen and golodirsen in patients with DMD. The study consists of a 96-week randomized, double-blind, placebo-controlled period, followed by a 48-week open-label period. The primary clinical endpoint of the study is the change from baseline in the six-minute walk test (6MWT) at Week 96. Additional clinical efficacy assessments will be performed at Week 144. Although the assessment of dystrophin protein expression (in biceps muscle biopsy samples) determined by western blot at Week 48 is listed as a secondary endpoint in the protocol, this will serve as the primary biological endpoint in the interim

analysis intended to support accelerated approval, as previously agreed with the Division (see above). Additional functional secondary endpoints are also assessed in the study. The trial is designed to enroll approximately 111 subjects with DMD amenable to exon 45 skipping, randomized 2:1 to either casimersen (n=74) or placebo, and approximately 111 subjects with DMD amenable to exon 53 skipping, randomized 2:1 to either golodirsen (n=74) or placebo (See Figure 1). The analysis and discussion in this memo will focus on the casimersen arm of the study going forward. Patients in the casimersen arm receive a dose of 30 mg/kg/week IV. Study 4045-301 is still ongoing, and will serve as the confirmatory study for golodirsen, which was granted accelerated approval in 2019, and for casimersen.

Figure 1: Study Schema for 4045-301



(Source: Summary of Clinical Efficacy, Fig. 4)

The study enrolled male patients aged 7 to 13 years, inclusive, with an established clinical diagnosis of DMD amenable to exon 45 skipping (e.g., deletions of exons such as 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55), taking a stable dose of corticosteroids for at least 24 weeks, stable pulmonary function (FVC % of predicted ≥ 50% and no requirement for nocturnal ventilation), and a mean 6MWT distance of ≥300 to ≤450 meters (without assistance) at both the Screening and Baseline visits. Patients with a LVEF [Left Ventricular Ejection Fraction] < 50% on the Screening echocardiogram (ECHO), or QTcF ≥ 450 msec on the Screening and Baseline ECG, were excluded.

Other dystrophin analyses included:

- Intensity of dystrophin expression determined by immunohistochemistry [IHC] analysis
- Percent dystrophin-positive fibers (PDPF) as determined by IHC
- Exon skipping by measurement and sequence verification of exon 45 skipped messenger RNA

Data Quality and Integrity
Drs. Thomas Biel and Ashutosh Rao (team lead) from the Office of Biopharmaceutical Products (OBP) reviewed the assays used to analyze the muscle biopsies, and determined that the western blot method was appropriately validated and conducted to reliably measure relative dystrophin content in the patient samples. They also determined that the reverse transcriptase digital droplet PCR (RT-ddPCR) method was validated, and state that "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".

As agreed during the pre-NDA meeting on June 5, 2019, 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. OBP 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 20 images for artifacts and blemishes that would prevent the qualitative assessment for dystrophin location to the sarcolemma. OBP determined that the provided images demonstrate that dystrophin may localize to the sarcolemma.

Statistical Analysis
For each time point (Baseline vs. Week 48 of Part 2), replicate gel runs were performed to determine dystrophin level (% normal) by western blot. There were two replicates from each block (Block A and Block B) at baseline, and the same at Week 48. Therefore, there were 4 replicates in total at baseline, and 4 at Week 48. The values from the 4 replicates were averaged at each of those times. The average of replicate values from available gel runs were used in the analyses. In the case of only one available gel result, that value was used in the analyses. 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%). Imputation methods were specified for assay results outside of the limits of quantification.

A two-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 two-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.

For the interim analysis, a Type 1 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 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 a contract research organization (CRO) unblinded statistical team that was not otherwise involved in the trial design or conduct of Study 4045-301, other than for support of the DMC and for 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.

Patient Disposition

The interim analysis focused on the first 45 patients with mutations amenable to exon 45 skipping enrolled in Study 4045-301. There was one patient who 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 biopsy. Of these 44 patients, one had a genetic mutation that was predicted to produce a truncated dystrophin isoform that lacked the epitope of currently validated antibodies for Western blot (SR-19-002). The dystrophin expression of this patient was not available by the time of the interim analysis. Therefore, the interim analysis set consists of 43 evaluable patients (27 casimersen, 16 placebo) with mutations amenable to exon 45 skipping.

Patient Demographics

The baseline demographics of the interim analysis population of the casimersen arm of 4045-301 (n=43) is described in Table 2.

Table 2: Demographic and Other Baseline Characteristics (4045-301, Interim Muscle Biopsy Set)

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/m²[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: Module 2.73. Summary of Clinical Efficacy, Table 2.

Results

Primary endpoint

A statistically significant increase in dystrophin was observed with once-weekly IV casimersen compared to placebo. Increases in dystrophin levels were observed from baseline in both the placebo and casimersen group; however, the casimersen group had a statistically significantly greater increase in dystrophin protein levels from Baseline to Week 48 compared

to the placebo group (mean difference of 0.59%; p = 0.004; Table 3). These results were verified by the FDA statistical and clinical reviewers. The statistical reviewer also conducted a 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 3: Dystrophin Levels Determined by Western Blot in Study 4053-101

	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 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: Module 2.73. Summary of Clinical Efficacy, Table 3.

Sensitivity Analyses

Sensitivity analyses using different methods of imputation conducted by the applicant were reviewed by the FDA biometrics reviewer and found to be qualitatively similar to the main analysis method. These analyses also showed a statistically significant between-groups increase in mean dystrophin expression at Week 48 in favor of casimersen treatment.

It is notable that individual dystrophin levels were variable at baseline. Although the mean baseline mean dystrophin levels was 0.54% of normal in the placebo group and 0.92% of

normal in the casimersen group, there were outliers, with observed levels as high as 2.6% of normal in the placebo group, and 6.5% of normal in the casimersen group. Additionally, an increase in the mean and median post-treatment dystrophin levels was observed both in the placebo group, and in the casimersen group. Dr. Hosford notes in his review that this may possibly reflect the presence of revertent fibers and/or heterogeneity as a function of the biopsy. However, the increase in dystrophin levels was statistically significantly greater in the casimersen group than in the placebo group, with robust p-values using different statistical analysis methods, supporting the pharmacodynamic effect of casimersen to increase dystrophin expression. Dr. Hosford also performed an analysis of the data excluding outlier values; the difference between the placebo and the casimersen group remained statistically significant in that analysis.

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 statistical reviewer conducted a sensitivity analysis based on 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). This analysis also supports the treatment effect of casimersen in increasing dystrophin levels at Week 48.

Subgroup Analyses
In subgroup analyses, there did not appear to be a difference in treatment effects by age or weight.

Exon skipping
As discussed above, the OBP reviewers determined that the RT-ddPCR method was appropriate to quantify the skipped and unskipped mRNA dystrophin transcript in the clinical specimens obtained from the 4045-301 clinical study.

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 4). The biometrics reviewer, Dr. Ling, notes in her review that although all baseline percent exon-skipping values > 0.05 were in the casimersen group, there was a clear separation between the two groups 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.

Although there was no pre-specified hierarchical analysis or adjustment for multiplicity for the analysis of exon skipping, the p-value is very small, and would remain significant for any adjustments for multiplicity.

Table 4: 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]

As previously agreed with the Agency at the pre-NDA meeting on June 5, 2019, the applicant did not submit a quantitative analysis of immunohistochemistry (IHC), including dystrophin intensity and percent dystrophin-positive fibers. Instead, the applicant provided representative images that are purported to demonstrate the correct localization of dystrophin to the sarcolemma. Selected representative immunofluorescent (IF) images were reviewed by the OBP and clinical reviewers. The reviewers determined that the provided images demonstrate that dystrophin may localize to the sarcolemma.

Efficacy Conclusions

The interim analysis of muscle biopsy data from Study 4045-301 has rigorously established that casimersen is able to produce statistically significant increases in truncated dystrophin at a dosage of 30 mg/kg once weekly.

Truncated dystrophin quantification by western blot showed a mean change in dystrophin level from 0.9% of normal at Baseline to 1.7% at Week 48 in the casimersen group, compared to a mean change from 0.5% of normal at Baseline to 0.8% of normal at Week 48 in the placebo group. Although there was marked variability in individual dystrophin levels at Baseline, and

an increase in post-treatment dystrophin level was observed in both the casimersen and the placebo group, the increase in dystrophin level was statistically significantly greater in the casimersen group than in the placebo group (mean difference of 0.59%; $p = 0.004$), with robust p-values using different statistical analysis methods. These findings support the pharmacodynamic effects of casimersen to increase dystrophin expression.

The increases observed on western blot are also supported by confirmation of exon 45 skipping by measurement and sequence verification of exon 45 skipped mRNA. 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; $p < 0.001$).

Overall, the positive and highly statistically persuasive results, with support on the secondary endpoint of exon skipping, make reliance on a single efficacy study appropriate to support approval.

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 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. We will review the efficacy results in the context of these criteria for accelerated approval.

DMD clearly meets the criteria of a serious and life-threatening condition.

There are currently four drugs approved for the treatment of DMD: eteplirsen, golodirsen, viltolarsen and deflazacort. The indications for eteplirsen, golodirsen and viltolarsen are for populations distinct from that proposed for casimersen. Eteplirsen is approved for patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, and golodirsen and viltolarsen are approved for patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. It is also noted that eteplirsen, golodirsen, and viltolarsen were approved under the accelerated approval pathway based on a surrogate endpoint and clinical benefit has not yet been verified for any of these products; therefore; as described in the Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics, they are not considered “available therapies” for the purpose of determining unmet need. Deflazacort is indicated for a broad DMD population, irrespective of genetic mutation. However, deflazacort has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile.

As described in the Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics, a drug may address an unmet need where there is available therapy, if “a drug with a novel mechanism of action (but comparable safety and effectiveness) could have the potential to provide an advantage over available therapy in some patients. In such a case, the

novel mechanism of action should have a well-understood relationship to the disease pathophysiology. In addition, there should be a reasonable basis for concluding that a significant number of patients may respond differently to the new drug compared with available therapy." The role of dystrophin is well-characterized in the pathophysiology of DMD. Casimersen has a novel mechanism of action of skipping exon 45 in the dystrophin gene, leading to increased production of truncated dystrophin, with the potential to improve muscle function. While a clinical benefit remains to be confirmed, the safety of casimersen does not appear worse than that of steroids.

Additionally, the expedited programs guidance describes that benefit compared to existing therapy can be demonstrated when a drug is used "in combination with available therapy (i.e., as demonstrated in an add-on study)". In the clinical study, all patients were taking background therapy with steroids, including deflazacort. Therefore, casimersen offers the potential to provide a benefit additional to that of steroids.

The applicant has demonstrated a statistically persuasive, albeit small, increase in de novo (truncated) dystrophin protein in DMD patients with a mutation amenable to exon 45 skipping with weekly intravenous administration of casimersen 30 mg/kg, in a study with a scientifically-sound design, and using rigorous analytical methods. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for casimersen is similar in size to that established for eteplirsen and golodirsen, drugs that received accelerated approval based on a previous conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. Based on this precedent, and barring any evidence to suggest otherwise, the statistically significant increase in de novo (truncated) dystrophin protein demonstrated in Study 4045-301 supports accelerated approval of casimersen for the treatment of DMD in patients with a genetic mutation amenable to exon 45 skipping.

The confirmatory randomized, double-blind, placebo-controlled study (Study 4045-301 - ESSENCE) intended to confirm clinical benefit is ongoing.

8. Safety

Dr. Hosford conducted the safety review of this application.

Studies 4045-101, 4045-301, and 4045-302 are the primary sources of safety data for the review.

Study 4045-101 was a first-in-human, multicenter, double-blind, placebo-controlled, safety, tolerability, and PK study in patients with DMD with genetic mutations amenable to exon 45 skipping. Study 4045-101 assessed four ascending dose levels of casimersen IV (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. It was followed by an open-label extension period, with dosing with casimersen at 30 mg/kg weekly up to 144 weeks.

Study 4045-301 was described in Section 7. At the data cut-off date of May 31, 2019, 88 subjects were enrolled in Study 4045-301; 57 were receiving casimersen and 31 were receiving placebo. None had completed the study.

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 May 31, 2019, 11 subjects from study 4045-101 were enrolled in this study.

Dr. Hosford's review indicates that a total of 76 DMD patients were exposed to casimersen at the time of the NDA submission, including 68 patients with >24 weeks months of exposure, 59 patients with >48 weeks of exposure, and 19 patients with >120 weeks of exposure. All patients were exposed to the 30 mg/kg dose of casimersen that is proposed for marketing. The cumulative casimersen exposure in the overall safety database is 129.6 subject-years. The median casimersen exposure in the group of all casimersen-treated subjects is 84.1 weeks (1.6 years). The safety database is adequate in the context of a rare disease such as DMD.

Dr. Hosford reviewed the coding of the adverse event terms for accuracy in the submission and aggregated similar terms for the safety analyses.

The following are the principal conclusions of Dr. Hosford's safety review of the application:

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

A 10-year-old male DMD patient who was enrolled in Study 4045-301 and assigned to casimersen treatment died due to rhabdomyolysis following a surgical procedure with sevoflurane general anesthesia (with propofol and fentanyl) for central venous port placement on day 400 of the study. As discussed in Dr. Hosford's review, rhabdomyolysis is observed in DMD and is more common after general anesthesia, including anesthesia using sevoflurane. Rhabdomyolysis has also been reported following administration of fentanyl or propofol. Hyperkalemia associated with rhabdomyolysis likely contributed to cardiac arrest. The death was a complication of the surgical procedure; however, as the surgical procedure was conducted specifically for the purpose of drug administration, causality may be imputed to the drug.

Discontinuations. No patient in the casimersen clinical development program was reported to have discontinued study treatment due to a treatment-emergent adverse event (TEAE).

Serious Adverse Events. There were 17 (22%) casimersen-treated patients who experienced a serious adverse event (SAE) in the casimersen clinical development program. This is comparable to the percentage of patients on placebo who experienced an SAE in Study 4045-301. The most frequently reported SAEs were fractures, which had a comparable frequency across treatment groups. Rhabdomyolysis occurred in five patients, and will be discussed in more detail below. A death due to rhabdomyolysis and cardiac arrest is described above.

All Adverse Events (serious plus non-serious). For the analysis of incidence of TEAEs, Dr. Hosford analyzed the controlled study population from Study 4045-301 (interim data). The

most frequently occurring adverse events (>20% and at a rate at least 5% greater than placebo) are presented in Table 5.

Table 5: Treatment-Emergent Adverse Events Reported in at Least 20% of Subjects Treated with Casimersen and at a Rate at Least 5% Greater than Placebo (Study 4045-301)

Adverse Reaction	Casimersen (n = 57)	Placebo (n = 31)
Upper Respiratory Tract Infections*	65%	55%
Cough	33%	26%
Pyrexia	33%	23%
Headache	32%	19%
Arthralgia	21%	10%
Oropharyngeal Pain	21%	7%

*Includes upper respiratory infection, nasopharyngitis, pharyngitis, and rhinitis.
Source: Analysis by Dr. Hosford and Dr. Rui Li (clinical analyst).

Other adverse events 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).

Laboratory and clinical assessments and vital signs. Dr. Hosford evaluated the clinical laboratory assessments for mean change and for outliers by treatment and visit. Analyses of markers of renal injury are discussed below under Adverse Events of Interest. No other findings regarding laboratory values, vital signs, or electrocardiograms (ECGs) were identified as being of clinical concern. See Section 5 for a discussion of the QT assessment.

Adverse Events of Interest

Hypersensitivity Reactions. Hypersensitivity reactions have been identified as a potential safety concern with eteplirsen and golodirsen. Dr. Hosford reviewed the risk of hypersensitivity reactions by reviewing TEAEs, the SMQ for hypersensitivity reactions, and laboratory evaluations. Dr. Hosford found that adverse event terms that are suggestive of hypersensitivity reactions appeared to be generally balanced between the casimersen and placebo groups. Additionally, he did not identify any laboratory assessments that clearly demonstrate casimersen-induced hypersensitivity. He concludes that there is not clear evidence at this time that casimersen causes drug hypersensitivity (b) (4)

Renal adverse events. Kidney is a well-known target organ for ASOs, and a class warning for kidney toxicity is in the prescribing information for golodirsen and viltolarsen based on nonclinical findings. Kidney toxicity was also identified as a potential safety concern for casimersen in nonclinical studies, although the safety margins were greater than those observed with viltolarsen and golodirsen. Casimersen is primarily distributed to the kidney,

and excreted intact in urine following parenteral administration. As kidney toxicity has been identified as a potential risk, Dr. Hosford performed a focused review for this safety signal. Dr. Hosford reviewed individual TEAE reports, broad SMQs for acute renal injury, and laboratory markers of renal injury.

Although there were no cases of acute renal injury identified, there was an overall higher rate of serious and nonserious TEAEs, study drug interruptions due to TEAEs, and laboratory findings suggestive of renal injury in the casimersen-treated group than in the placebo-group. There was one SAE reported of increased urine protein/creatinine ratio, and five non-serious adverse events of proteinuria (based on urine dipstick), with none occurring in the placebo group. There were more patients who experienced a urine dipstick above 1+ in the casimersen group than in the placebo group. Overall, the findings suggest potential renal effects of casimersen and, along with nonclinical renal toxicity findings, support inclusion of the kidney toxicity class warning for ASOs in the label. Additional pharmacovigilance will be requested in the postmarketing setting.

Rhabdomyolysis. Six serious or non-serious TEAEs of rhabdomyolysis were reported during the casimersen development program. Two subjects (6%) in the placebo group (N = 31), and 4 subjects (7%) in the casimersen group (N = 57) experienced this event. 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. One of the events had a fatal outcome and is described above under the section on Deaths.

Rhabdomyolysis is not uncommon in DMD patients, and most of the cases that were reported had identified triggers of physical activity or sevoflurane. Dr. Hosford has concluded that these cases appear to be consistent with the greater risk of rhabdomyolysis known with DMD, and not attributable to casimersen. At this time, there does not appear to be a signal for rhabdomyolysis with casimersen, and routine pharmacovigilance appears to be adequate. The signal will be reassessed when data from the completed Study 4045-301 are available.

Infusion-related Reactions (IRRs) and Catheter-associated Infusion Site Reactions (ISRs). IRRs were identified by the applicant by seeking reported TEAEs that occurred within 24 hours of infusion of study drug. Headache, pyrexia, abdominal pain, and upper respiratory tract infections were identified as possible IRRs. These will be described in Section 6 in the label. No other notable IRRs or ISRs were identified.

Immunogenicity.
Immunogenicity assessments for dystrophin and casimersen antibodies in Study 4045-301 will be required as a PMR.

Port-related Events.
Dr. Hosford identified 3 port-related SAEs (bacteremia, septic embolus, and vena cava thrombosis) that all occurred in a single patient. The risks of infections or complications due to indwelling ports were previously identified during the golodirsen review. Following the identification of that safety issue, the applicant initiated patient and caregiver education about

the care of ports to minimize the potential for infection. These educational activities remain in place through the SareptaAssist program. The mitigation strategies appear reasonable.

Safety conclusions
The safety experience with casimersen supports an acceptable risk/benefit profile. Overall, the most frequent adverse events observed with casimersen were mild, including upper respiratory tract infection, cough, pyrexia, and headache. Renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for renal toxicity in humans. No serious renal adverse reaction, however, was reported in casimersen clinical studies. The seriousness of the indication, along with the unmet medical need, make the risk for renal toxicity acceptable, and manageable through labeling (as a warning) and pharmacovigilance. Additionally, although not observed in the safety database for this submission, it is noted that there is a possible risk of infection and other complications related to the indwelling catheters that may be used to administer casimersen. This risk, however, is not specific to casimersen.

PMRs will be issued for assessments of QT prolongation (see Section 5) and immunogenicity.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of casimersen is acceptable for the intended population, the clinical trial designs were acceptable, and the findings on the surrogate marker were clear.

10. Pediatrics

This application contains pediatric data described in Sections 7 and 8. Pediatric Research Equity Act (PREA) requirements were not triggered for this orphan indication.

11. Other Relevant Regulatory Issues

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

Dr. Hosford concludes that the applicant has adequately disclosed financial interests and arrangements with clinical investigators.

Inspections were performed by the Office of Scientific Investigations (OSI) for clinical sites, and the Office of Study Integrity and Surveillance (OSIS) for bioanalytical issues. OSI determined that the study data generated are acceptable and may be used in support of this NDA. OSIS determined that bioanalytical data are reliable to support a regulatory decision.

The Controlled Substance Staff (CSS) determined that there was no abuse potential of casimersen prior to the NDA submission.

12. Labeling

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

13. Postmarketing Recommendations

The Division of Risk Management (DRISK) reviewer for the application concluded that a risk evaluation and mitigation strategy (REMS) is not necessary for casimersen.

The following will be postmarketing requirements:

- 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 is 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 to dystrophin in patients from Study 4045-301 (b) (4) (b) (4) Test samples collected using fully validated anti-dystrophin assays that detect IgM, IgG and IgE antibodies. Provide antibody titers for samples that are positive for antibodies to dystrophin. Assess 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.
- Develop and validate assays to measure antibodies to casimersen. The assays should measure IgM, IgG and IgE antibody isotypes. Evaluate the samples from patients in Study 4045-101 and Study 4045-301 (b) (4) for antibodies to casimersen. 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 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).

14. Recommended Comments to the Applicant

None.

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

/s/

TERESA J BURACCHIO
02/25/2021 08:44:20 AM

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