

Efficacy and Safety of Golodirsen and Casimersen Compared With Placebo in Duchenne Muscular Dystrophy (ESSENCE): Phase 3 Results and Post Hoc Analysis

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Background

- Golodirsen and casimersen are phosphorodiamidate morpholino oligomers (PMOs) used for the treatment of Duchenne muscular dystrophy (DMD) in patients with pathogenic variants amenable to exon 53 and 45 skipping, respectively^{1,2}
- Golodirsen and casimersen have demonstrated long-term tolerability and safety in treated clinical trial patients (up to 6 years) and in real-world patients since approvals in 2019 and 2021, respectively¹⁻⁵
- ESSENCE (NCT02500381) evaluated the efficacy and safety of golodirsen and casimersen compared with placebo (PBO) in a phase 3, double-blind, multicenter study with an open-label extension⁶
- To further contextualize the results from ESSENCE, an expanded set of post hoc analyses developed through a principled, hypothesis-driven approach was performed
- Here, heterogeneity challenges related to DMD progression, including the complexities of a study design with a combined treatment group with challenging recruitment, and the impact of COVID-19 on ESSENCE were 2 key factors evaluated in post hoc analyses

Methods

Study design

- This study consisted of a double-blind, PBO-controlled treatment period for weeks 1 to 96, followed by an open-label treatment period for up to 48 additional weeks (**Figure 1**)
- The primary endpoint was change from baseline (CFB) in 4-step ascend velocity (step/s) at week 96 vs PBO

Post hoc analyses

The following post hoc analyses were designed to address sources of variation affecting the ESSENCE primary analysis:

Time to event

- Time to event (TTE) measures the time from baseline to the first meaningful decline in 4-step ascend velocity (>0.3 steps/s)⁷
- TTE analysis is less influenced by variability in disease progression associated with DMD heterogeneity because patients who do not experience a meaningful decline during the study period do not have events and thus do not contribute noise to the estimated treatment effect
- Cox proportional hazards regression analysis of TTE was controlled for genotype, age group, and baseline 4-step ascend velocity

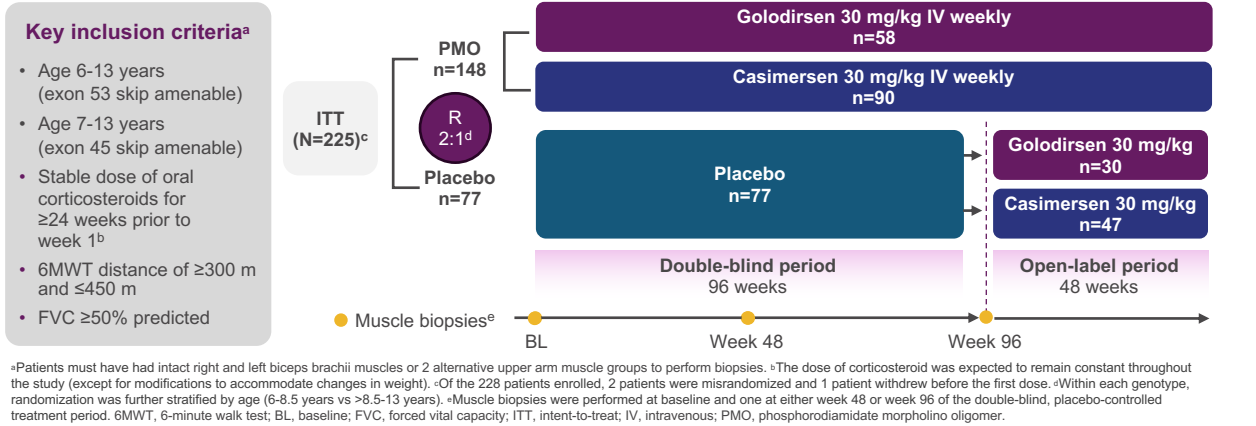
Predicted decline subgroup

- The intent-to-treat (ITT) population was stratified based on a recent independently published prognostic model that ranked patients using a composite prognostic score incorporating baseline characteristics (age, 4-step ascend velocity, rise from floor [RFF] velocity, 10-meter walk/run [10MWR] velocity, corticosteroid duration and type) to predict risk of future decline in 4-step ascend velocity⁸
 - The analysis stratified all patients based on whether they were expected to decline over the next year (baseline prognostic score <0.0)

COVID-19 impact period

- Patients whose baseline 4-step ascend velocity assessments occurred during the COVID-19 impact period (March 2020–July 2021)^{9,10} were excluded from the ITT population to assess the impact of bias in baseline assessments during this period; this population was termed the “refined ITT population”
 - Here, July 2021 was considered the end of the COVID-19 impact period based on external evidence that the COVID-19 vaccination rates peaked in the middle of 2021, followed by a progressive resumption of normal daily activities^{9,10}
- To minimize the potential variability related to COVID-19 operational disruptions, an analysis of covariance model was conducted with treatment, genotype, treatment-by-genotype interaction, and baseline age as continuous covariates

Figure 1 Study Design



*Patients must have had intact right and left biceps brachii muscles or 2 alternative upper arm muscle groups to perform biopsies. *The dose of corticosteroid was expected to remain constant throughout the study (except for modifications to accommodate changes in weight). *Of the 228 patients enrolled, 2 patients were misrandomized and 1 patient withdrew before the first dose. *Within each genotype, randomization was further stratified by age (6-8.5 years vs ≥8.5-13 years). *Muscle biopsies were performed at baseline and one at either week 48 or week 96 of the double-blind, placebo-controlled treatment period. 6MWT, 6-minute walk test; BL, baseline; FVC, forced vital capacity; ITT, intent-to-treat; IV, intravenous; PMO, phosphorodiamidate morpholino oligomer.

Results

Patients

- Of the 228 patients enrolled from 2016 to 2022, including through the COVID-19 pandemic and across 24 countries, 225 were included in the ITT population (**Figure 1**)
- Baseline characteristics and functional assessments are included in the Supplement (**Supplemental Table 1; available via QR code**)

Primary analysis and safety

- The primary endpoint, CFB at week 96 in 4-step ascend velocity, showed a numerical mean (standard deviation [SD]) change of −0.27 (0.39) steps/s in the PMO group (n=138) vs PBO (n=74; −0.34 [0.37]), with a least squares mean (LSM) difference of 0.06 (95% confidence interval [CI], −0.05 to 0.16; P=0.309)
- Most treatment-emergent adverse events (TEAEs) were mild or moderate and resolved without treatment through 96 weeks; there were no treatment-related TEAEs leading to discontinuation, and no new safety signals were reported through 144 weeks⁵
- The ESSENCE study has been reported in full previously⁶; the results reported here focus on the post hoc analyses

Time to event

- Patients in the PMO group had an ~31% reduction in the hazard of time to first decline of 4-step ascend velocity >0.3 steps/s compared with PBO (hazard ratio [95% CI], 0.685 [0.483-0.972]; P=0.0339) (**Figure 2**)
 - Over 96 weeks, including the COVID-19 impact period, patients in the PMO group experienced an approximately 23-week (>5-month) delay in the median time to first meaningful decline compared with PBO

Predicted decline subgroup

- Among all patients expected to decline over the next year (prognostic score <0.0), treatment with PMO significantly reduced the decline in 4-step ascend velocity at week 96 by 0.153 steps/s (95% CI, 0.018-0.288; P=0.026) (**Table 1; Figure 3**)
- Among patients not expected to decline over the next year (prognostic score ≥0.00; ceiling effect), the mean trajectories remained relatively stable over the first year with limited mean decline by week 96 (**Figure 3**); slower decline in 4-step ascend velocity limits sensitivity to detect treatment-related differences over the short study duration

Table 1 Baseline Characteristics and Functional Assessments in the Predicted Decline Subgroup Analysis With a Prognostic Score <0.0

Parameter	Predicted decline subgroup with a prognostic score <0.0		
	PMO n=87	PBO n=42	Overall N=129
Age, years			
Mean (SD)	10.2 (2.1)	10.1 (2.0)	10.2 (2.0)
Min, max ^a	6.7, 14.0	6.6, 14.0	6.6, 14.0
6-8.5 years, n (%)	24 (27.6)	10 (23.8)	34 (26.4)
>8.5-13 years, n (%)	63 (72.4)	32 (76.2)	95 (73.6)
Genotype			
Exon-45 skippable, n (%)	56 (64.4)	23 (54.8)	79 (61.2)
Exon-53 skippable, n (%)	31 (35.6)	19 (45.2)	50 (38.8)
Race			
White, n (%)	78 (89.7)	36 (85.7)	114 (88.4)
Ethnicity			
Not Hispanic or Latino, n (%)	76 (87.4)	36 (85.7)	112 (86.8)
Height, cm			
Mean (SD)	126.6 (8.2)	126.0 (8.7)	126.4 (8.4)
Min, max	107.6, 146.0	111.0, 149.5	107.6, 149.5
Weight, kg			
Mean (SD)	32.1 (9.0)	32.0 (9.2)	32.1 (9.0)
Min, max	19.5, 62.1	19.0, 53.1	19.0, 62.1
BMI, kg/m ²			
Mean (SD)	18.6 (3.8) ^b	19.0 (4.3)	18.7 (3.9) ^c
Min, max	11.6, 29.8	12.6, 28.3	11.6, 29.8
Time since DMD diagnosis, months			
Mean (SD)	74.9 (34.6)	69.9 (32.5)	73.3 (33.8)
Min, max	2.2, 154.6	8.9, 141.8	2.2, 154.6
Duration of prior corticosteroid use, months			
Mean (SD)	54.7 (28.4)	46.5 (23.8)	52.0 (27.2)
Min, max	6.9, 127.1	8.9, 103.8	6.9, 127.1
4-step ascend velocity, steps/s			
Mean (SD)	1.09 (0.64) ^b	1.14 (0.62) ^d	1.11 (0.63) ^e
Min, max	0.00, 2.86	0.00, 2.86	0.00, 2.86
10MWR velocity, m/s			
Mean (SD)	1.79 (0.50) ^b	1.74 (0.48)	1.77 (0.49) ^c
Min, max	0.90, 3.08	0.98, 3.28	0.90, 3.28
6MWT distance, m			
Mean (SD)	379.26 (40.81)	378.18 (44.54)	378.91 (41.89)
Min, max	300.50, 450.50	301.50, 449.50	300.50, 450.50
RFF velocity, rise/s			
Mean (SD)	0.15 (0.10) ^f	0.16 (0.10) ^d	0.15 (0.10) ^g
Min, max	0.00, 0.42	0.00, 0.39	0.00, 0.42
NSAA total score			
Mean (SD)	21.64 (6.88)	21.56 (6.26)	21.62 (6.66)
Min, max	7.50, 34.00	9.00, 32.00	7.50, 34.00
Baseline prognostic score			
Mean (SD)	−0.25 (0.15) ^h	−0.26 (0.16) ⁱ	−0.26 (0.15) ^j
Min, max	−0.75, −0.05	−0.65, −0.07	−0.75, −0.05

^aSome patients were 13 years old at the time of screening. ^bn=86. ^cn=128. ^dn=41. ^en=127. ^fn=84. ^gn=125. ^hn=82. ⁱn=40. ^jn=122. 6MWT, 6-minute walk test; 10MWR, 10-meter walk/run; BMI, body mass index; DMD, Duchenne muscular dystrophy; max, maximum; min, minimum; NSAA, North Star Ambulatory Assessment; PBO, placebo; PMO, phosphorodiamidate morpholino oligomer; RFF, rise from floor; SD, standard deviation.

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Figure 2 Time to First Meaningful Decline (>0.3 Steps/s) in 4-Step Ascend Velocity Through Week 96

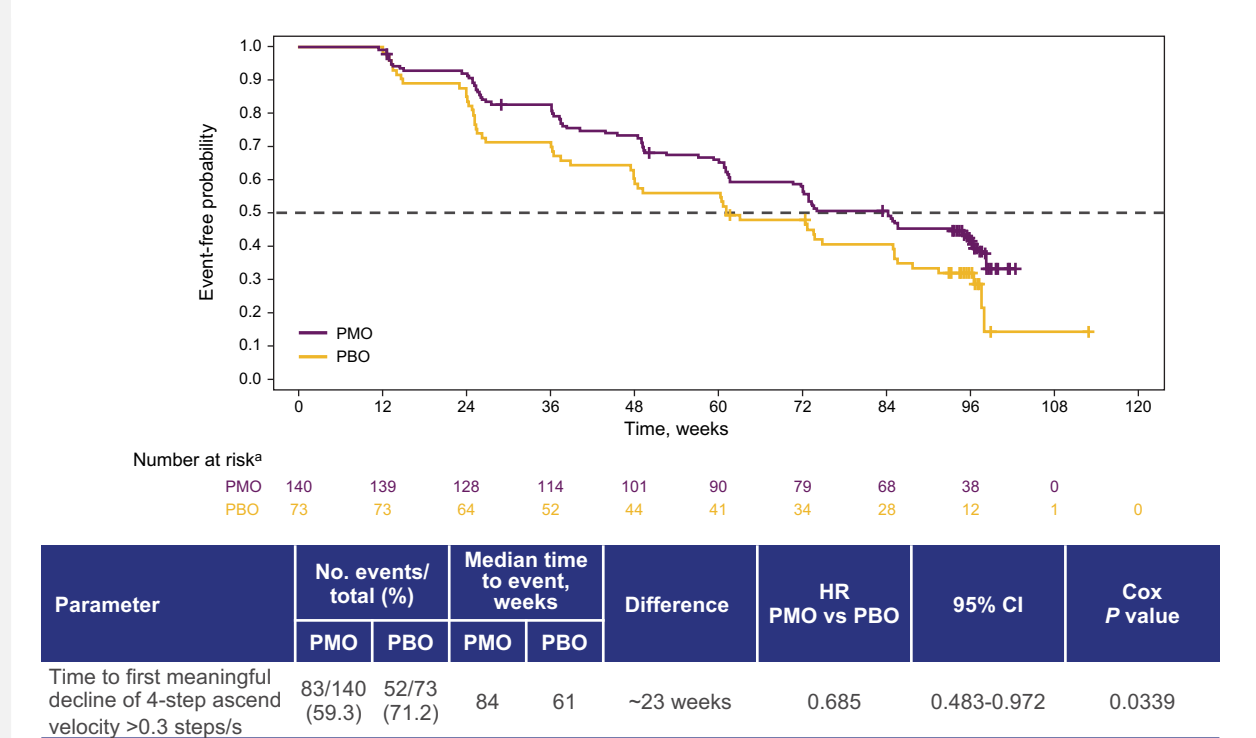
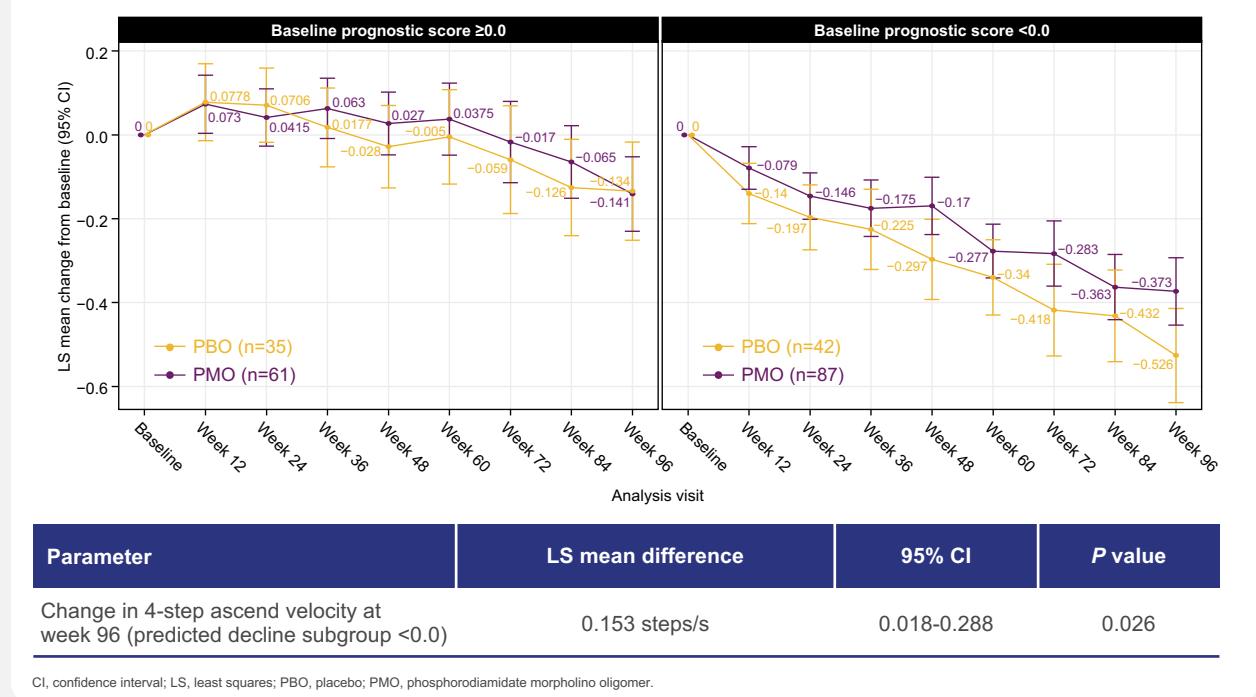


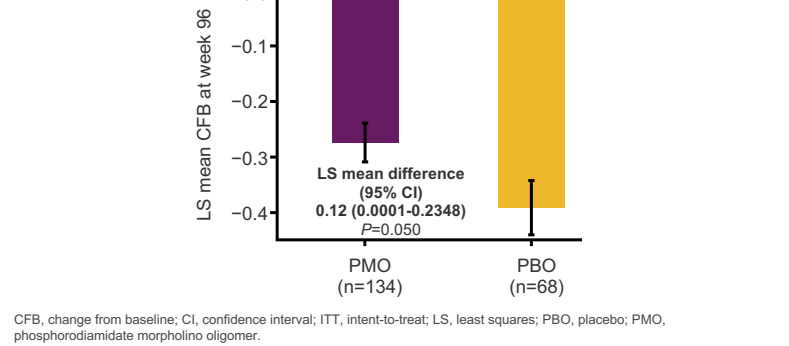
Figure 3 Changes From Baseline in 4-Step Ascend Velocity Stratified by Baseline Prognostic Score (Expected 1-Year Change ≥0 vs <0)



Post hoc analysis: Refined ITT to assess the effect of treatment in a population without COVID-19-related disruptions at baseline

- A total of 23 patients (~10% of the ITT population) had baseline 4-step ascend velocity assessments during the COVID-19 impact period
- In the ITT set excluding the 23 COVID-19-impacted patients (refined ITT population), the LS mean difference (95% CI) CFB of 4-step ascend velocity at week 96 was 0.12 steps/s (0.0001-0.2348; P=0.050) (**Figure 4**)

Figure 4 4-Step Ascend Velocity at Week 96 in the Refined ITT Population



Conclusions

- The primary endpoint was not met in ESSENCE
- Hypothesis-driven post hoc analyses indicate that heterogeneity related to DMD progression and the COVID-19 impact reduced the sensitivity of the ESSENCE primary analysis
- Across 3 complementary post hoc analyses designed to overcome these factors—time to event, predicted decline subgroup, COVID-19 impact period—the PMO group showed a consistent reduction in 4-step ascend decline at week 96 vs PBO
- In the TTE analysis, patients in the PMO group experienced a delay of more than 5 months in the median time to first decline in 4-step ascend velocity, which could translate into a longer-term benefit beyond the study follow-up period
- Among participants predicted to decline based on a published prognostic score, treatment with PMO reduced the decline in 4-step ascend velocity at week 96; highlighting that assessment of functional outcomes in patients with DMD expected to decline may improve power to detect treatment effects on that outcome over the study period
- Excluding participants whose baseline assessments were impacted by the COVID-19 pandemic strengthened the observed treatment effect
- Collectively, these post hoc analyses of ESSENCE contribute to the evolving totality of evidence regarding golodirsen and casimersen

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