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Casimersen Treatment in Patients With Duchenne Muscular Dystrophy: Safety, Tolerability, and Pharmacokinetics Over 144 Weeks of Treatment

Kathryn Wagner,[1] Nancy Kuntz,[2] Erica Koenig,[3] Lilly East,[3] Sameer Upadhyay,[3] Baoguang Han,[3] Perry B. Shieh[4]; on behalf of the Casimersen Study 4045-101 and ESSENCE Clinical Investigators

[1]Kennedy Krieger Institute, Johns Hopkins School of Medicine, Baltimore, MD; [2]Ann & Robert H. Lurie Children's Hospital, Chicago, IL; [3]Sarepta Therapeutics, Inc., Cambridge, MA; [4]Ronald Reagan UCLA Medical Center, Los Angeles, CA

BACKGROUND

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene[1]; mutations leading to deletions flanking exon 45 account for 8% of all DMD patients[2]
- Casimersen binds to dystrophin pre-mRNA to allow skipping of exon 45, restoring the mRNA reading frame and allowing translation of a truncated dystrophin protein
- Study 4045-101 (NCT02530905) was a first-in-human, Phase 1/2, 2-part clinical trial designed to assess safety, tolerability, and pharmacokinetics of casimersen in DMD patients with mutations amenable to exon 45 skipping who had limited ambulation or were nonambulatory
- ESSENCE (NCT02500381) is an ongoing, Phase 3, multicenter study in ambulatory patients with DMD amenable to exon 45 skipping or exon 53 skipping

OBJECTIVE

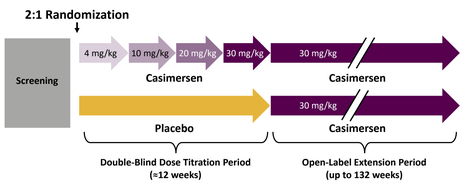
- To report the safety, tolerability, and pharmacokinetics of casimersen in patients with DMD and confirmed mutations amenable to exon 45 skipping (Study 4045-101) and to report interim results on the effect of casimersen on dystrophin expression in the ESSENCE study

METHODS

Study 4045-101 Design

- Study 4045-101 was a multicenter, randomized, double-blind, placebo-controlled, dose-titration, Phase 1/2 study
- During the double-blind dose-titration period, patients were randomized 2:1 to receive ascending doses of casimersen or placebo once weekly via IV infusion for 12 weeks (**Figure 1**)
- Subsequently, patients received casimersen 30 mg/kg in an open-label extension period for up to an additional 132 weeks

Figure 1. Study 4045-101 Design



- Patient inclusion criteria
  - Males aged 7–21 years with DMD and a confirmed genetic mutation amenable to exon 45 skipping
  - Stable cardiac and pulmonary function
  - On a stable dose or had not received oral corticosteroids for ≥24 weeks prior to study initiation
  - Nonambulatory or unable to walk ≥300 m on the 6-minute walk test (6MWT)

ESSENCE Study Design

- ESSENCE is an ongoing, 96-week, double-blind, placebo-controlled, Phase 3 study with a subsequent 48-week open-label period
- Patients are randomized 2:1 to casimersen 30 mg/kg once weekly or placebo
- Patient inclusion criteria
  - Males aged 7–13 years with DMD and a confirmed genetic mutation amenable to exon 45 skipping
  - 6MWT distance ≥300 and ≤450 m
  - Stable pulmonary function, percent predicted forced vital capacity (FVC%p) >50%
  - On a stable dose of oral corticosteroids for ≥6 months

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RESULTS

Study 4045-101 Patients

- Of 12 patients enrolled, 11 (91.7%) completed Study 4045-101; 1 patient discontinued during the open-label period
- Patients randomized to casimersen were generally slightly older and had more advanced disease than those randomized to placebo (**Table 1**)
- Mean (SD) total time on study was 144.7 (3.45) weeks and total casimersen treatment was 139.6 (9.26) weeks

Table 1. Baseline Characteristics of Patients in Study 4045-101[a]

Parameter	Placebo (n=4)	Casimersen (n=8)	Total (N=12)
Age, years	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	21.9 (1.2)	25.9 (4.8)	24.6 (4.3)
6MWT distance,[b] m	115.4 (134.2)	0.9 (2.5)	39.1 (90.0)
Time since DMD diagnosis, months	91.8 (33.7)	136.1 (47.9)	121.3 (47.4)
Duration of corticosteroid use, months	84.5 (38.3)	80.1 (34.5)	81.6 (34.1)

BMI=body mass index. Values are mean (SD) unless noted otherwise. [a]Baseline was defined as the last value prior to the first dose of study drug. [b]Patients who were not ambulatory were considered to have a 6MWT distance of 0 m.

Study 4045-101 Safety

- All patients experienced ≥1 treatment-emergent adverse event (TEAE; **Tables 2 and 3**)
- No patient discontinued study drug or reduced study drug dosage because of TEAEs
- Most TEAEs were mild in severity during the double-blind period (89%) and combined double-blind and open-label casimersen treatment periods (91%)
- Procedural pain and nasopharyngitis were the most commonly reported TEAEs during the double-blind and combined casimersen treatment periods, respectively
- AEs and laboratory results showed no evidence of renal toxicity and no suggestion of a significant risk of renal abnormality with casimersen
- Treatment-related TEAEs included 1 case of moderate iron deficiency and 1 case of mild flushing in 2 casimersen-treated patients, and mild contact dermatitis in 1 patient who received placebo
  - Casimersen-related TEAEs resolved during the study; the placebo-related TEAE was ongoing at end of study
- 5 serious TEAEs occurred in 3 patients receiving casimersen 30 mg/kg during the combined treatment periods
  - Bacteremia, septic embolus, and vena cava thrombosis in 1 patient were related to a venous port placed for casimersen administration
  - 2 patients experienced bone fracture (tibia or femur)
  - All 5 events were considered not related to casimersen, resolved during the study, and did not recur with further dosing
- No patterns, trends, or abnormalities were observed in hematology, coagulopathy, chemistry, or other clinical laboratory parameters
- No cardiac signal was noted in conduction time or functional assessment by echocardiogram
  - One case of transient ventricular tachycardia was reported, but the event was considered unrelated to casimersen treatment and the electrocardiogram normalized without sequelae

Table 2. TEAEs Reported in the Double-Blind Period in Study 4045-101

Patients, n (%)	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)
≥1 TEAE	4 (100)	5 (62.5)	3 (37.5)	3 (37.5)	4 (50.0)	7 (87.5)	8 (100)
≥1 serious TEAE	0	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)
≥1 TEAE related to treatment	1 (25.0)	1 (12.5)	0	0	0	1 (12.5)	2 (25.0)
TEAEs reported in ≥25% of patients							
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	2 (50.0)	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 number of TEAEs by severity							
Mild	11	9	3	9	13	26	47
Moderate	0	0	0	1	1	3	4
Severe	0	0	0	0	2	2	2

Table 3. TEAEs Reported During Casimersen Treatment in the Combined Double-Blind and Open-Label Periods in Study 4045-101

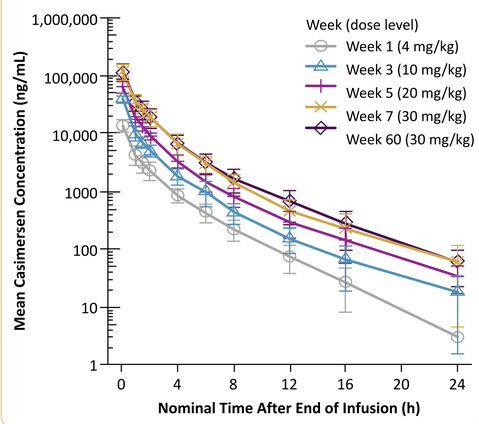
Patients, n (%)	Total (N=12)
≥1 TEAE	12 (100)
≥1 serious TEAE	3 (25.0)
≥1 TEAE related to treatment	2 (16.7)
TEAEs reported in ≥25% of patients	
Nasopharyngitis	9 (75.0)
Cough	4 (33.3)
Headache	4 (33.3)
Procedural pain	4 (33.3)
Upper respiratory tract infection	4 (33.3)
Vomiting	4 (33.3)
Nausea	3 (25.0)
Pain in extremity	3 (25.0)
Oropharyngeal pain	3 (25.0)
Rash	3 (25.0)
Tibia fracture	3 (25.0)
Total number of TEAEs by severity	
Mild	159
Moderate	14
Severe	2

Only TEAEs with an onset date after administration of the first dose of casimersen are included.

Study 4045-101 Pharmacokinetics

- Pharmacokinetic (PK) analyses suggest casimersen exposure is approximately dose proportional within the tested range of 4–30 mg/kg
- Mean casimersen half-life ranged from 2.9–3.8 hours
- Mean plasma casimersen concentration vs time profiles (**Figure 2**), and all other PK parameters, were similar at Weeks 7 and 60 for the 30-mg/kg dose, suggesting little to no accumulation in plasma with weekly dosing

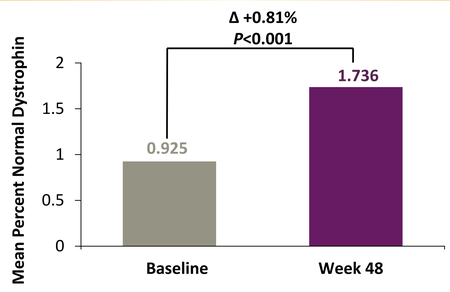
Figure 2. Plasma Casimersen Concentration Over Time by Dose and Week in Study 4045-101



ESSENCE Study Dystrophin Expression

- Interim results from the ongoing Phase 3 ESSENCE study show a significant increase in dystrophin protein from baseline to Week 48 in casimersen-treated patients (P<0.001; **Figure 3**); change from baseline was greater in the casimersen arm compared with the placebo arm (P=0.004)
- Of the 27 patients receiving casimersen, all displayed an increase in exon 45 skipping (P<0.001) over baseline, representing a 100% response rate (data not shown)
- A significant positive correlation between exon 45 skipping and dystrophin production was observed (Spearman rank correlation = 0.627, P<0.001)

Figure 3. Dystrophin Protein Expression in the ESSENCE Study



CONCLUSIONS

- Casimersen 30 mg/kg was well tolerated in patients with DMD and confirmed mutations amenable to exon 45 skipping who had limited ambulation or were nonambulatory at baseline
- Most reported TEAEs were mild in severity; 2 were related to treatment, and no patients discontinued study drug or reduced dosage due to TEAEs
- No clinically significant laboratory abnormalities or worsening in electrocardiograms and echocardiograms were noted
  - No suggestion of a significant risk of renal abnormality or renal toxicity with casimersen
- PK analyses suggest little to no plasma accumulation of casimersen following weekly dosing at 30 mg/kg
- Interim results from the ongoing ESSENCE study showed casimersen significantly increased exon 45 skipping and dystrophin protein expression
- Together, these results support further evaluation of casimersen safety and efficacy in patients with DMD amenable to exon 45 skipping

REFERENCES

1. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251-67.
2. Aartsma-Rus A, et al. *Hum Mutat.* 2009;30:293-9.

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