

Casimersen in Patients With Duchenne Muscular Dystrophy Amenable to Exon 45 Skipping: Interim Results From the Phase 3 ESSENCE Trial

Susan Iannaccone,¹ Han Phan,² Volker Straub,³ Francesco Muntoni,⁴⁻⁶ Erica Koenig,⁷ Jyoti Malhotra,⁷ Baoguang Han,⁷ Eddie Darton,⁷ Eugenio Mercuri⁸

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



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Objective

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

Key Takeaway

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

- 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 exon 45 skip-amenable patients, casimersen significantly increased exon skipping and dystrophin expression at 48 weeks relative to baseline and compared with placebo
- No patients discontinued casimersen due to adverse events (AEs)
- The safety and efficacy of casimersen will continue to be evaluated in this ongoing trial

BACKGROUND

- Mutations leading to deletions flanking exon 45 account for 8% of all patients with Duchenne muscular dystrophy (DMD)¹
- Casimersen is FDA approved for the treatment of DMD in patients with exon 45 skip-amenable mutations
- Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA, restoring the reading frame to allow production of an internally shortened but functional dystrophin protein

RESULTS

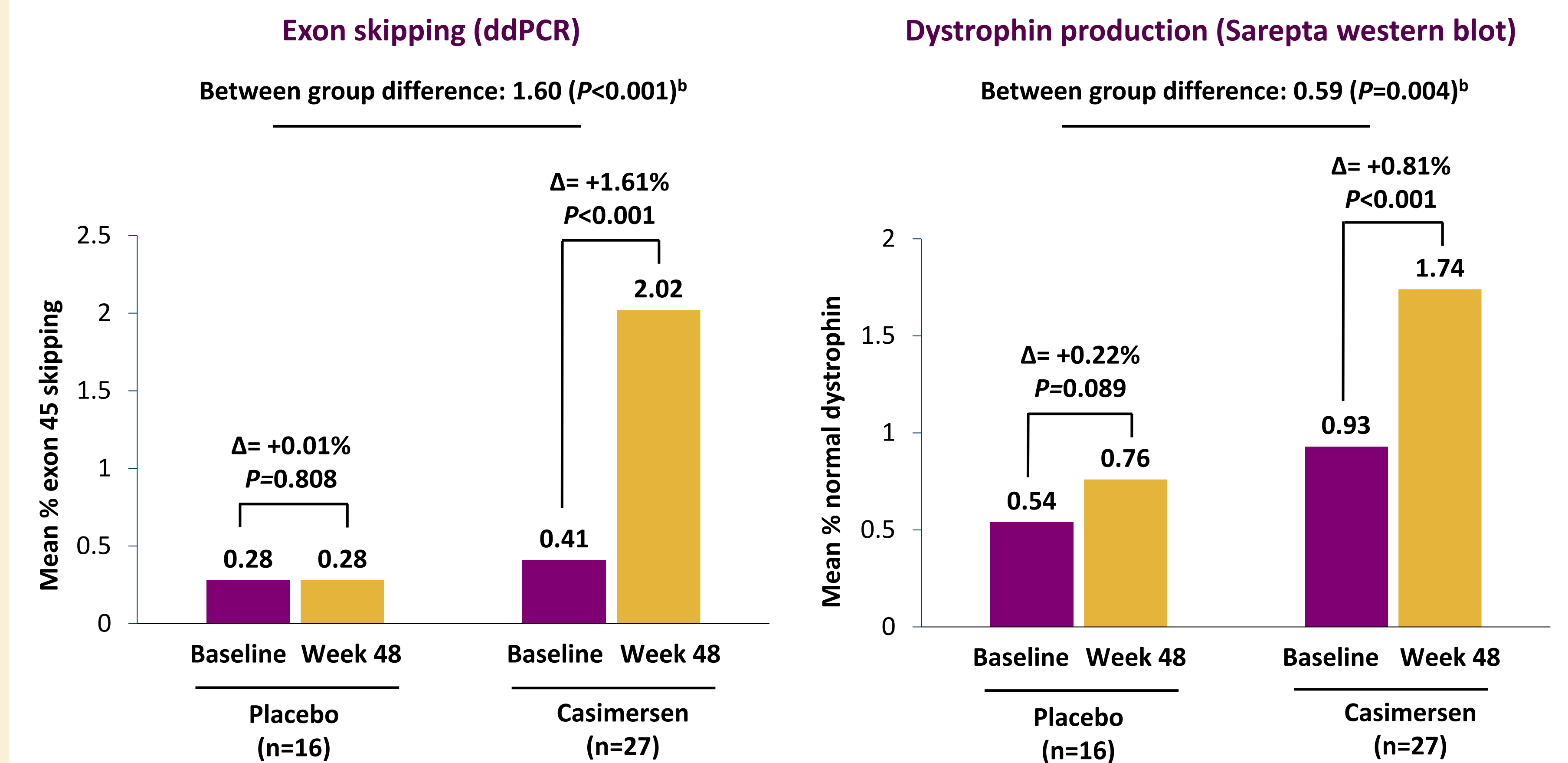
Interim analysis of 48-week muscle biopsy anonymized data from the first 43 exon 45 skip-amenable patients

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/m ²	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)

BMI=body mass index; DMD=Duchenne muscular dystrophy. NR=not reported to preserve blinding of individual patients. Values are mean (SD) unless otherwise noted. ^aInterim muscle biopsy set. ^bPlacebo n=15, casimersen n=26, total n=41. ^cPlacebo n=26, total n=42.

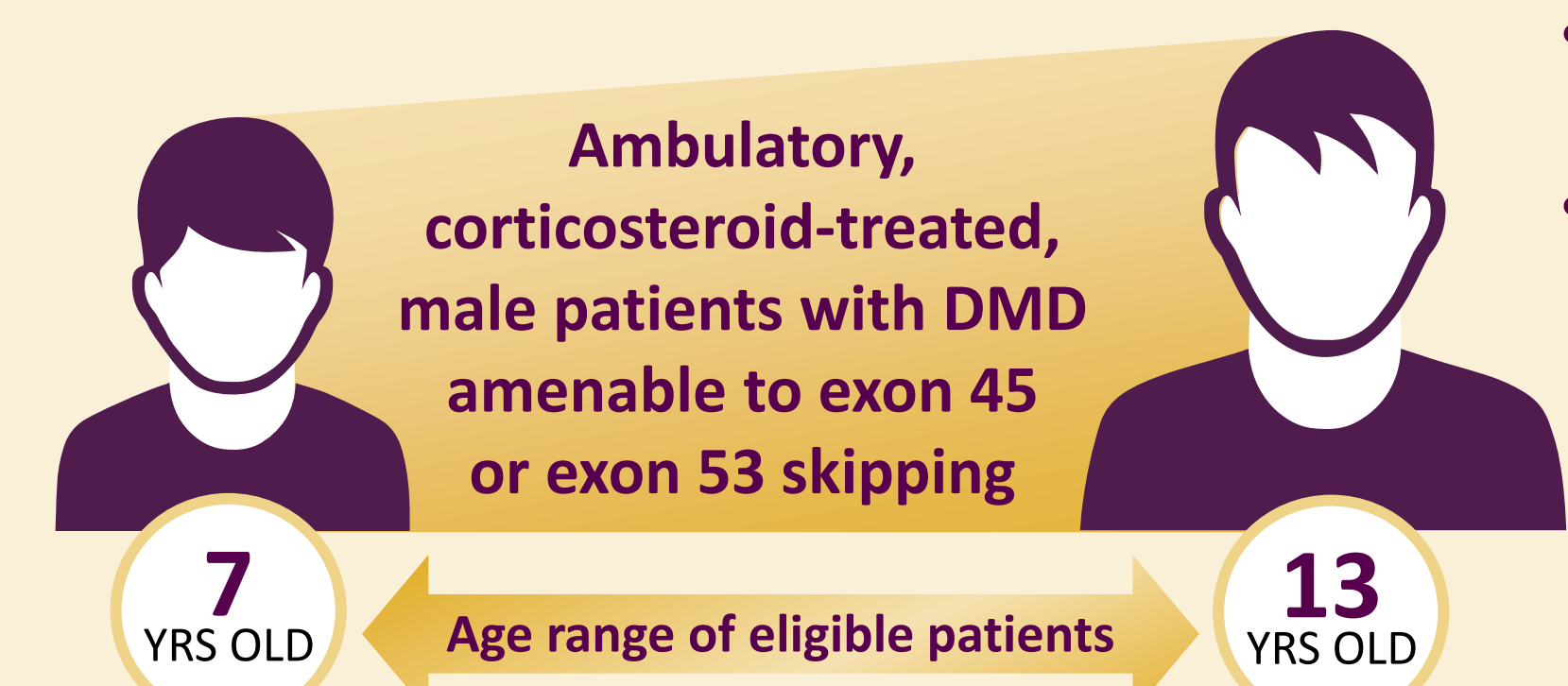
Casimersen increased exon skipping and dystrophin expression after 48 weeks^a



- 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)
 - 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 ($P<0.001$), with a significantly greater increase in dystrophin levels compared with placebo ($P=0.004$)
- Significant positive correlation between exon 45 skipping and dystrophin production (Spearman rank correlation, 0.627; $P<0.001$), demonstrating that de novo dystrophin production is mechanistically linked to exon 45 skipping
- Immunofluorescence results were consistent with correct localization of the restored dystrophin protein to the sarcolemma in casimersen-treated patients (data not shown)

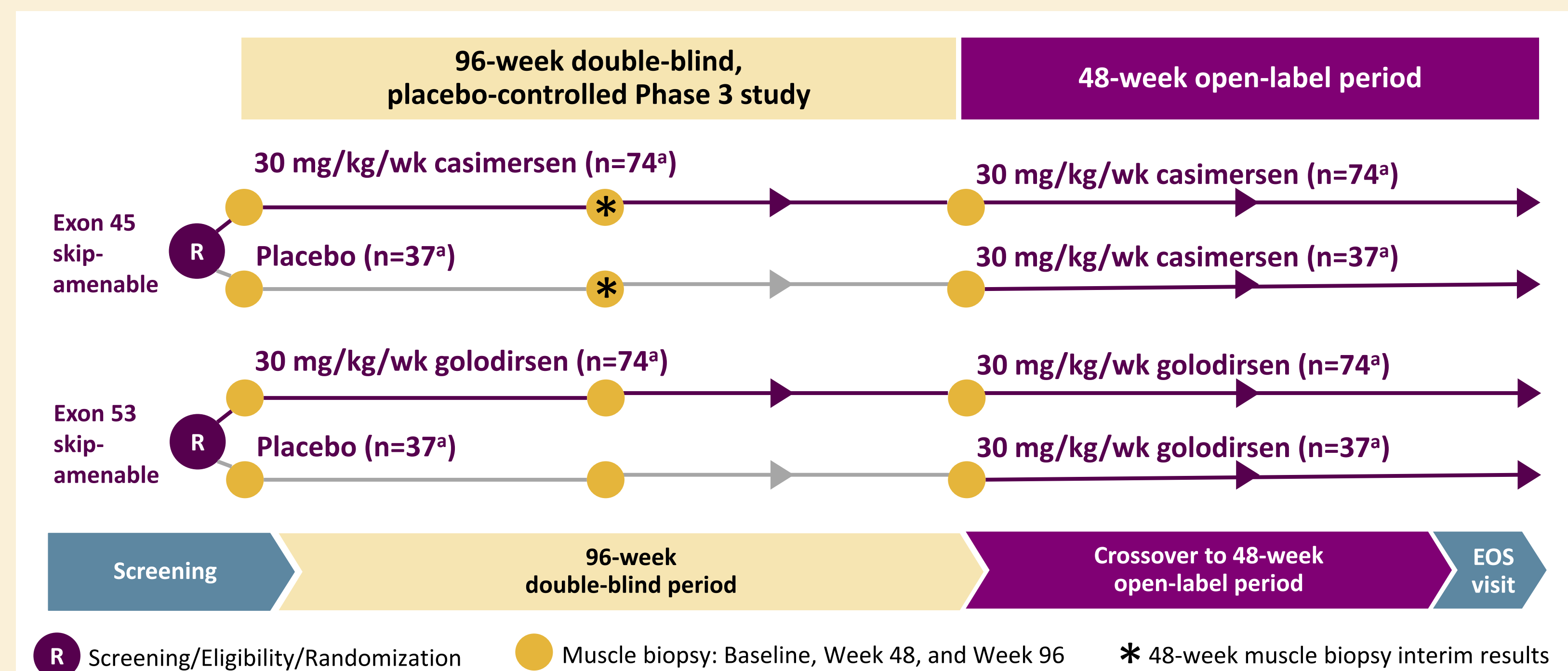
ddPCR=droplet digital polymerase chain reaction. ^aInterim muscle biopsy set. ^bDifference in the mean changes between treatment groups; P value calculated by two-sample permutation test.

STUDY DESIGN



- 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

Exon 45 skip-amenable patients are randomized 2:1 to receive casimersen 30 mg/kg or placebo intravenously once weekly



^an=number of patients planned to participate in the study. EOS=end of study.

- Primary endpoint**
- 6MWT change from baseline to Week 96
- Secondary endpoints**
- 6MWT change from baseline at Week 144
 - Dystrophin protein change from baseline at Weeks 48 and 96
 - Ambulation assessments^a at Weeks 96 and 144
 - FVC%p change from baseline to Weeks 96 and 144
- Additional endpoint**
- Exon skipping change from baseline at Weeks 48 and 96
- Safety endpoints**
- AEs, serious AEs, deaths, discontinuations due to AEs

^aAbility to rise independently from floor; time to loss of ambulation; change from baseline in North Star Ambulatory Assessment score

Safety

- No treatment-emergent AEs led to discontinuation of study drug
- AEs occurring in $\geq 20\%$ of casimersen-treated patients and reported $\geq 5\%$ more frequently in the casimersen group than in the placebo group are shown in the Table
 - Additional AEs ($\geq 10\%$ cutoff) reported $\geq 5\%$ more frequently with casimersen versus placebo were dizziness/light-headedness, ear infection, ear pain, nausea, and post-traumatic pain

AEs occurring in $\geq 20\%$ of casimersen-treated patients and 5% more frequently than placebo^a

Adverse event, 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)

^aAs of May 31, 2019; ^bSafety set; ^cIncludes upper respiratory infection, pharyngitis, nasopharyngitis, rhinitis.

REFERENCE

1. Aartsma-Rus A, et al. *Hum Mutat.* 2009;30:293-299.

ACKNOWLEDGMENTS & DISCLOSURES

The authors and Sarepta Therapeutics, Inc., thank the patients and their families. ESSENCE (NCT02500381) was funded by Sarepta Therapeutics, Inc. Editorial support was provided by Kristin M. Allan, PhD, of Eloquent Scientific Solutions, and was funded by Sarepta Therapeutics, Inc. **Disclosures:** SI received research support from Biogen, CureSMA, the US Department of Defense, Fibrogen, MDA, NIH, Novartis, PPMD, PTC Therapeutics, Revergen, Sarepta Therapeutics, Inc., and Scholar Rock, and serves on advisory boards for Biogen, Genentech/Roche, Novartis, Sarepta Therapeutics, Inc., and Scholar Rock. HP is a 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 branch. VS has received speaker honoraria from Sanofi Genzyme, is or has recently been on advisory boards for Audentes Therapeutics, AveXis, Biogen, Exonics Therapeutics/Vertex, Roche, Sarepta Therapeutics, Inc., and Wave Therapeutics, and has research collaborations with Sanofi Genzyme and Ultragenyx. FM has received consultancies from Sarepta Therapeutics, Inc., for advisory boards and symposia participation. EK, JM, BH, and ED are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. EM has served as a remunerated consultant for Sarepta Therapeutics, Inc.