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Pulmonary Function in Advanced-Stage Patients With Duchenne Muscular Dystrophy Treated With Casimersen

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Background

- Progressive pulmonary function decline in patients with Duchenne muscular dystrophy (DMD) is a major cause of early mortality, accounting for ~40% of primary causes of death[1,2]
- Post hoc clinical trial analyses have demonstrated that eteplirsen and golodirsen may significantly attenuate pulmonary decline as measured by percent predicted forced vital capacity (FVC%p) compared with matched external controls (ECs)[3-8]
  - The annual rate of FVC%p decline was found to be 3.5% vs 6.0% (*P*=0.0001) for eteplirsen-treated and mutation-matched ECs,[5] and 2.9% vs 6.7% (*P*<0.01) for golodirsen-treated and mutation-matched EC patients[8]
- The treatment effect of casimersen on respiratory function has not been previously evaluated

Objective

- To evaluate pulmonary outcomes (FVC%p) of patients with advanced DMD following treatment with casimersen in clinical trials compared with matched ECs treated with glucocorticosteroids (GCs)

Methods

Patient population

- Patients aged 10-25 years with DMD and exon 45 skip-amenable mutations were included. Additional inclusion criteria included the following
  - ≥2 visits with FVC%p reported ≥6 months apart from the index visit
  - During the study period, treated with one of the following
    - Casimersen as part of clinical trials (casimersen cohort)
    - GCs as part of the natural history studies or clinical trial placebo arms, with no evidence of casimersen treatment at any available visit (EC cohort)
- Index was defined as the first observed FVC%p assessment within the specified age range
- Two age groups were assessed: 10-18 years (main cohort) and 10-25 years (extended cohort)
- Patients in the casimersen cohort included eligible patients from the 4045-101 (NCT02530905) randomized, placebo-controlled phase 1 casimersen study[9] and a subset of the 4045-302 (NCT03532542) open-label extension study of casimersen or golodirsen[10]
- Patients in the EC cohort included eligible patients from the CINRG-DNHS (NCT00468832)[11] and the PRO-DMD-01 (NCT01753804) natural history studies,[12] the untreated control of the PROMOVI (NCT02255552) eteplirsen study,[13] and the 4045-302 (NCT03532542) study of casimersen or golodirsen[10]

Outcomes

- The primary outcome was the annual rate of FVC%p decline
- The secondary outcome was time to meaningful clinical respiratory milestones (FVC%p declining to or below 60%, 50%, and 30%)[15]
  - FVC%p ≤60% is the recommended threshold for initiating cough assist device[16]
  - FVC%p ≤50% is the recommended threshold for initiating nighttime non-invasive ventilation[16]

Statistical methods and models

- Genotype matching, propensity score matching, and average treatment effect on the treated weighting were conducted to account for differences in baseline characteristics (**Figure 1**)

Figure 1 *Two-Stage Matching-Weighting Approach Allowed All PMO-Treated Patients and ECs to Be Used[14]*

Match patients by genotype	Estimate PS	Identify new index for EC	Re-estimate PS	Apply weights to all patients
Exact matching by genotype was conducted for the casimersen cohort	PS were estimated among index visits of casimersen-treated patients and all candidate visits of ECs satisfying the inclusion criteria, following the approach of the main analysis	For ECs, the earliest visit with highest propensity score was selected as new index visit	PS were re-estimated among index visits for casimersen-treated patients and new index visits for ECs, following the same approach of the main analysis	IPTW was used to calculate the ATT weights based on new PS; patients treated with PMO had a weight of 1 and ECs had a weight of PS/(1 – PS)

ATT, average treatment effect on the treated; EC, external control; IPTW, inverse probability of treatment weighting; PMO, phosphorodiamidate morpholino oligomer; PS, propensity scores.

- The annual rate of FVC%p change was assessed using linear mixed-effects models (LMEM) and adjusted for steroid type, steroid duration, and non-ambulatory status at index
  - The predicted average annual rate of FVC%p decline and the times to FVC%p declining to or below 60% and 50% were based on a linear extrapolation of the model-estimated FVC%p decline from the average observed FVC%p readings
- Time to clinical respiratory milestones was assessed using Kaplan-Meier (KM) curves and Cox proportional hazards models for patients who had not yet met these milestones

Results

Patient selection

- A total of 11 casimersen-treated and 52 EC patients were matched and weighted for inclusion in the main cohort (**Figure 2**)

Figure 2 *Patient Selection*

	Casimersen	EC
Patients with DMD from eligible clinical trials	152	814
With ≥2 FVC%p assessments at ages ≥10 and ≤18 years in at least 6 months apart during the study period (first such visit was defined as index)	99	382
Amenable to exon-45 skipping	11	52[a]
After propensity score matching	11	11
After 2 stage matching-weighting	11	52

The flow chart for patients aged 10-25 (extended cohort) is similar (N=12 for casimersen patients and N=58[b] for EC patients).
[a]Of the 52 patients, 2 were from PROMOVI, 1 was from 4045-302, 23 were from CINRG-DNHS, and 26 were from PRO-DMD-01. [b]Of the 58 patients, 2 were from PROMOVI, 1 was from 4045-302, 27 were from CINRG-DNHS, and 28 were from PRO-DMD-01.
DMD, Duchenne muscular dystrophy; EC, external control; FVC%p, percent predicted forced vital capacity.

Patient characteristics

- At baseline, patients treated with casimersen were well balanced with EC for age and FVC%p (**Table 1**)

Table 1 *Patient Baseline Characteristics After Two-Stage Matching-Weighting and Duration of Follow-Up*

	Casimersen N=11 [A]	EC N=52 [B]	Mean difference [B] – [A]	SMD	*P* value	Casimersen N=12 [A]	EC N=58 [B]	Mean difference [B] – [A]	SMD	*P* value
	Age 10-18 years at index					Age 10-25 years at index				
Age, years[a]										
Mean ± SD	13.5 ± 2.3	13.5 ± 2.0				14.1 ± 2.9	14.1 ± 3.7			
Min, max[b]	10.1, 16.2	10.1, 16.8				10.1, 20.3	10.1, 23.4			
Median	14.1	13.5	–0.1 ± 0.7	0.028	0.933	14.1	13.3	0.0 ± 1.0	0.006	0.985
FVC%p[a]										
Mean ± SD	84.5 ± 17.1	84.8 ± 27.5				81.7 ± 19.0	81.9 ± 32.4			
Min, max	58.4, 117.8	15.0, 134.0				50.4, 117.8	7.0, 134.0			
Median	88.5	87.0	0.3 ± 6.4	0.013	0.963	86.4	88.0	0.2 ± 6.9	0.009	0.974
Non-ambulatory	72.7%	36.7%				75.0%	38.6%			
Missing, %	0.0%	17.6%	–36.0%	1.045	<0.05[c]	0.0%	16.3%	–36.4%	1.037	<0.05[c]
Duration of follow-up, years[a]										
Mean ± SD	3.4 ± 1.4	1.5 ± 1.2				4.9 ± 1.0	2.0 ± 1.9			
Min, max	1.4, 5.5	0.5, 7.5				2.3, 5.6	0.5, 8.5			
Median	3.7	1.0	–1.9 ± 0.5	1.459	<0.001[c]	5.2	1.2	–2.8 ± 0.4	1.869	<0.001[c]

t-tests were used to compare continuous variables, and chi-squared tests were used for categorical variables. Logistic models used to estimate propensity scores failed to converge due to quasi-separation when non-ambulatory status or steroid treatment variables were included as covariates. SMD >0.1 indicates meaningful imbalance between casimersen and EC cohorts.[14]
[a]There was no missing data. [b]The age range of the EC cohort was allowed to fall outside the range of the casimersen cohort as long as an acceptable balance as indicated by the SMD was achieved. [c]Statistically significant.
EC, external control; FVC%p, percent predicted forced vital capacity; SD, standard deviation; SMD, standardized mean difference.

Attenuation of FVC%p decline

- For patients aged 10-18 years, the rate of FVC%p decline was –5.54 (95% CI, –6.58 to –4.5) in the casimersen cohort and –8.17 (95% CI, –10.03 to –6.30; *P*<0.001) in the EC cohort (**Table 2**)
- For patients aged 10-25 years, the rate of FVC%p decline was –5.69 (95% CI, –6.35 to –5.02) in the casimersen cohort and –6.93 (95% CI, –8.07 to –5.78; *P*<0.001) in the EC cohort (**Table 2**)
- The overall annual rate of FVC%p decline was attenuated in casimersen-treated patients compared with ECs as indicated by the difference between the annual decline rate of the cohorts (**Table 2**)
  - For patients aged 10-18 years, the attenuation was 2.63 percentage points (95% CI, 0.75 to 4.52; *P*<0.01)
  - For patients aged 10-25 years, the attenuation was 1.24 percentage points (95% CI, 0.12 to 2.36; *P*<0.05)

Table 2 *Annual Decline of FVC%p (LMEM)*

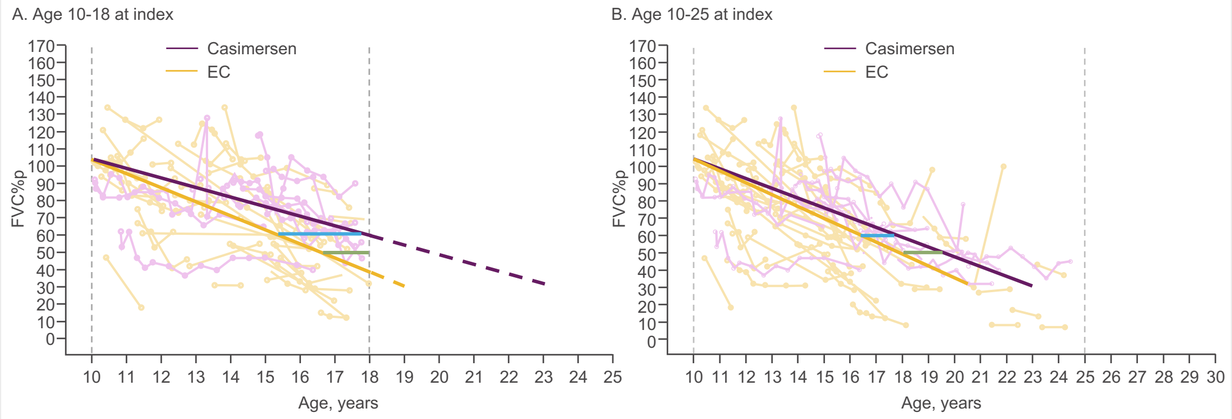
	Age 10-18 at index	Age 10-25 at index
Annual rate of FVC%p decline in casimersen cohort,[a] FVC%p (95% CI)	–5.54 (–6.58 to –4.5)	–5.69 (–6.35 to –5.02)
Annual rate of FVC%p decline in EC cohort,[a] FVC%p (95% CI)	–8.17 (–10.03 to –6.30)***	–6.93 (–8.07 to –5.78)***
Attenuation of FVC%p decline by casimersen cohort,[a] FVC%p (95% CI)	2.63 (0.75 to 4.52)**	1.24 (0.12 to 2.36)*

[a]Measured in percentage points per year.
*P<0.05; **P<0.01; ***P<0.001.
CI, confidence interval; EC, external control; FVC%p, predicted percentage forced vital capacity; LMEM, linear mixed effects model.

Projected time to FVC%p ≤60% and ≤50%

- Before the age of 18, casimersen delayed the projected time to FVC%p declining to or below 60% by 2.6 years and 50% by 1.4 years (**Figure 3A**)
- Before the age of 25, casimersen delayed the projected time to FVC%p declining to or below 60% by 1.4 years and 50% by 1.7 years (**Figure 3B**)
- Most patients in both arms did not experience FVC%p decline to or below 50% during follow-up (**Figure 3**)

Figure 3 *FVC%p Linear Trajectory*



The recommended thresholds for initiating cough assist device and nighttime non-invasive ventilation are FVC%p ≤60% and FVC%p ≤50%, respectively.[16]
The light blue line represents the delay in projected time to FVC%p declining to or below 60% by casimersen (2.6 years for patients aged 10-18 and 1.4 years for patients aged 10-25). The green line represents the delay in projected time to FVC%p declining to or below 50% by casimersen (1.4 years for patients aged 10-18 and 1.7 years for patients aged 10-25).
EC, external control; FVC%p, percent predicted forced vital capacity.

Secondary outcomes

- Due to limited sample size and follow-up, median time to respiratory milestones (FVC%p declining to or below 60%, 50%, and 30%) could not be reliably estimated with KM curves. For patients aged 10-25 years, the weighted:
  - Cumulative number of events in the casimersen and EC groups were 5 and 4.19, respectively, for FVC%p ≤60%, and 6 and 2.92, respectively, for FVC%p ≤50%. No patients in the casimersen cohort declined to FVC%p of ≤30%
  - Median time to event in the casimersen and EC groups was 2.93 years and 1.68 years (*P*=0.037), respectively, for FVC%p ≤60%, and 3.12 years and 3.35 years (*P*=0.46), respectively, for FVC%p ≤50%
- In addition, the KM curves crossed for most of these milestones, suggesting a violation of the proportional hazards assumption and precluding reliable interpretation of Cox regression models

Conclusions

- This retrospective analysis of clinical trial data for casimersen-treated and mutation-matched EC patients with advanced DMD used a two-stage matching and weighting approach to identify a suitable EC cohort of natural history patients as a robust comparator
- Casimersen was associated with a significant attenuation in the rate of decline in FVC%p
- Casimersen showed a potentially clinically meaningful benefit for predicted time to use of cough assist device, though the sample size and follow-up were limited in the KM analysis
- The results presented in this study are consistent with previous eteplirsen and golodirsen respiratory analyses.[3-8] Notably, unlike the eteplirsen and golodirsen studies, most patients in this study were non-ambulatory

Limitations

- This study had several limitations due to the small sample size and statistical modeling assumptions, including:
  - Potential confounding effects of baseline ambulation status on rates of pulmonary decline
  - The main model not taking into account the cumulative effects of treatment
  - Assuming a linear decline of pulmonary function with age for patients 10 to 18 years when pulmonary function in this age range has been shown to be dynamic, with an initial rise followed by subsequent plateau and decline[17]
  - Only assessing FVC%p (a snapshot measurement at discrete timepoints) as a pulmonary outcome while other measures may better capture the dynamic, non-linear changes in pulmonary function[17]

Clinically meaningful attenuation of pulmonary decline was demonstrated in patients with advanced DMD treated with casimersen compared with matched ECs among a mostly non-ambulatory cohort aged ≥10 years, consistent with previous findings for eteplirsen and golodirsen

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