Received: 25 November 2020 | Revised: 1 June 2021 | Accepted: 6 June 2021

DOI: 10.1002/mus.27347

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Safety, tolerability, and pharmacokinetics of casimersen in patients with Duchenne muscular dystrophy amenable to exon 45 skipping: A randomized, double-blind, placebo-controlled, dose-titration trial

Kathryn R. Wagner MD, PhD[1,2] | Nancy L. Kuntz MD[3] | Erica Koenig PhD[4] | Lilly East PhD[5] | Sameer Upadhyay MD[6] | Baoguang Han PhD[7] | Perry B. Shieh MD, PhD[8]

[1]Center for Genetic Muscle Disorders, Kennedy Krieger Institute, Baltimore, Maryland, USA

[2]Departments of Neurology and Neuroscience, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

[3]Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois, USA

[4]Clinical Development, Sarepta Therapeutics, Inc, Cambridge, Massachusetts, USA

[5]Clinical Pharmacology, Sarepta Therapeutics, Inc, Cambridge, Massachusetts, USA

[6]Pharmacovigilance, Sarepta Therapeutics, Inc, Cambridge, Massachusetts, USA

[7]Biostatistics, Sarepta Therapeutics, Inc, Cambridge, Massachusetts, USA

[8]Department of Neurology, University of California, Los Angeles, California, USA

Correspondence
Perry B. Shieh, University of California, Los Angeles, 300 Medical Plaza, Suite B-200, Los Angeles, CA 90095.
Email: pshieh@mednet.ucla.edu

Funding information
Sarepta Therapeutics, Inc

Abstract

Introduction/Aims: Duchenne muscular dystrophy (DMD) is caused by mutations in the *DMD* gene resulting in the absence of dystrophin. Casimersen is a phosphorodiamidate morpholino oligomer designed to bypass frameshift *DMD* mutations and produce internally truncated, yet functional, dystrophin protein in patients amenable to exon 45 skipping. Our primary study objective was to evaluate safety and tolerability of casimersen; the secondary objective was to characterize the plasma pharmacokinetics.

Methods: This multicenter, phase 1/2 trial enrolled 12 participants (aged 7-21 years, who had limited ambulation or were nonambulatory) and comprised a 12-week, double-blind dose titration, then an open-label extension for up to 132 weeks. During dose titration, participants were randomized 2:1 to weekly casimersen infusions at escalating doses of 4, 10, 20, and 30 mg/kg (≥2 weeks per dose), or placebo.

Abbreviations: AE, adverse event; AUC, area under the concentration-time curve; AUC_{∞}, area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed concentration; DMD, Duchenne muscular dystrophy; ECG, electrocardiogram; ECHO, echocardiogram; FDA, United States Food and Drug Administration; IRR, infusion-related reaction; mRNA, messenger RNA; PK, pharmacokinetics; PMO, phosphorodiamidate morpholino oligomer; SAE, serious adverse event; $t_{1/2}$, terminal phase half-life; t_{max}, time of observed maximum concentration; TEAE, treatment-emergent adverse event; V_{ss}, volume of distribution at steady state.

Portions of this study were presented at the Muscle Study Group Annual Scientific Meeting, September 2019, Snowbird, Utah, and at the World Muscle Society 2020 Virtual Congress, September-October, 2020.

Results: Participants received casimersen for a mean 139.6 weeks. Treatment-emergent adverse events (TEAEs) occurred in all casimersen- and placebo-treated participants and were mostly mild (over 91.4%) and unrelated to casimersen or its dose. There were no deaths, dose reductions, abnormalities in laboratory parameters or vital signs, or casimersen-related serious AEs. Casimersen plasma concentration increased with dose and declined similarly for all dose levels over 24 hours post-infusion. All pharmacokinetic parameters were similar at weeks 7 and 60.

Discussion: Casimersen was well tolerated in participants with DMD amenable to exon 45 skipping. Most TEAEs were mild, nonserious, and unrelated to casimersen. Plasma exposure was dose proportional with no suggestion of plasma accumulation. These results support further studies of casimersen in this population.

KEYWORDS

casimersen, Duchenne muscular dystrophy, exon skipping, phosphorodiamidate morpholino oligomer, RNA oligonucleotide

1 | INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare, fatal, X-linked neuromuscular disease that is typically caused by mutations in the *DMD* gene, disrupting translation of the dystrophin protein, and leading to muscle degeneration and progressive muscle weakness.[1]

DMD is presently incurable and treatments have historically either been supportive or focused on alleviating symptoms.[2] Antisense oligonucleotides (ASOs) have emerged as an attractive therapeutic strategy to treat the pathobiology of DMD and bypass the mutations underlying the disease.[3,4] They act as exon-skipping therapies, splicing out the exon adjacent to the mutated region in the targeted pre-mRNA, and thereby correcting the open reading frame to produce an internally truncated yet functional dystrophin protein.

Until recently, three phosphorodiamidate morpholino oligomers (PMOs), eteplirsen, golodirsen, and viltolarsen had received accelerated approval from the United States Food and Drug Administration (FDA) for the treatment of DMD in patients with confirmed *DMD* gene mutations that are amenable to exon 51 (eteplirsen) and 53 (golodirsen, viltolarsen) skipping.[5-7] All three treatments increase dystrophin production and are well tolerated, without compromising renal or hepatic function, and maintain serum chemistry and properties within expectations given the progression of DMD.[4,8-11] In addition, eteplirsen was shown to slow the decline in ambulatory function in ambulatory patients, and slow the decline of pulmonary function in both ambulatory and nonambulatory patients.[12-15] Studies in ambulatory patients showed that golodirsen also slowed decline in ambulatory and pulmonary function,[16] and viltolarsen enhanced performance on timed function tests.[8]

Based on safety and efficacy data for these PMOs targeting exon 51 and exon 53, the continued development of additional PMOs that target other exon deletions is warranted.

Casimersen was recently granted accelerated approval by the FDA for the treatment of patients with DMD and confirmed genetic mutations amenable to skipping of *DMD* exon 45,[17] comprising approximately 8% of patients with DMD.[18] A recent natural history study of patients with deletions amenable to exon 45 skipping showed that this mutation was associated with a variable pattern of disease progression;[19] however, other natural history studies reported ambulation outcomes were similar to those of patients amenable to exon 51 or exon 53 skipping.[20,21] In this study we evaluated the safety, tolerability, and pharmacokinetics (PK) profile of casimersen compared with placebo in participants with exon 45 skip–amenable DMD.

2 | METHODS

2.1 | Study design

This multicenter, randomized, double-blind, placebo-controlled, dose-titration phase 1/2 trial took place at three sites in North America (NCT02530905). Independent ethics committees or institutional review boards at each site approved the protocol. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from each participant over 18 years of age; for those under 18 years, written informed consent was obtained from the parent(s) or legal guardian(s) with the assent of the study participant.

2.2 | Participants

Eligibility criteria included male sex, 7 to 21 years old, with a clinical diagnosis of DMD and a confirmed genetic mutation amenable to exon 45 skipping. Participants must have had stable cardiac and pulmonary function and been on a stable dose or received no oral corticosteroids for at least 24 weeks before study initiation. All needed to be nonambulatory or unable to walk at least 300 meters on the 6-minute walk test to evaluate casimersen in advanced-stage patients.

Participants were excluded if they had used any pharmacologic treatment, other than corticosteroids, that may have affected muscle strength or function within 12 weeks of study entry, including current or previous treatment with experimental agents BMN-195 (a small-molecule utrophin upregulator) or PRO045 (an antisense oligonucleotide directed against exon 45), use of other RNA antisense or gene therapy agents, or other experimental treatments. Participants were also excluded if they had a left ventricular ejection fraction <40% or corrected QT interval (calculated by Fridericia formula) ≥450 ms, or forced vital capacity less than 50% of predicted value at screening or baseline, or if they required nocturnal ventilation.

2.3 | Treatment

During the 12-week, double-blind, dose-titration period, participants were randomized 2:1 to casimersen or placebo using an interactive voice response system. Allocation was concealed; all participants, parents/caregivers, investigators, and study staff were blinded to treatment assignment. Participants randomized to casimersen received a weekly intravenous (IV) infusion at escalating dose levels, each for at least 2 weeks: 4 mg/kg in weeks 1 and 2; 10 mg/kg in weeks 3 and 4; 20 mg/kg in weeks 5 and 6; and 30 mg/kg beginning at week 7 (Figure S1). After the 12-week, double-blind, dose-titration period, the safety of once-weekly casimersen 30 mg/kg was evaluated in an open-label extension period up to 132 weeks.

2.4 | Study assessments

The primary objective was to evaluate the safety and tolerability of casimersen. Safety assessments included adverse events (AEs), vital signs, physical examinations, clinical laboratory evaluations, electrocardiograms (ECGs), and echocardiograms (ECHOs). Investigators assessed the severity of all AEs as mild, moderate, or severe, and determined whether AEs were related or unrelated to study treatment, procedures, or underlying disease. AEs were considered treatment-emergent (TEAEs) if they started, worsened, or became serious on or after the start of the first infusions and within 28 days after the last dose of study drug, or before receiving the first dose in the extension study. Serious AEs (SAEs) were those causing death, were life-threatening, resulted in inpatient hospitalization, caused persistent or significant disability or incapacity, or led to a major medical event or its prolongation. AEs occurring from the time of infusion start through 24 hours later and AEs that occurred on the day of infusion, either before, during, or after, and did not have a reported start time were adjudicated to determine whether they were infusion-related reactions (IRRs).

The secondary objective of the study was to characterize the plasma PK of casimersen after IV administration. Serial blood samples were collected at weeks 1, 3, 5, 7, and 60, each immediately before infusion, and 5 to 10 minutes and 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after completion of infusion to quantify casimersen concentration in the plasma. Urine was collected for PK analysis at weeks 1, 3, 5, 7, and 12 during the time intervals 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours from the start of infusion.

2.5 | Data analysis

The sample size for this study was based on qualitative considerations; no formal sample size calculations were performed. Twelve participants were considered sufficient to provide initial safety evaluation of casimersen and to provide adequate data to allow for estimation of PK parameters. The safety population included all randomized participants who received at least one dose of casimersen or placebo. The population for PK analysis comprised all randomized participants who received the planned full dose of study drug and for whom there were adequate PK samples from which to estimate PK parameters.

Descriptive statistics were used to summarize both continuous and categorical variables. For AEs and other safety-related data, analyses were performed for the double-blind phase as well as the active casimersen period, which included all assessments and events that occurred while participants received casimersen (ie, participants who received casimersen at any point during the study). Assessments and events that occurred in the double-blind period for participants who were on placebo during the double-blind period were excluded from the casimersen period.

In general, only TEAEs were summarized. The percentages of participants meeting potentially clinically significant abnormal laboratory, vital sign, ECG, and/or ECHO criteria, and the frequency of these findings, were summarized by analysis period and treatment group.

Serial plasma concentration data were used to determine PK parameters, including area under the concentration-time curve (AUC), total body clearance, maximum observed concentration (C_{max}), terminal phase half-life ($t_{1/2}$), time of maximum observed concentration (t_{max}), and volume of distribution at steady state (V_{ss}). Actual sampling times were used in the noncompartmental analysis. Per-protocol times were used to calculate mean plasma concentrations.

3 | RESULTS

3.1 | Participants

Twelve participants were enrolled in the double-blind and open-label studies; eight received casimersen and four received placebo. Eleven participants (91.7%) completed the study (Figure 1). The one participant who prematurely discontinued study drug received placebo during the double-blind period; the reason for discontinuation was withdrawal by the participant after 143 weeks in the study.

Participants randomized to casimersen were slightly older and had more advanced disease, longer mean time since DMD diagnosis, and shorter mean baseline 6-minute walk test distance than the placebo group (Table 1). The mean (standard deviation [SD]) total time on study was 144.7 (3.5) weeks, and the mean (SD) duration of time on casimersen treatment during the combined study periods was 139.6 (9.3) weeks.

3.2 | Safety

In the 12-week, double-blind period, all participants experienced at least one TEAE (Table 2). TEAEs related to treatment were reported

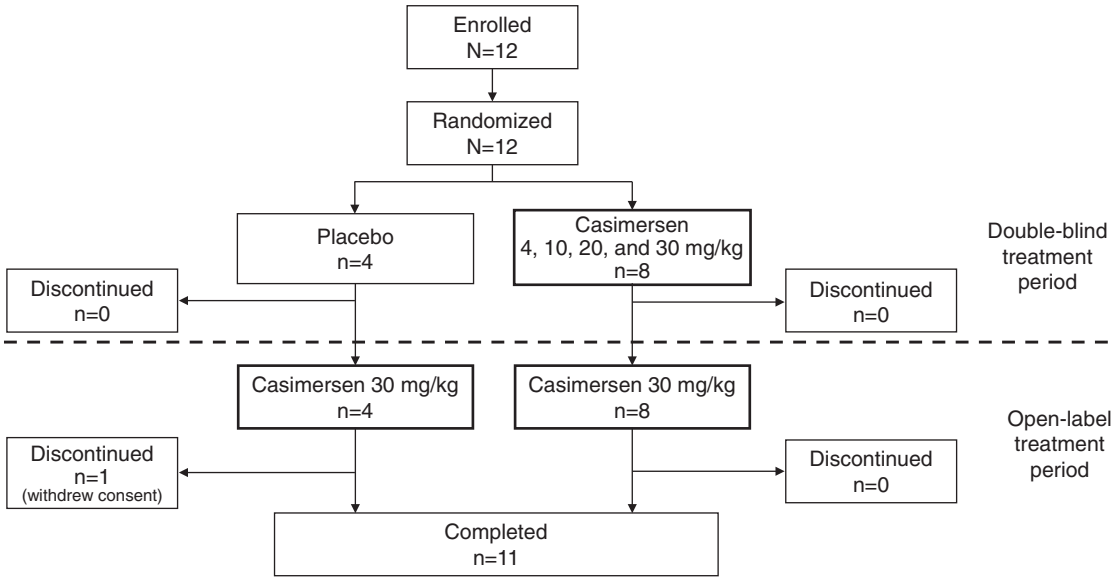

FIGURE 1 Participant disposition. Heavy boxes denote participants included in the casimersen treatment period

TABLE 1 Participant demographics and baseline characteristics

Parameter	Placebo (n = 4)	Casimersen (n = 8)	Total (N = 12)
Age, years, mean (SD)	12.0 (2.2)	14.4 (3.3)	13.6 (3.1)
Race, n (%)			
White	4 (100)	6 (75.0)	10 (83.3)
Asian	0	2 (25.0)	2 (16.7)
Ethnicity, n (%)			
Hispanic or Latino	0	1 (12.5)	1 (8.3)
Not Hispanic or Latino	4 (100)	7 (87.5)	11 (91.7)
BMI, kg/m^2, mean (SD)	21.9 (1.2)	25.9 (4.8)	24.6 (4.3)
6MWT distance, meters, mean (SD)[a,b]	115.4 (134.2)	0.9 (2.5)	39.1 (90.0)
Time since DMD diagnosis, months, mean (SD)	91.8 (33.7)	136.1 (47.9)	121.3 (47.4)
Duration of corticosteroid use, months, mean (SD)	84.5 (38.3)	80.1 (34.5)	81.6 (34.1)

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; DMD, Duchenne muscular disease; SD, standard deviation.
[a]Baseline defined as last value before the first dose of study drug.
[b]Participants who were not ambulatory were considered to have a 6MWT distance of 0 meter.

at the same frequency for participants in the casimersen (2 of 8 participants, 25%) and placebo (1 of 4 participants, 25%) groups and were not dose-related. There were no noted safety trends in TEAEs experienced during dose titration and no indication of more AEs occurring at higher doses. Most TEAEs were mild during both the double-blind (47 of 53 events, 88.7%) and open-label (159 of 175 events, 90.9%) treatment periods and considered unrelated to the study drug. No participant discontinued study drug or reduced their dosage because of TEAEs, and there were no deaths in the study.

The TEAEs most frequently reported during the double-blind treatment period were procedural pain, headache, and vomiting in the casimersen group. Treatment-related TEAEs included one case of moderate iron deficiency and one case of mild flushing in two casimersen-treated participants, and mild contact dermatitis in one participant who received placebo. Casimersen-related TEAEs resolved during the study period; the single placebo-related TEAE was ongoing at the end of the study. The TEAEs most frequently reported during the casimersen treatment in the combined double-blind and open-label period were nasopharyngitis, cough, headache, procedural pain, upper respiratory tract infection, and vomiting (Table 3). All were assessed by the blinded investigators as unrelated to casimersen treatment.

Five SAEs occurred in three participants receiving casimersen 30 mg/kg during the combined treatment periods. None of these five events were considered related to study drug; all events resolved during the study and did not recur with further dosing. Two participants had fractures that resolved. One participant experienced bacteremia (moderate), septic embolus (severe), and vena cava thrombosis (severe) related to a venous port placed for casimersen administration.

TABLE 2 TEAEs reported during the 12-week, double-blind treatment period

TEAEs[a]	Placebo (n = 4)	Casimersen 4 mg/kg (weeks 1-2) (n = 8)	Casimersen 10 mg/kg (weeks 3-4) (n = 8)	Casimersen 20 mg/kg (weeks 5-6) (n = 8)	Casimersen 30 mg/kg (weeks 7-8) (n = 8)	Casimersen 30 mg/kg (week 7 to end of double-blind period) (n = 8)	Total (N = 8)
Participants with any TEAE, n (%)	4 (100)	5 (62.5)	3 (37.5)	3 (37.5)	4 (50.0)	7 (87.5)	8 (100)
Serious TEAE	0	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)
TEAE related to treatment	1 (25.0)	1 (12.5)	0	0	0	1 (12.5)	2 (25.0)
Participants with TEAEs reported in ≥25% of participants, n (%)							
Procedural pain	1 (25.0)	0	0	2 (25.0)	2 (25.0)	3 (37.5)	4 (50.0)
Headache	0	1 (12.5)	0	0	1 (12.5)	2 (25.0)	3 (37.5)
Vomiting	0	0	0	2 (25.0)	1 (12.5)	2 (25.0)	3 (37.5)
Nausea	0	1 (12.5)	1 (12.5)	1 (12.5)	0	0	2 (25.0)
Nasopharyngitis	1 (25.0)	1 (12.5)	0	0	1 (12.5)	1 (12.5)	1 (12.5)
Pain in extremity	1 (25.0)	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)
Skin papilloma	1 (25.0)	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)
Contact dermatitis	1 (25.0)	0	0	0	0	0	0
Back pain	1 (25.0)	0	0	0	0	0	0
Ligament sprain	1 (25.0)	0	0	0	0	0	0
Oropharyngeal pain	1 (25.0)	0	0	0	0	0	0
Tinea versicolor	1 (25.0)	0	0	0	0	0	0
Total TEAEs by severity, n							
Mild	11	9	3	9	13	26	47
Moderate	0	0	0	1	1	3	4
Severe	0	0	0	0	2	2	2

Abbreviation: TEAE, treatment-emergent adverse event.
[a]TEAEs reported for casimersen-treated participants in the double-blind period are also included in the summaries for the casimersen period.

This participant recovered after treatment with antibiotics and tissue plasminogen activator and then resumed dosing with study drug.

No patterns, trends, or abnormalities were observed in hematology, coagulopathy, serum chemistry, other clinical laboratory parameters, or vital signs. All participants had normal blood urea nitrogen and cystatin C levels at baseline and at last visit. No cardiac signal was noted in conduction time or functional assessment by ECHO. One case of transient ventricular tachycardia was reported, but the event was considered unrelated to casimersen treatment and the ECG normalized without sequelae.

Three casimersen-treated participants and two placebo-treated participants experienced events adjudicated as IRRs during the 12-week double-blind period. In the total casimersen period, 13 adjudicated IRRs occurred in seven participants; three events did not have a recorded start time. All IRRs were nonserious, mild, and resolved. Two casimersen-treated participants experienced an IRR with the first infusion; the events were mild, occurred 1 to 2 hours after infusion, and resolved the same day. Potential hypersensitivity events occurred in seven participants during the casimersen period and included flushing, rash, and contact dermatitis; all were nonserious and mild, and resolved without treatment. There were no cases of anaphylaxis.

3.3 | Pharmacokinetics

Plasma concentrations of casimersen increased with increasing dose, and the mean concentration profiles declined through the elimination phase in a similar manner across all dose levels. Overall, C_{max} and AUC values increased with increasing dose level. The geometric mean C_{max} increased approximately ninefold from the 4-mg/kg dose level (week 1) to the 30-mg/kg dose level (week 7), whereas AUC_{∞} (AUC from time 0 extrapolated to infinity) increased approximately eightfold from 4 to 30 mg/kg (week 1 to week 7) (Table 4). Total clearance, V_{ss}, and t_{max} were similar across dose levels, whereas $t_{1/2}$ increased slightly with dose. Total clearance due to renal excretion ranged from 77% to 108%, suggesting renal clearance is the main route of elimination for casimersen.

Mean plasma casimersen concentration-vs-time profiles were similar at week 7 and week 60 for the 30-mg/kg dose level, suggesting little to no accumulation in the plasma after long-term weekly dosing (Figure 2). All PK parameters were similar at weeks 7 and 60 for the casimersen 30-mg/kg dose level (Table 4).

Urine PK analysis showed that casimersen is primarily excreted in urine as unchanged drug, with the fraction unchanged ranging from 77.1% to 108%. The largest amount excreted was generally observed during the first 4 hours after infusion start.

TABLE 3 TEAEs reported during casimersen treatment in the combined 12-week, double-blind and 132-week, open-label periods

TEAEs	Total casimersen group (N = 12)
Participants with any TEAE, n (%)	12 (100)
Serious TEAE	3 (25.0)
TEAE related to treatment	2 (16.7)
Participants with TEAEs reported in ≥25% of participants, n (%)	
Nasopharyngitis	9 (75.0)
Cough	4 (33.3)
Headache	4 (33.3)
Procedural pain	4 (33.3)
Upper respiratory tract infection	4 (33.3)
Vomiting	4 (33.3)
Nausea	3 (25.0)
Pain in extremity	3 (25.0)
Oropharyngeal pain	3 (25.0)
Rash	3 (25.0)
Tibia fracture	3 (25.0)
Total TEAEs by severity, n	
Mild	159
Moderate	14
Severe	2

Abbreviation: TEAE, treatment-emergent adverse event.

4 | DISCUSSION

In this phase 1/2 study, casimersen was well tolerated in boys with DMD amenable to exon 45 skipping. Few TEAEs were reported overall and most were mild, nonserious, and unrelated to casimersen. Most AEs were consistent with conditions that may be anticipated in children in general, or as complications or comorbidities of DMD.

No AEs of special interest met the search criteria for leukopenia, neutropenia, drug-induced hepatotoxicity, severe cutaneous reactions, infusion-site reactions, renal, or cardiac events; however, one participant had three SAEs that were related to the study procedure of receiving a port. No anaphylaxis or serious hypersensitivity events associated with casimersen were reported, and no trends or abnormalities were observed in hematology, coagulopathy, chemistry, or other clinical laboratory parameters. It should be noted that elevations of alanine aminotransferase and aspartate aminotransferase are common in DMD because these enzymes are also released from injured skeletal muscle. No cardiac signals were noted. This safety profile is consistent with the approved PMOs eteplirsen, golodirsen, and vitolarsen.[3,8,9]

PK analyses from the present study showed a short plasma half-life for casimersen that was similar to that of eteplirsen (3-4 hours), golodirsen (3.4 hours), and viltolarsen (2.5 hours).[5-7] Although preclinical studies indicate kidney toxicity could be a class risk for antisense oligonucleotides,[22] this study found no evidence of kidney toxicity based on AE and laboratory results, and there was no suggestion of a significant risk of kidney abnormality or toxicity. Consistently, no signs of kidney toxicity were observed for the other approved PMOs, for which the kidney is also the primary route of excretion (approximately 65%, 60%, and 93% for eteplirsen, golodirsen, and vitolarsen, respectively).[5,6,23] The short half-life and rapid renal clearance may underlie

TABLE 4 Summary of key plasma casimersen noncompartmental PK parameters by dose level and week

Parameter	Week 1: casimersen 4 mg/kg (n = 8)	Week 3: casimersen 10 mg/kg (n = 8)[a]	Week 5: casimersen 20 mg/kg (n = 8)	Week 7: casimersen 30 mg/kg (n = 8)	Week 60: casimersen 30 mg/kg (n = 12)
C_{max}, ng/mL	13,700 (25.0)	39,400 (11.7)	64,400 (27.4)	119,000 (33.6)	115,000 (31.5)
t_{max}, h	1.11 (0.9-1.2)	1.03 (0.9-1.2)	1.03 (0.8-1.2)	0.94 (0.8-1.2)	0.95 (0.8-1.1)
AUC_{∞}, h·ng/mL	23,300 (29.5)	58,300 (16.0)	101,000 (17.7)	189,000 (27.5)	182,000 (33.9)
V_{ss}, L/kg	0.369 (24.4)	0.343 (12.5)	0.407 (23.4)	0.319 (31.4)	0.367 (28.9)
CL, L/h/kg	0.177 (29.1)	0.181 (15.9)	0.205 (18.5)	0.163 (27.7)	0.180 (35.0)
$t_{1/2}$, h	2.9 (1.0)	3.3 (0.6)	3.7 (0.6)	3.8 (0.7)	3.5 (0.4)

Note: Values are presented as geometric mean (geometric coefficient of variation percentage) for all parameters, except for t_{max} and $t_{1/2}$; t_{max} is presented as median (minimum-maximum); $t_{1/2}$ is presented as mean (SD).

Abbreviations: AUC_{∞}, area under the concentration-time curve from time 0 extrapolated to infinity; CL, total body clearance after intravenous administration; C_{max}, maximum observed concentration; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, terminal phase half-life; t_{max}, time of observed maximum concentration; V_{ss}, volume of distribution at steady state.

[a]At week 3, n = 7 for AUC_{∞}, V_{ss}, CL, and $t_{1/2}$.

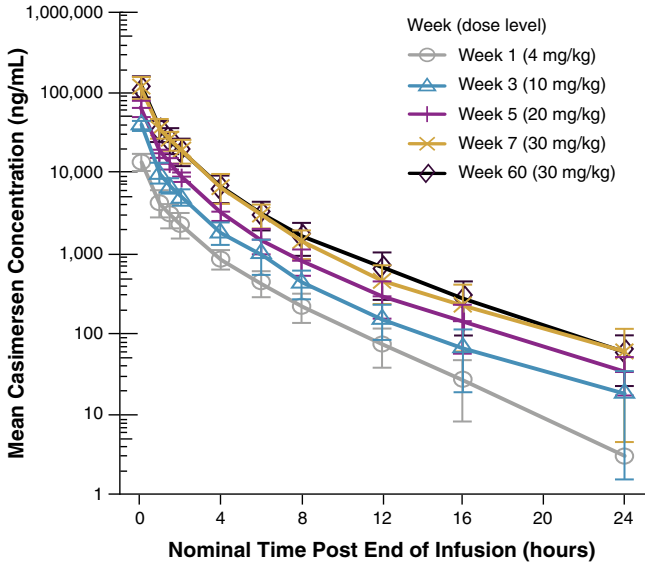

FIGURE 2 Casimersen plasma concentration by time postinfusion, according to dose level and week of treatment. Mean (SD) plasma casimersen concentration increased with dose, and the mean concentration decreased similarly across doses over 24 hours postinfusion. Profiles were comparable at week 7 and week 60 for the 30-mg/kg dose, suggesting little to no accumulation after weekly dosing. Y-axis is a semi-log scale. Abbreviation: SD, standard deviation

the lack of renal effects with casimersen. Overall, the PK analyses show similarity of casimersen with the other three approved PMOs for DMD.[3,8,9]

PK analyses from this study also suggest that casimersen plasma exposure (AUC and C_{max}) is approximately dose proportional within the tested range of 4 to 30 mg/kg, and total clearance, V_{ss}, $t_{1/2}$, and t_{max} were similar across dose levels. The comparability of exposure parameters (C_{max} and AUC) at weeks 7 and 60, and the short plasma half-life of casimersen, suggest little to no accumulation in the plasma after weekly dosing of 30 mg/kg.

The primary limitation of this study was its small sample size, constrained by the rarity of DMD, and the even smaller subset of patients amenable to exon 45 skipping.

Casimersen is currently being investigated in a phase 3, multicenter, placebo-controlled, 96-week study, followed by a 48-week open-label extension (ESSENCE trial, NCT02500381). The ESSENCE trial includes ambulatory participants to provide further evidence on the clinical efficacy, safety, and PK of long-term casimersen treatment in a broad patient population.

5 | CONCLUSIONS

Casimersen 30 mg/kg has an acceptable safety profile and was well tolerated in patients with DMD and confirmed mutations amenable to exon 45 skipping who had limited ambulation or were nonambulatory. These results support further studies evaluating the safety and efficacy of casimersen in larger cohorts of patients with DMD and confirmed mutations of the *DMD* gene amenable to exon 45 skipping.

ACKNOWLEDGMENTS

This study was funded by Sarepta Therapeutics, Inc. Aaron Novack, PhD, and Ihor Sehinovych, PharmD, of Sarepta reviewed the manuscript for scientific accuracy. Medical writing support was provided by Valerie P. Zediak, PhD, of Eloquent Scientific Solutions, and funded by Sarepta.

CONFLICT OF INTEREST

K.R.W. has served as a paid consultant for Asklepios BioPharmaceutical, Inc, Dynacure, Dyne Therapeutics, PTC Therapeutics, F. Hoffmann-LaRoche, Ltd, Sarepta Therapeutics, Inc, and Vita Therapeutics. N.L.K. has served as a paid consultant on advisory boards for Audentes, AveXis, Biogen, Cytokinetics, PTC Therapeutics, Roche, and Sarepta Therapeutics, Inc. E.K., L.E., S.U., and B.H. are employees of Sarepta Therapeutics, Inc, and may own stock/options in the company. P.B.S. has served as a paid consultant on ad hoc advisory boards for Alexion, AveXis, Biogen, and Sarepta Therapeutics, Inc, and has served on speakers' bureaus for Alexion, AveXis, Biogen, CSL Behring, Genentech, and Grifols.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, data analysis and/or interpretation, revised the manuscript critically for intellectual content, and approved the final manuscript for submission. K.R.W., N.L.K., and P.B.S. are study investigators. B.H. provided statistical analysis. L.E. provided pharmacokinetic analysis. E.K. and S.U. provided analysis of clinical data.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to the data that support the findings of this study from Sarepta Therapeutics Inc. by contacting medinfo@sarepta.com.

ORCID

Perry B. Shieh https://orcid.org/0000-0001-7145-7663

REFERENCES

1. Crisafulli S, Sultana J, Fontana A, Salvo F, Messina S, Trifiro G. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. *Orphanet J Rare Dis*. 2020;15:141.
2. Mah JK. Current and emerging treatment strategies for Duchenne muscular dystrophy. *Neuropsychiatr Dis Treat*. 2016;12:1795-1807.
3. Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *Lancet*. 2011;378:595-605.

4. Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. *Drug Des Devel Ther*. 2017;11:533-545.
5. Sarepta Therapeutics, Inc. Exondys® (eteplirsen) injection, for intravenous use. US prescribing information. 2020.
6. Sarepta Therapeutics, Inc. Vyondys® (golodirsen) injection, for intravenous use. US prescribing information. 2021.
7. NS Pharma, Inc. Viltepso® (viltolarsen) injection, for intravenous use. US prescribing information. 2021.
8. Clemens PR, Rao VK, Connolly AM, et al. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: a phase 2 randomized clinical trial. *JAMA Neurol*. 2020;77:982-991.
9. Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology*. 2020;94:e2270-e2282.
10. Heo YA. Golodirsen: first approval. *Drugs*. 2020;80:329-333.
11. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74:637-647.
12. Alfano LN, Charleston JS, Connolly AM, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. *Medicine*. 2019;98:e15858.
13. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol*. 2016;79:257-271.
14. Kinane TB, Mayer OH, Duda PW, Lowes LP, Moody SL, Mendell JR. Long-term pulmonary function in Duchenne muscular dystrophy: comparison of eteplirsen-treated patients to natural history. *J Neuromuscul Dis*. 2018;5:47-58.
15. Khan N, Eliopoulos H, Han L, et al. Eteplirsen treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2019;6:213-225.
16. Muntoni F, Servais L, Straub V, et al. Long-term safety and efficacy of golodirsen in male patients with Duchenne muscular dystrophy amenable to exon 53 skipping. Muscular Dystrophy Association Virtual Conference Hub; 2020. https://mdaconference.org/index.php/node/936
17. Sarepta Therapeutics, Inc. Amondys 45 (casimersen) injection, for intravenous use. US prescribing information. 2021.
18. Aartsma-Rus A, Fokkema I, Verschuuren J, Ginjaar I, van Deutekom J, van Ommen GJ, den Dunnen JT. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. *Hum Mutat* 2009;30(3):293-299.
19. Brogna C, Coratti G, Pane M, et al. Long-term natural history data in Duchenne muscular dystrophy ambulant patients with mutations amenable to skip exons 44, 45, 51 and 53. *PLoS One* 2019;14:e0218683.
20. Bello L, Morgenroth LP, Gordish-Dressman H, Hoffman EP, McDonald CM, Cirak S. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. *Neurology* 2016;87:401-409.
21. Zhang S, Qin D, Wu L, et al. Genotype characterization and delayed loss of ambulation by glucocorticoids in a large cohort of patients with Duchenne muscular dystrophy. *Orphanet J Rare Dis* 2021;16:188.
22. Engelhardt JA. Comparative renal toxicopathology of antisense oligonucleotides. *Nucleic Acid Ther*. 2016;26:199-209.
23. Komaki H, Takeshima Y, Matsumura T, et al. Viltolarsen in Japanese Duchenne muscular dystrophy patients: a phase 1/2 study. *Ann Clin Transl Neurol*. 2020;7:2393–2408.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Wagner KR, Kuntz NL, Koenig E, et al. Safety, tolerability, and pharmacokinetics of casimersen in patients with Duchenne muscular dystrophy amenable to exon 45 skipping: A randomized, double-blind, placebo-controlled, dose-titration trial. *Muscle & Nerve*. 2021;64(3):285–292. https://doi.org/10.1002/mus.27347