CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	213026
Link to EDR	\\CDSESUB1\evsprod\nda213026\0006
Submission Date	01/10/2020 through 06/25/2020 (Rolling submission)
Submission Type	505(b)(1); Priority Review
Brand Name	AMONDYS 45
Generic Name	Casimersen
Dosage Form and Strength	100 mg/2 mL solution in a single-dose vial
Dosing Regimen and Route of Administration	30 mg/kg administered once weekly as IV infusion over 35 to 60 minutes
Proposed Indication	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping
Applicant	Sarepta Therapeutics, Inc.
Associated IND	118086
OCP Review Team	Yifei Zhang, Ph.D.; Hobart Rogers Pharm.D., Ph.D.; Bilal AbuAsal, Ph.D.; Atul Bhattaram, Ph.D.; Christian Grimstein, Ph.D. & Sabarinath Sreedharan, Ph.D.
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1. EXECUTIVE SUMMARY

Sarepta Therapeutics, Inc. submitted a New Drug Application (NDA213026) for casimersen (AMONDYS 45, SRP-4045) for the treatment of Duchenne Muscular Dystrophy (DMD) in (b) (4) patients with a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. DMD is a rare neuromuscular disease affecting males. The deletion mutations in the dystrophin gene disrupt the mRNA reading frame, and prevent production of functional dystrophin protein, which is a critically important part of a protein complex that protects muscle fibers from damage during contraction. Approximately 8% of DMD patients have a deletion mutation that is amenable to exon 45 skipping.

Casimersen is a synthetic antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass with 22 morpholino backbone subunits. It targets a pre-messenger ribonucleic acid (mRNA) to alter the splicing process and exclude exons 45 during post-transcriptional processing of mRNA. This can restore the mRNA reading frame in patients with mutations amenable to exon 45 skipping, resulting in the production of an internally truncated but functional dystrophin protein.

The applicant is seeking accelerated approval of AMONDYS 45 based on a reported increase in dystrophin production in skeletal muscle in the registration trial (4045-301). This is an ongoing, Phase 3, double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate the efficacy and safety of 30 mg/kg once-weekly intravenous infusions of casimersen or golodirsen, in patients with genotypically confirmed DMD with deletion mutations amenable to skipping exon 45 or 53, respectively. The evidence for the ability of casimersen to increase dystrophin levels comes from an interim analysis with 43 evaluable patients who have mutations amenable to exon 45 skipping in Study 4045-301. The primary endpoint for the interim analysis of Study 4045-301 is change from baseline to Week 48 in dystrophin protein levels (in muscle biopsy samples) determined by Western blot after weekly 30 mg/kg IV infusion of casimersen or placebo. The other pharmacodynamic endpoint related to dystrophin expression in this submission is change from baseline at Week 48 in exon skipping, as assessed by measurement and sequence verification of exon 45 skipped mRNA. The final analysis of the completed study will serve as the confirmatory study demonstrating the clinical benefit of casimersen, using the change in 6-minute walk test (6MWT) from baseline to Week 96 as the primary efficacy endpoint.

The clinical pharmacology development program included a dose-titration PK/safety study in DMD patients (4045-101), a mass balance study in healthy male subjects (4045-102), and a renal impairment study (4045-103) in non-DMD adult males with stage 2 or stage 3 chronic kidney disease (CKD) compared to subjects with normal renal function. The clinical development program also includes Study 4045-302, which is an ongoing, Phase 3, multicenter, long-term extension to Studies 4045-101 and 4045-301.

The primary objectives of this review are: (1) to verify the reported PK parameters of casimersen; (2) to evaluate the effect of renal impairment on casimersen plasma exposure and the feasibility of dose optimization for renally-impaired subjects; and (3) to evaluate the approval of casimersen to all mutations in DMD gene amenable to exon 45 skipping.

1.1 Recommendations

The Office of Clinical Pharmacology reviewed this NDA and the specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of effectiveness is based on a reported increase in dystrophin from the interim analysis of an ongoing Phase 3 study (4045-301) in patients with a mutation in the DMD gene amenable to exon 45 skipping.
General dosing instructions	The recommended dose is 30 mg/kg by intravenous (IV) infusion once weekly over 35 to 60-minutes. Dilution in 0.9% Sodium Chloride Injection is required to make a total volume of 100-150 mL prior to administration.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is recommended for patients based on intrinsic and extrinsic factors. • Restoration of the reading frame by casimersen is assumed to be beneficial for all DMD mutations amenable to exon 45 skipping and thus can be indicated for all mutations amenable to exon 45 skipping.
Labeling	The proposed labeling concepts are generally acceptable. The review team recommends close monitoring of patients with known impaired renal function during treatment with casimersen.
Bridge between the to-be-marketed and clinical trial formulations	There is no difference between the clinical trial formulation and the to be marketed formulation.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Study 4045-101 evaluated the pharmacokinetics of casimersen in DMD patients following administration of intravenous doses ranging from 4 mg/kg/week to 30 mg/kg/week (i.e., recommended dosage). Casimersen exposure increased in a dose-proportional manner, with minimal accumulation following weekly dosing up to week 60.

Mechanism of Action: Casimersen is a synthetic PMO that interacts with dystrophin pre-mRNA to alter the splicing process, resulting in exclusion of exon 45 during mRNA processing. Skipping of exon 45 restores the mRNA reading frame and induces production of internally truncated but functional dystrophin protein in patients with genetic mutations that are amenable to exon 45 skipping.

Absorption: Casimersen is administered by intravenous infusion, and bioavailability is assumed to be 100%. Median Tmax was approximately 1 hour (at the end of infusion).

Distribution: In human plasma, casimersen demonstrated protein binding ranging from 8.4% to 31.6%, which is independent of casimersen concentration in the tested range (8 to 800 µg/mL). The mean apparent volume of distribution at steady state (Vss) was 367 mL/kg (%CV = 28.9) following 30 mg/kg administered intravenously.

Metabolism: 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.

Elimination: The plasma clearance (CL) of casimersen was 180 mL/hr/kg at the 30 mg/kg dose. The elimination half-life ($t_{1/2}$) was 3.5 hours (SD 0.4 hours). Casimersen is predominantly renally eliminated with more than 90% excreted unchanged in urine.

Specific Populations

Renal Impairment: Renal clearance is the major route of elimination of casimersen according to the clinical pharmacology studies (4045-101, 4045-102, 4045-103). Study 4045-103 evaluated the PK of a single dose 30 mg/kg casimersen in non-DMD adults with Stage 2 CKD (n=8), Stage 3 CKD (n=8), and matched healthy subjects (n=9). The estimated glomerular filtration rate (eGFR) was calculated at screening using the Modification of Diet and Renal Disease (MDRD) equation. In subjects with Stage 2 CKD (eGFR ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2), casimersen Cmax was similar with that in matched healthy subjects (eGFR ≥90 mL/min/1.73 m^2), and AUC increased approximately 1.2-fold. In subjects with Stage 3 CKD (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the Cmax 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.

The eGFR values calculated using serum creatinine are not applicable to DMD patients, mainly due to decreased creatine production associated with muscle dystrophy. Other eGFR equations have not been validated in DMD population. Therefore, no specific dose adjustment recommendations can be provided for casimersen.

Hepatic Impairment: The effect of hepatic impairment on the exposure of casimersen was not studied. An absorption, metabolism, and excretion study of a single 1800 mg IV dose of casimersen (radiolabeled [^{14}C], containing approximately 100 µCi) in 8 healthy male subjects showed that urinary excretion in the unchanged form was the predominant route of elimination for casimersen (more than 90% excreted unchanged in urine). In addition, casimersen was metabolically stable after incubation with human hepatic microsomes. Therefore, the systemic clearance of casimersen is not expected to be affected by hepatic impairment. No dose adjustment is needed for patients with hepatic impairment.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose of casimersen is 30 milligrams per kilogram of body weight administered once weekly over 35 to 60-minutes by intravenous (IV) infusion via an in-line 0.2 micron filter. The drug should be diluted with 0.9% Sodium Chloride Injection to make a total volume of 100-150 mL before infusion. This is the highest dose tested in humans, which showed increased dystrophin levels in study 4045-301.

2.2.2 Therapeutic individualization

Drug Interaction with Major CYP Enzymes and Transporters: In vitro assessments suggest that casimersen has low potential for drug-drug interactions with CYP enzymes and drug transporters. Casimersen was not a substrate of major CYP enzymes in vitro. Casimersen did not inhibit CYP1A2, CYP2B6, CYP2C8, or CYP2D6 at concentrations more than 10-fold higher than the Cmax from the recommended dose 30 mg/kg in DMD patients. At very high concentrations (> 1 mg/mL), casimersen was a potential inhibitor of CYP3A4/5, CYP2C9 and CYP2C19. Casimersen did not induce CYP1A2, CYP2B6 or CYP3A4 at either mRNA or protein (enzyme activity) level when incubated with human hepatocytes. Casimersen showed no inhibition of major drug transporters at clinically relevant concentrations.

Renal Impairment: Study 4045-103 was a dedicated renal impairment study. Following a single 30-mg/kg IV infusion of casimersen, non-DMD adult subjects with Stage 2 or Stage 3 chronic kidney disease showed higher casimersen exposure compared to demographically-matching subjects with normal renal function, with AUC increased approximately 1.2-folds and 1.8-folds, respectively. The Cmax was unchanged in subjects with stage 2 CKD and was increased approximately 1.2-folds with stage 3 CKD.

However, dose adjustment for casimersen using creatinine-based equations is not feasible due to biased eGFR in DMD patients whose serum creatinine level are typically reduced. Further research is needed to evaluate the performance of other eGFR equations for estimating the renal function in DMD patients.

The review team recommends conveying in the label regarding the observed increase in casimersen exposure with renal impairment.

Hepatic Impairment: Casimersen is predominantly excreted in urine in the unchanged form. Hepatic metabolism has minimum contribution to the elimination of casimersen and is not expected to affect the drug exposure. No dose adjustment is needed for patients with hepatic impairment.

Genetic Mutations: 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.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

• Renal impairment study results should be incorporated in to Sections 8.6 and 12.3 of the label. Dose adjustment based on serum creatinine-based eGFR is not feasible for DMD patients.

• It is reasonable to conclude that the restoration of the reading frame by casimersen should be beneficial for all DMD mutations amenable to exon 45 skipping. Hence casimersen should be indicated for all DMD mutations amenable to exon 45 skipping.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

DMD is a degenerative and ultimately fatal disease caused by genetic mutations that result in the inability to produce functional dystrophin protein. For DMD patients with mutations amenable to exon 45 skipping, current interventions are largely supportive in nature, focusing on alleviation of symptoms without addressing the underlying deficit of dystrophin protein. Pharmacological treatments with glucocorticoids such as Emflaza® (deflazacort) have been used with some benefits. Other supportive measures include bracing, muscle-stretching exercises to avoid onset of contractures, tendon release surgery, eventual wheelchair use, and assisted ventilation.

Currently there are three PMOs approved for the treatment of DMD. Eteplirsen (EXONDYS 51®) was granted accelerated approval in 2016 in the United States for the treatment of DMD patients with mutations amenable to exon 51 skipping, based on demonstration of dystrophin production. Golodirsen (SRP-4053, VYONDYS 53®) and Viltolarsen (VILTEPSO®) were approved for the treatment of patients with DMD mutations amenable to exon 53 skipping following the same regulatory pathway.

Casimersen is a PMO for the treatment of DMD in patients who have a mutation of the dystrophin gene that is amenable to exon 45 skipping. The clinical development program for casimersen comprises five clinical studies (Appendix 4.2, Table 3). Three of these studies (4045-101, 4045-301, and 4045-302) were conducted in patients with DMD mutations amenable to exon 45 skipping, and 2 studies (4045-102 and 4045-103) were conducted in the non-DMD population. Investigation of casimersen for DMD was designated as a Fast Track development program on 24 July 2014. Orphan Drug Designation and Rare Pediatric Disease Designation for casimersen in the treatment of DMD was granted on 04 June 2019. The applicant is seeking accelerated approval for casimersen based on dystrophin levels reported from Study 4045-301.

AMONDYS 45 is a concentrated solution to be diluted to make a final volume of 100-150 mL with 0.9% Sodium Chloride Injection prior to IV infusion. It is supplied as a sterile, isotonic, phosphate-buffered solution in single-use, 2-mL vials, with each vial containing 2 mL of casimersen at 50 mg/mL. The solution is a clear to slightly opalescent, colorless liquid. Casimersen at 30 mg/kg will be administered once-weekly as an IV infusion over a period of approximately 35 to 60 minutes. The infusion of drug should be completed within 4 hours of dilution. The formulation used in all casimersen clinical studies was identical to the proposed 2-mL commercial formulation.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA, resulting in alternative splicing and exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. Skipping of exon 45 is intended to restore the dystrophin mRNA reading frame and allow for production of an internally truncated but functional dystrophin protein in those patients.
Active Moieties	The active moiety is casimersen, an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass containing 22 linked subunits. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine).
QT Prolongation	A TQT study was not conducted. A PMR will be issued for collection of ECG assessments to inform the QT assessment (currently ongoing in Study 4045-301). Please refer to the Late Cycle Meeting Background Package in DARRTS on December 22, 2020.
General Information	
Bioanalysis	Quantification methods for casimersen were developed and validated in human plasma and urine. Samples were prepared by solid-phase extraction and analyzed by LC-MS/MS.
Dose Proportionality	In DMD patients, casimersen exposure increased in a dose-proportional manner over the dose range of 4 to 30 mg/kg/week.
Accumulation	No evidence of casimersen accumulation was observed following once weekly dosing for 60 weeks. This is expected given the short elimination half-life ($t_{1/2}$) of casimersen of ~3.5 hours.
Variability	Inter-subject variability (as %CV) for casimersen Cmax and AUC ranged from 12 to 34% and 16 to 34%, respectively.
Absorption	
Bioavailability	Casimersen is administered by IV infusion and the bioavailability is expected to be 100%.
Cmax and AUC	The geometric mean of Cmax and $AUC_{0-\infty}$ of casimersen were 115 µg/mL and 182 h*µg/mL in DMD patients at the recommended IV dose of 30 mg/kg.
Tmax	Tmax is at the end of infusion (approximately 35 to 60 minutes).

Food effect (Fed/fasted)	Casimersen is administered through IV infusion and food is not expected to affect the exposure.
Distribution	
Volume of Distribution	The mean apparent volume of distribution at steady state (Vss) was 367 mL/kg (%CV = 28.9) at the recommended dosage of 30 mg/kg administered intravenously.
Plasma Protein Binding	Binding of casimersen to human plasma protein ranged from 8.4% to 31.6% and was not concentration-dependent.
Transporter-based DDI	Casimersen is not a substrate or inhibitor of major transporters at clinically relevant concentrations.
Metabolism	
Primary Metabolic Pathway(s)	Casimersen is metabolically stable. No metabolites were detected in plasma or urine.
Metabolism-based DDI	In-vitro data showed that casimersen is not an inhibitor or inducer of major CYP enzymes at clinically relevant concentrations.
Excretion	
Primary Excretion Pathways	Casimersen is excreted unchanged in the urine. The elimination half-life ($t_{1/2}$) was approximately 3.5 hours. The mean total recovery of radioactivity in all excreta (urine and feces) in mass balance study (4045-102) was 92.1%, with mean urinary excretion accounting for 92.1%.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness for this application, seeking accelerated approval, is based on the interim analysis of dystrophin data from 43 DMD patients in Study 4045-301, which showed significantly greater increase in dystrophin protein level as measured by Western Blot, from baseline to week 48 in casimersen treatment group compared to placebo.

The study 4045-301 is an ongoing, Phase 3, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of once-weekly intravenous infusions of 30 mg/kg casimersen or golodirsen in patients with genotypically confirmed DMD mutations amenable to skipping exon 45 or 53, respectively. The study includes a 96-week double-blind treatment period and an open-label extension period up to 48 weeks. The interim analysis was conducted when the first group of patients with mutations amenable to exon 45 skipping had a Week 48 biopsy collected and dystrophin expression measured. The interim analysis set consists of 43 evaluable patients, with mean age of 9.2 years (range of 7 to 13 years). The primary biological endpoint for the interim analysis of Study 4045-301 is the change from Baseline to Week 48 in dystrophin protein levels (in muscle biopsy samples) determined by Western blot. The casimersen group had a statistically significantly greater increase in dystrophin protein levels, as measured by Western blot, from Baseline to Week 48 than the placebo group (mean change of 0.811% for casimersen and 0.217% for placebo; mean difference=0.594%; p=0.004). The final analysis of the completed study will serve as the confirmatory study demonstrating the clinical benefit

of casimersen. Please refer to the clinical and OBP reviews for more information on efficacy and safety assessments and dystrophin assay.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed 30 mg/kg dose and once weekly dosing regimen were tested in the ongoing Study 4045-301, in which the interim analysis supports this application based on increase in dystrophin expression compared to placebo. This was also the maximum dose tested in humans with casimersen. The same dosing regimen is being used in Study 4045-302, the long-term extension to Studies 4045-101 and 4045-301. There is no information available on the efficacy/safety of casimersen at weekly dose higher than 30 mg/kg in DMD patients.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Alternative dosing regimen is not recommended for subpopulations based on intrinsic factors of patients. The effects of various intrinsic factors on casimersen exposure are described below.

Dosing in Patients with Renal Impairment

Casimersen is predominantly excreted unchanged in the urine. A phase 1, multicenter, open-label, parallel cohort study (4045-103) was conducted to evaluate the effect of renal impairment on the PK of a single 30 mg/kg IV dose of casimersen in non-DMD adult male subjects. The subjects have Stage 2 CKD (n=8, eGFR ≥60 and <90 mL/min/1.73 m^2), Stage 3 CKD (n=8, eGFR ≥30 and <60 mL/min/1.73 m^2), or normal kidney function (n=9, eGFR ≥90 mL/min/1.73 m^2). The estimated glomerular filtration rate (eGFR) was calculated at Screening using the Modification of Diet and Renal Disease (MDRD) equation. Blood samples were collected prior to the start of infusion, at the end of infusion, and at 0.25, 0.5, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 72 hours after the end of infusion to determine casimersen concentrations in plasma. The exposure parameters of CKD2 and CKD3 subjects were compared with demographically-matched healthy subjects using a paired t-test (**Table 1**).

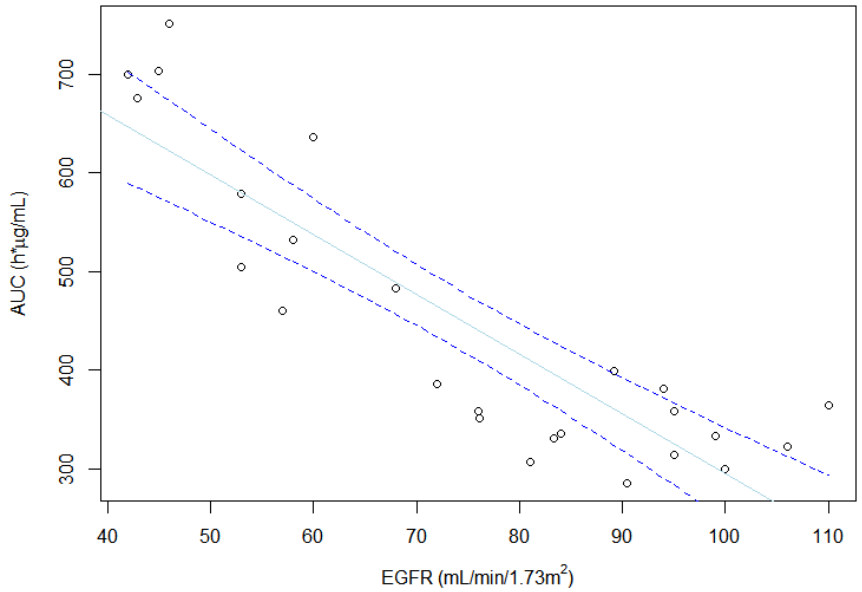
Table 1 Statistical Analysis of the Pharmacokinetic Parameters of Casimersen [Study 4045-103]

		Chronic Kidney Disease Group			Normal Kidney Function Group		Ratio of Geometric	90% Confidence	
Parameter (units)		N	Geometric Means	Comparison	N	Geometric Means	Means (%)	Interval of the Ratio	p-value
C_{max} (ng/mL)	Stage 2	8	205132	Stage 2 vs Normal	8	179580	114	(98.2, 133)	0.139
	Stage 3	8	228482	Stage 3 vs Normal	8	184814	124	(112, 136)	0.004
AUC_{0-t} (h*ng/mL)	Stage 2	8	395758	Stage 2 vs Normal	8	325307	122	(102, 145)	0.069
	Stage 3	8	603710	Stage 3 vs Normal	8	337307	179	(157, 204)	<.001
$AUC_{0-\infty}$ (h*ng/mL)	Stage 2	8	395989	Stage 2 vs Normal	8	325441	122	(102, 145)	0.069
	Stage 3	8	604544	Stage 3 vs Normal	8	337455	179	(157, 205)	<.001
t_{max} (h) #	Stage 2	8	1.00	Stage 2 vs Normal	8	0.90	0.075	(-.008, 0.158)	0.156
	Stage 3	8	0.82	Stage 3 vs Normal	8	0.90	-0.012	(-.100, 0.050)	0.703

Source: Sponsor's analysis. Study 4045-103 CSR, Table 11. NDA213026 (213026 - 0001 - (1) - 2020-01-10 - ORIG-1 /Multiple Categories/Subcategories) - Study 4045-103 - Report Body (#44) # Median, median differences, and approximate 90% confidence interval for the difference are presented.

In subjects with Stage 2 CKD, casimersen Cmax was similar with that in matched healthy subjects, and AUC increased approximately 1.2-fold. In subjects with Stage 3 CKD, the Cmax and AUC increased approximately 1.2-fold and 1.8-fold, respectively, both of which were significant (**Table 1** and **Figure 1**).

Figure 1 Relationship between casimersen exposure and eGFR calculated by MDRD equation (National Kidney Foundation)



Source: Reviewer's analysis. (Data from adpp.xpt and adsl.xpt, \\cdsesub1\evsprod\NDA213026\0001\m5\datasets\4045-103\analysis\adam\datasets\)
eGFR (mL/min/1.73m^2) = 175 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

Serum creatinine is affected by the progression of muscle dystrophy. Therefore, creatinine-based renal function equations such as MDRD, Cockcroft-Gault, and Schwartz equations are not expected to provide accurate estimation for renal function. Alternate biomarkers such as cystatin C were proposed in literature. However, the accuracy of cystatin C-based equations for estimating GFR has not been validated in DMD population, and further investigation is needed before they can be used for dose adjustment.

The review team therefore concluded that it is not feasible to recommend dose adjustment based on the creatinine-based renal function equations in DMD patients. The results of the renal impairment study in non-DMD adult subjects (**Table 1**) should be described in the label.

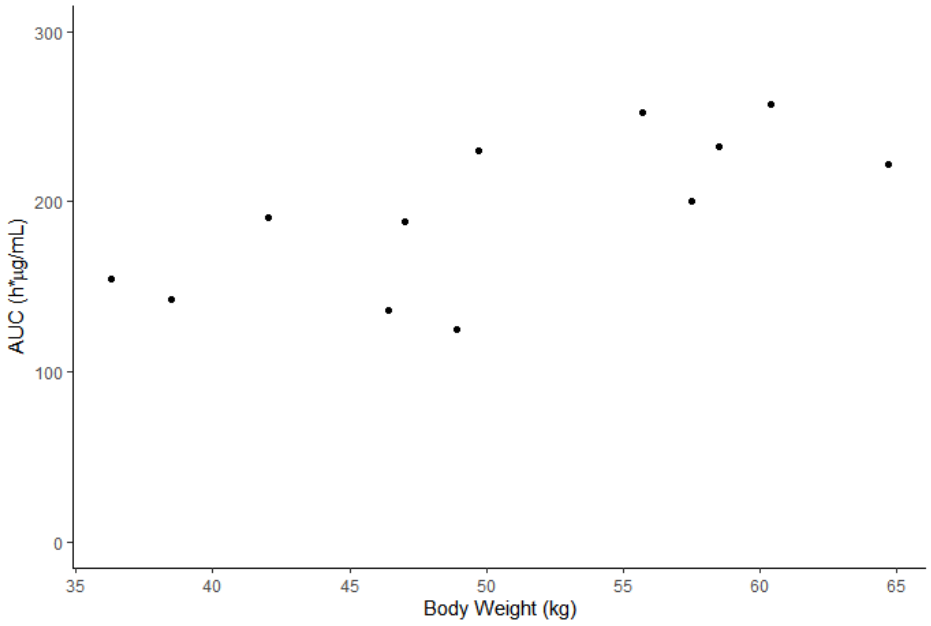
Hepatic Impairment

No dedicated hepatic impairment study was conducted for casimersen. Casimersen is metabolically stable and almost completely excreted unchanged in the urine. Hepatic metabolism is not expected to affect the exposure of casimersen. Therefore, no dose adjustment is recommended for patients with hepatic impairment.

Age, Body Weight, and Type of Mutations

In study 4045-101, the PK profile of casimersen was evaluated in pediatric male DMD patients with an age range of 9-20 years and a body weight range of 36.3 kg - 64.7 kg. Reviewer's analysis on study 4045-101 shows that, after receiving 30 mg/kg casimersen by once-weekly infusion, casimersen exposure showed an increasing trend with body weight (**Figure 2**).

Figure 2 Relationship between casimersen exposure and body weight in DMD patients



Source: Reviewer's analysis. (Data from adpp.xpt and adsl.xpt, \\cdsesub1\evsprod\NDA213026\0001\m5\datasets\4045-101\analysis\adam\datasets\)

Due to the limited sample size, the review team concluded that it is not feasible to evaluate the impact of age, body weight, or types of mutations on the reported dystrophin expression.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. With IV infusion, the exposure of casimersen is not expected to be affected by food.

In vitro assessments suggest that casimersen has low potential for drug-drug interactions with CYP enzymes and drug transporters at clinically relevant concentrations. Casimersen was not metabolized by human hepatic microsomes. No inhibition exceeding 50% was observed in vitro for CYP1A2, CYP2B6, CYP2C8, or CYP2D6 at casimersen concentrations around 50-fold higher than the mean Cmax (115 µg/mL) from the recommended dose of 30 mg/kg in DMD patients. Casimersen was a potential inhibitor of CYP3A4/5, CYP2C9 and CYP2C19 in vitro (mean Ki values are 10.6 mg/mL, 1.37 mg/mL and 2.02 mg/mL, respectively); however, considering the short plasma half-life and lack of plasma accumulation with the weekly dosing regimen, clinical drug interaction with substrates for these enzymes is unlikely. When incubated with human hepatocytes, casimersen did not induce CYP1A2, CYP2B6 or CYP3A4 at

either mRNA or protein (activity) level. Casimersen was not a substrate or strong inhibitor of the key human drug transporters tested (OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, and MRP2).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical method for casimersen quantification were developed and validated in human plasma and urine. Samples were prepared by a solid-phase extraction procedure and analyzed by liquid chromatography with tandem mass spectrometry detection (LC/MS/MS). The methods met the acceptance criteria for bioanalytical methods according to the Bioanalytical Method Validation Guidance for Industry and were shown to be selective and robust to different lots of plasma and to dilution. Performance characteristics and validation attributes for each bioanalytical method are presented in **Table 2**.

Table 2 Bioanalytical method validation results for casimersen in human plasma and urine

Parameter	Plasma		Urine
	Low Range Curve	High Range Curve	
Analyte	Casimersen (SRP-4045)		
Internal Standard (IS)	SRP-4044	SRP-4044	SRP-4053
Lower Limit of Quantitation (ng/mL)	10 ng/mL	1,000ng/mL	500 ng/mL
Average Recovery of Drug (%)	30.9% - 41.4%	25.2% - 26.4%	27.2% - 30.7%
Average Recovery of IS (%)	28.5%	25.6%	15.2%
Standard Curve Concentrations (ng/mL) and linearity R^2	10.0, 20.0, 50.0, 150, 400, 1200, 1800, and 2000 ng/mL R-Squared = 0.9978	1000, 2000, 5000, 15000, 40000, 120000, 180000, 200000 ng/mL, R-Squared = 0.9983	500, 1000, 2500, 5000, 20000, 60000, 90000, and 100000 ng/mL, R-Squared = 0.9944
QC Intraday Precision (%)	0.9% to 4.3%	1.4% to 3.7%	1.9% to 6.7%
QC Intraday Accuracy (%)	-5.0% to 5.0%	-7.1% to 3.3%	–12.7% to -1.0%
QC Interday Precision (%)	2.2% to 3.4%	0.4% to 4.4%	2.1% to 4.9%
QC Interday Accuracy (%)	-2.1% to 2.4%	-5.0% to -1.3%	–9.3% to -4.5%
Long-Term Stability of Casimersen in Matrix (Days)	24 Hours at room temperature, 1456 days at -20°C	24 Hours at room temperature, 1321 days at -20°C	6 Hours at room temperature, 313 days at -20°C
Extract Stability at room temperature	95 hours	119 hours	48 hours
Freeze-Thaw Stability	5 cycles; freeze at –20°C and thaw at room temperature		
Selectivity	No interference in 6 lots of blank matrix		

4.2 List of Clinical Studies in the Development Program

Table 3 Clinical Development Program for Casimersen

Study Phase, Study Number	Study Design	Dosing Regimen and Route of Administration	Study Population
Phase 1 (4045-101) Completed	MC, R, DB, PC study DB: 12-week dose escalation OL: 132 weeks	DB: Casimersen 4, 10, 20, and 30 mg/kg once weekly for 12 weeks (for a minimum of 2 weeks at each dose level) compared with placebo; IV infusion OL: Casimersen 30 mg/kg once weekly for up to 132 weeks; IV infusion	Advanced stage patients with DMD amenable to exon 45 skipping (n=12)
Phase 1 (4045-102) Completed	SC, OL, uncontrolled, ADME study	Single 1800-mg dose [^{14}C]-casimersen (containing ~100 µCi of radiocarbon); IV infusion	Healthy male Subjects (n=8)
Phase 1 (4045-103) Completed	MC, OL, single-dose, parallel-cohort study	Single casimersen 30 mg/kg dose; IV infusion	Adult male non-DMD subjects with Stage 2 or Stage 3 CKD (n=8 for each), compared with adult male subjects (n=9) with normal kidney function matched by age (within 10 years) and BMI (within 20%)
Phase 3 (4045-301) Ongoing, interim dystrophin data available for 43 subjects	MC, R, DB, PC study DB: 96 weeks OL: up to an additional 48 weeks	DB: Casimersen, golodirsen, or placebo 30 mg/kg once weekly for 96 weeks; IV infusion OL: Casimersen or golodirsen (based on genotype) 30 mg/kg once weekly for up to 48 weeks upon completion of DB; IV infusion	DMD patients with deletion mutations amenable to skipping exon 53 (for golodirsen) or 45 (for casimersen)
Phase 3 (4045-302) ongoing	MC, OL, long-term extension to Studies 4045-101 and 4045-301, up to 144 weeks	Golodirsen 30 mg/kg or casimersen 30 mg/kg once weekly for up to 144 weeks; IV infusion	DMD patients

Abbreviations: MC, multicenter; R, randomized; DB, double-blind; OL, open-label; SC, single-center.

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