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

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

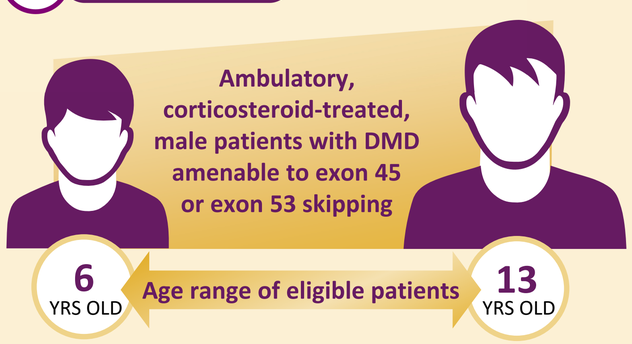
BACKGROUND

- Mutations leading to deletions flanking exon 45 account for 8% of all patients with Duchenne muscular dystrophy (DMD)[1]
- Casimersen is US Food and Drug Administration–approved for the treatment of DMD in patients 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 and dystrophin expression at 48 weeks relative to baseline and 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

STUDY DESIGN



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

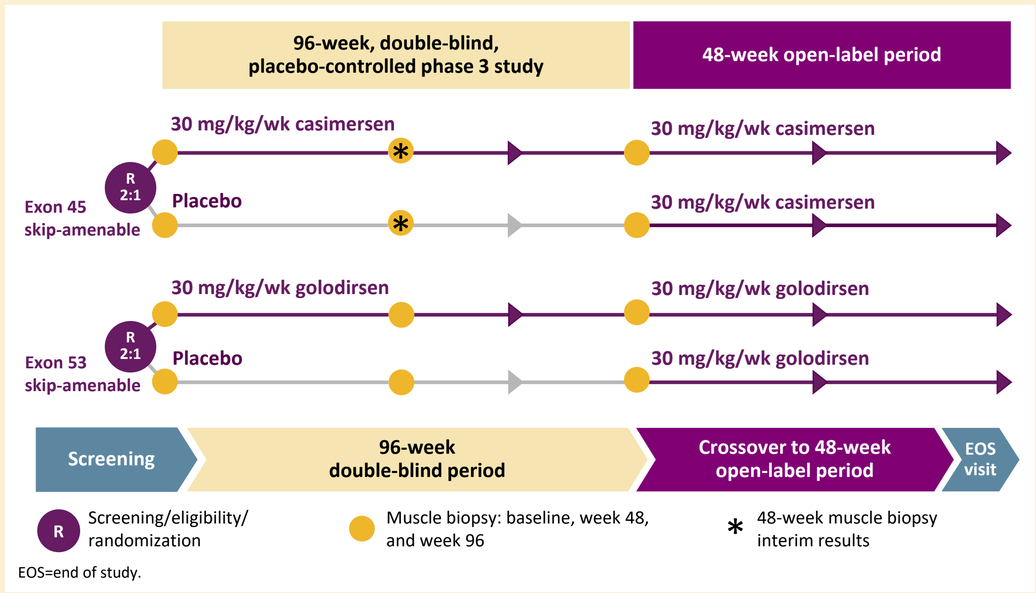
- 6MWT change from baseline at week 144
- Dystrophin protein change from baseline at weeks 48 and 96
- Ambulation assessments (ability to rise independently from floor; time to loss of ambulation; change from baseline in North Star Ambulatory Assessment score) at weeks 96 and 144
- FVC%p change from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

Additional endpoint

- Exon skipping change from baseline at weeks 48 and 96

Safety endpoints

- AEs, serious AEs, deaths, discontinuations due to AEs



EOS=end of study.

RESULTS

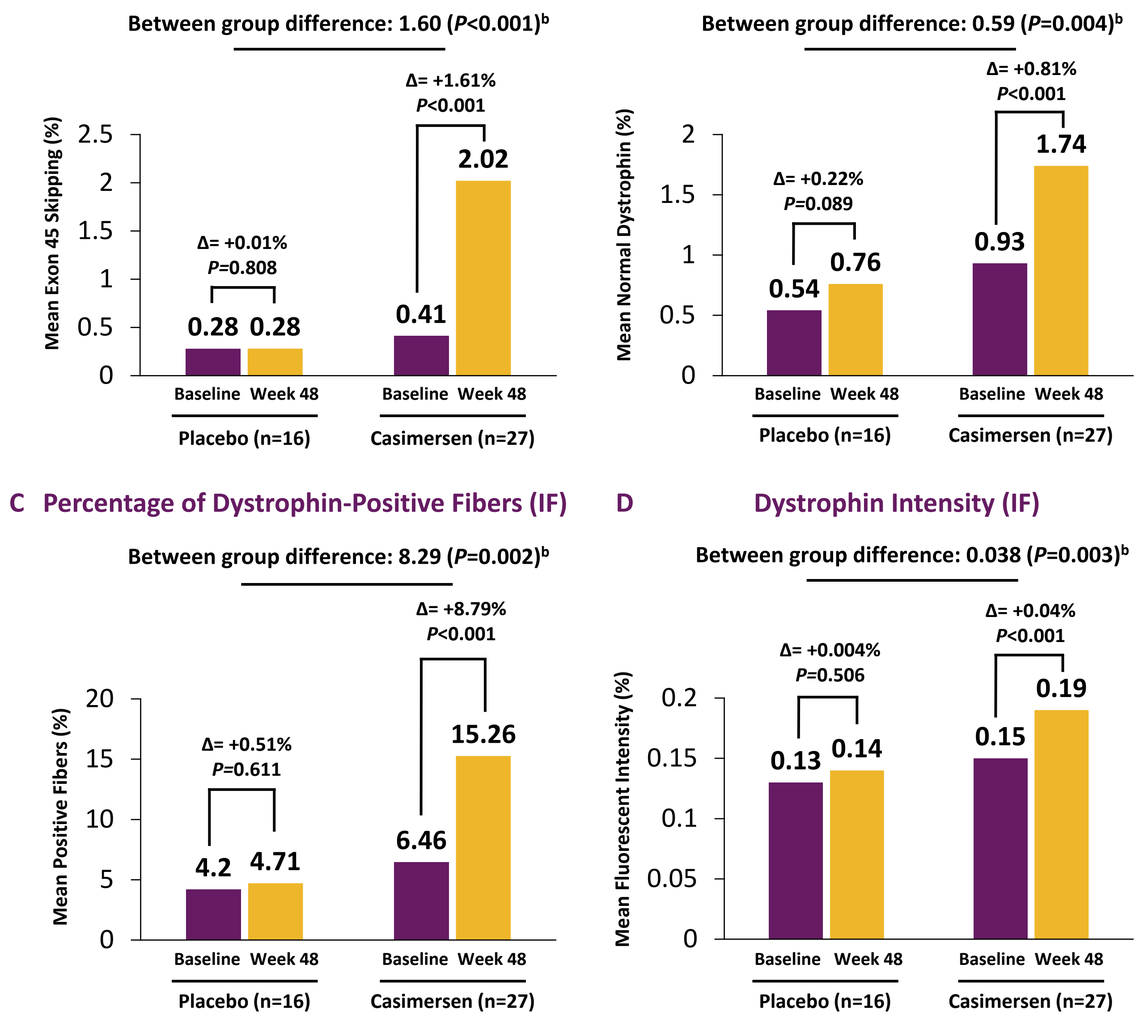
Interim analysis of 48-week muscle biopsy anonymized data from the first 43 patients with exon 45 skip-amenable mutations

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/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)

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.

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.

- 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 percent dystrophin-positive fibers significantly increased from baseline to week 48 (6.46% vs 15.26%; $P<0.001$; **Figure C**), and compared with placebo (mean difference=8.29%; $P=0.002$)
  - Mean fluorescence intensity was also significantly increased in the casimersen-treated patients compared with placebo-treated patients at week 48 ($P=0.003$; **Figure D**)

Safety

- No treatment-emergent AEs led to discontinuation of study drug
- 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% cutoff) reported ≥5% more frequently with casimersen vs placebo were dizziness/light-headedness, ear infection, ear pain, nausea, and posttraumatic pain

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, rhinitis. AE=adverse event.

REFERENCE

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

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