P.39 Presented at the 2023 MDA Clinical and Scientific Conference; March 19–22, 2023; Dallas, TX, and Virtual

Casimersen in Patients With Duchenne Muscular Dystrophy: Interim Safety and Muscle Biopsy Results From the Phase 3 ESSENCE Trial

Susan Iannaccone,[1] Han Phan,[2] Volker Straub,[3] Francesco Muntoni,[4-6] Jyoti Malhotra,[7] Rong Chu,[7] Eddie Darton,[7] Eugenio Mercuri[8]

[1]UT Southwestern Medical Center, Dallas, TX; [2]Rare Disease Research Center, Atlanta, GA; [3]Newcastle University John Walton Muscular Dystrophy Research Centre and the Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [4]Dubowitz Neuromuscular Centre, UCL Institute of Child Health and Great Ormond Street Hospital for Children, London, UK; [5]Great Ormond Street Hospital, London, UK; [6]NIHR Great Ormond Street Hospital Biomedical Research Centre, London, UK; [7]Sarepta Therapeutics, Inc., Cambridge, MA; [8]Paediatric Neurology and Centro Clinico Nemo, Catholic University and Policlinico Gemelli, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Rome, Italy

Please scan QR code to download poster and further details

Objective

To report available results from a prespecified interim analysis of 48-week muscle biopsy data from the first 43 patients with exon 45 skip-amenable mutations in the phase 3 ESSENCE trial (NCT02500381)

Key Findings

Interim results from ESSENCE show casimersen is well tolerated and significantly increases exon skipping and dystrophin expression

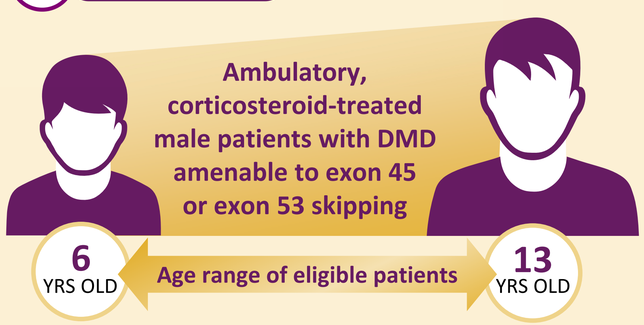
BACKGROUND

- Mutations of the Duchenne muscular dystrophy (DMD) gene that are amenable to exon 45 skipping account for up to 8% of all patients with DMD[1]
- Amondys 45 (casimersen) is US Food and Drug Administration–approved for the treatment of patients with DMD with confirmed mutation of the dystrophin gene that is amenable to exon 45 skipping
- Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing and allowing the production of an internally shortened but functional dystrophin protein
- The phase 3 ESSENCE trial is an ongoing, double-blind, placebo-controlled study of casimersen and golodirsen over 96 weeks followed by a 48-week open-label period

CONCLUSIONS

- In a prespecified interim analysis of patients with exon 45 skip-amenable mutations, casimersen significantly increased exon skipping, dystrophin expression, and localization to the sarcolemma at 48 weeks relative to baseline and placebo
- No patients discontinued casimersen due to AEs
- The safety and clinical efficacy of casimersen will continue to be evaluated in this ongoing trial

METHODS



Patients amenable to exon 45 skipping are randomized 2:1 to receive casimersen 30 mg/kg or placebo intravenously once weekly

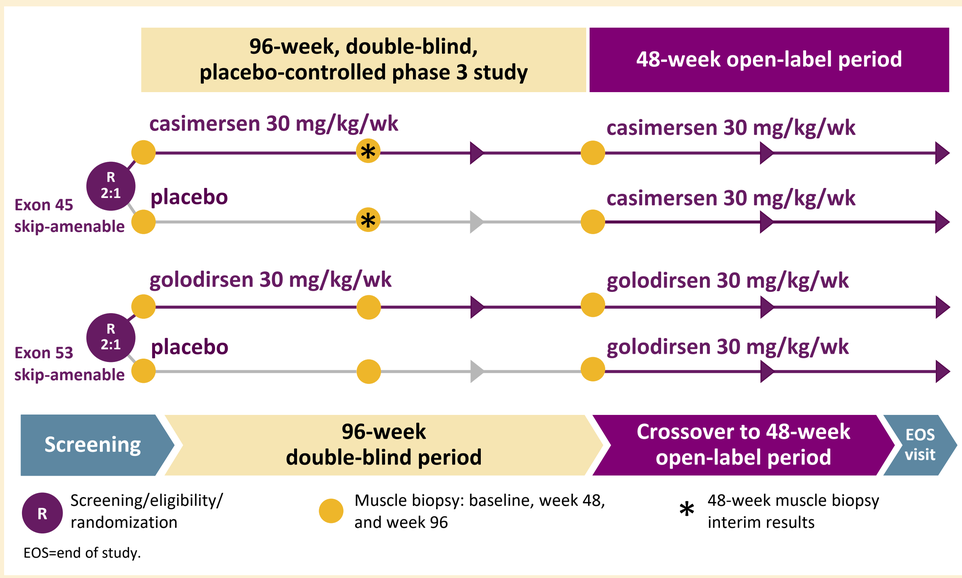
Additional inclusion criteria
- 6-minute walk test (6MWT) distance ≥300 and ≤450 m
- Stable pulmonary function, with percent predicted forced vital capacity (FVC%p) >50%
- On a stable dose of oral corticosteroids for ≥6 months

Primary endpoint
- 6MWT change from baseline at week 96

Secondary endpoints
- 6MWT change from baseline at week 144
- Dystrophin protein change from baseline at weeks 48 and 96
- Ambulation assessments (ability to rise independently from floor; time to loss of ambulation; change from baseline in North Star Ambulatory Assessment score) at weeks 96 and 144
- FVC%p change from baseline at weeks 96 and 144

Additional endpoint
- Exon-skipping change from baseline at weeks 48 and 96

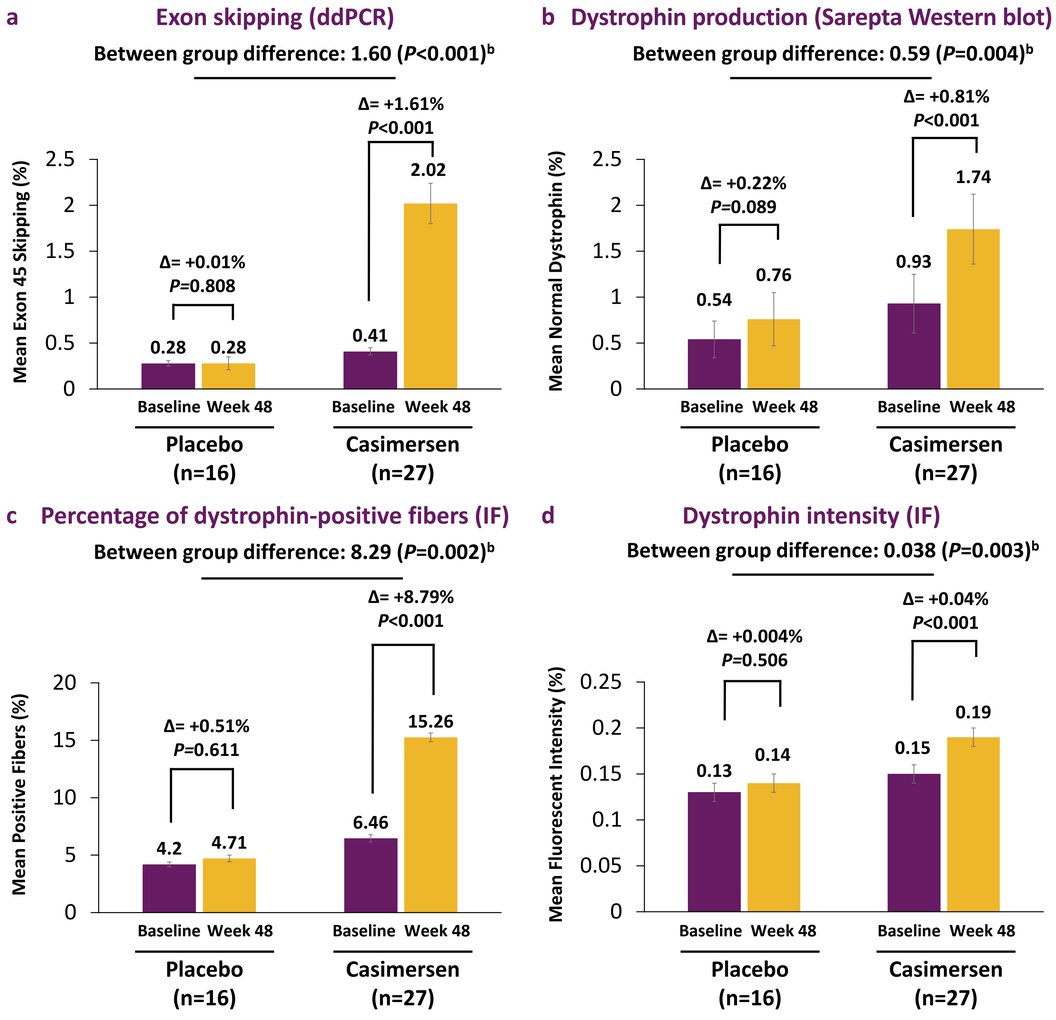
Safety endpoints
- Adverse events (AEs), serious AEs, deaths, discontinuations due to AEs



RESULTS Interim analysis of 48-week muscle biopsy anonymized data from the first 43 patients with exon 45 skip-amenable mutations

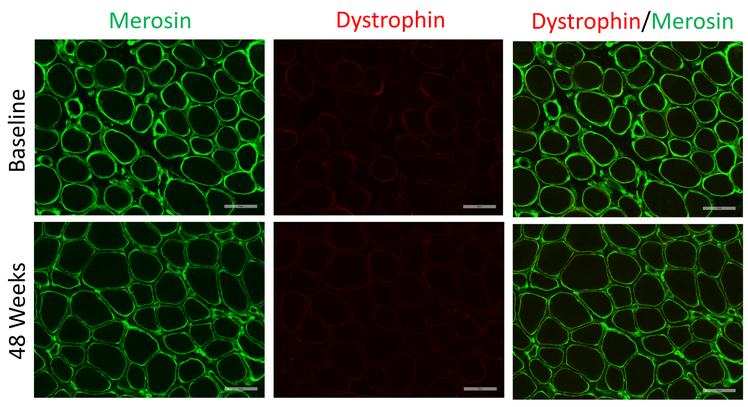
- Of the 27 patients receiving casimersen, all displayed an increase in exon 45 skipping (P<0.001) over baseline (**Figure a**), representing a 100% response rate (data not shown)
  - Placebo-treated patients did not demonstrate an increase in exon skipping (P=0.808)
- Mean dystrophin levels significantly increased from baseline after 48 weeks of casimersen treatment (P<0.001; **Figure b**), with a significantly greater increase in dystrophin levels compared with placebo (P=0.004)
- A significant positive correlation between exon 45 skipping and dystrophin production (Spearman rank correlation, 0.627; P<0.001) demonstrated that de novo dystrophin production is mechanistically linked to exon 45 skipping
- Mean percentage of dystrophin-positive fibers significantly increased from baseline to week 48 (P<0.001; **Figure c**), and compared with placebo (P=0.002)
  - Mean fluorescence intensity was also significantly increased in casimersen-treated patients compared with placebo-treated patients at week 48 (P=0.003; **Figure d**)
- Immunofluorescence staining of muscle biopsy at baseline and week 48 showed dystrophin localization at the sarcolemma in casimersen-treated but not placebo-treated patients (**Figures e, f**)

Casimersen Increased Exon Skipping and Dystrophin Expression After 48 Weeks[a]

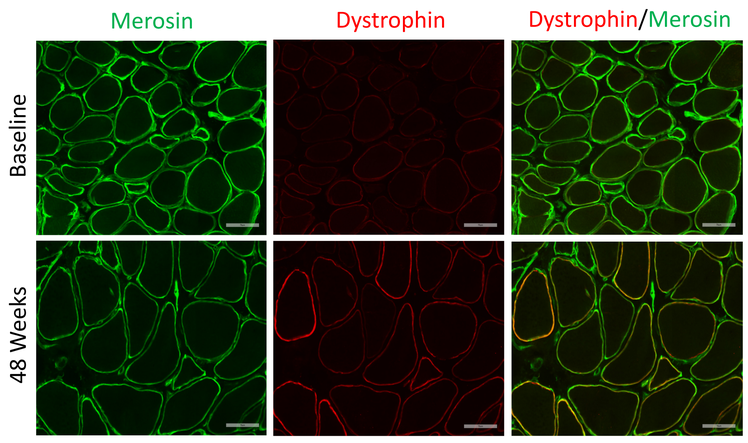


[a]Interim muscle biopsy set. [b]Difference in the mean changes between treatment groups; *P* value calculated by 2-sample permutation test.
ddPCR=droplet digital polymerase chain reaction; IF=immunofluorescence.

e Representative image of placebo-treated patient



f Representative image of casimersen-treated patient



Merosin (membrane label)

Safety

- AEs occurring in ≥20% of casimersen-treated patients and those reported ≥5% more frequently in the casimersen group than in the placebo group are shown in the table
  - Additional AEs (≥10% cut-off) reported ≥5% more frequently with casimersen vs placebo were dizziness light-headedness, ear infection, ear pain, nausea, and post-traumatic pain
- No treatment-emergent AEs led to discontinuation of study drug

AEs Occurring in ≥20% of Casimersen-Treated Patients and ≥5% More Frequently Than Placebo[a]

AE, n (%)	Placebo (n=31)[b]	Casimersen 30 mg/kg (n=57)[b]
Upper respiratory tract infections[c]	17 (55)	37 (65)
Cough	8 (26)	19 (33)
Pyrexia	7 (23)	19 (33)
Headache	6 (19)	18 (32)
Arthralgia	3 (10)	12 (21)
Oropharyngeal pain	2 (7)	12 (21)

[a]As of May 31, 2019. [b]Safety set. [c]Includes upper respiratory infection, pharyngitis, nasopharyngitis, and rhinitis. AE=adverse event.

REFERENCE

1. Aartsma-Rus A, et al. *Hum Mutat.* 2009;30:293-9.

ACKNOWLEDGMENTS & DISCLOSURES

The authors and Sarepta Therapeutics, Inc., thank the patients and their families. **Funding:** ESSENCE (NCT02500381) was funded by Sarepta Therapeutics, Inc. Editorial support was provided by Paraskevi Briassouli, PhD, of Eloquent Scientific Solutions and was funded by Sarepta Therapeutics, Inc. **Disclosures: SI:** Received research support from Biogen, CureSMA, US Department of Defense, Fibrogen, MDA, NIH, Novartis, PPMD, PTC Therapeutics, Reveragen, Sarepta Therapeutics, Inc., and Scholar Rock, and serves on advisory boards for Biogen, Genentech/Roche, Novartis, Sarepta Therapeutics, Inc., and Scholar Rock. **HP:** Principal Investigator for Emalex, Fibrogen, Italfarmaco, Pfizer, Santhera, Sarepta Therapeutics, Inc., and Takeda, and serves on the FDA Pediatric Advisory Committee and CDC Newborn Screening and Molecular Biology Branch. **VS:** Served on advisory board for Sarepta Therapeutics, Inc., and has research collaborations with Sarepta Therapeutics, Inc. **FM:** Received Sarepta Therapeutics, Inc., consultancies for advisory boards and symposia participation. **JM, RC, ED:** Employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. **EM:** Served as a remunerated consultant for Sarepta Therapeutics, Inc. Portions of this poster have been presented at the World Muscle Society 2021 Virtual Congress, September 20–24, 2021; the 50th Annual Meeting of the Child Neurology Society, September 29–October 2, 2021, Boston, MA; and the Muscular Dystrophy Association Clinical & Scientific Conference, March 13–16, 2022, Nashville, TN.

RESULTS CONT'D

Interim analysis of 48-week muscle biopsy anonymized data from the first 43 patients with exon 45 skip-amenable mutations

Baseline Characteristics[a]

Parameter	Placebo (n=16)	Casimersen (n=27)	Total (N=43)
Age, years	9.3 (1.8)	9.1 (1.9)	9.2 (1.8)
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)
BMI,[b] kg/m²	19.3 (4.1)	18.9 (4.4)	19.0 (4.3)
Time since DMD diagnosis, months	68.1 (36.6)	65.6 (35.6)	66.5 (35.6)
Duration of corticosteroid use,[c] months	43.1 (22.2)	48.9 (27.2)	46.7 (25.3)
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)

Values are mean (SD) unless otherwise noted. [a]Interim muscle biopsy set. [b]Placebo n=15, casimersen n=26, total N=41. [c]Casimersen n=26, total N=42.
BMI=body mass index; DMD=Duchenne muscular dystrophy; NR=not reported to preserve blinding of individual patients.

Presented at the 2023 MDA Clinical and Scientific Conference; March 19–22, 2023; Dallas, TX, and Virtual