

QTc Assessment of Golodirsen and Casimersen in Duchenne Muscular Dystrophy

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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}
- In previous clinical trials, golodirsen and casimersen demonstrated long-term tolerability and safety in treated patients (up to 6 years); recorded treatment-emergent adverse events (TEAEs) were mostly mild in nature and unrelated to treatment; no TEAEs led to discontinuations and no severe TEAEs or severe AEs were deemed treatment related¹⁻⁴
- ESSENCE (NCT02500381), a phase 3, double-blind, multicenter study with an open-label extension, evaluated the efficacy and safety of golodirsen and casimersen compared with placebo⁵
- No new safety signals were observed in ESSENCE; golodirsen and casimersen were well tolerated over 144 weeks,⁵ consistent with previous clinical and real-world experience^{3,4,6}
- Although no clinically meaningful cardiac safety signals have been observed in patients receiving golodirsen and casimersen,^{1-3,5} it is important to assess any possible effect of these compounds on QT prolongation risk in patients with DMD
- Here, QD prolongation risk was assessed in patients with DMD receiving golodirsen or casimersen who participated in the ESSENCE trial

Methods

Study design

- ESSENCE consisted of a double-blind, placebo-controlled treatment period for weeks 1 to 96, followed by an open-label treatment period for up to 48 additional weeks (**Figure 1**)

Pharmacokinetic sampling collection

- Pharmacokinetic (PK) sampling for golodirsen/casimersen was collected before dosing, immediately prior to the end of the infusion, and 1 to 3 hours following the end of the infusion during the
 - Double-blind period at weeks 1 and 96
 - Open-label period at weeks 1 and 48
- PK data were collected only at designated clinical sites

Results

Baseline demographic and clinical characteristics

- Baseline demographic and clinical characteristics were generally comparable across treatment groups within both the double-blind and open-label populations (**Table 1**)
- The study population was predominantly White and non-Hispanic/Latino, with limited representation from other racial and ethnic subgroups

Table 1 Baseline Characteristics

Parameter	Double-blind population			Open-label population	
	Golodirsen n=21	Casimersen n=31	Placebo n=28	Golodirsen n=30	Casimersen n=36
Age, years					
Mean (SD)	8.0 (1.4)	9.1 (2.2)	8.8 (1.9)	8.2 (1.7)	9.2 (2.2)
Min, max	6.0, 12.0	6.0, 13.0	6.0, 12.0	6.0, 12.0	6.0, 13.0
Race, n (%)					
White	17 (81.0)	27 (87.1)	21 (75.0)	23 (76.7)	29 (80.6)
Asian	0	3 (9.7)	1 (3.6)	1 (3.3)	3 (8.3)
American Indian or Alaska Native	2 (9.5)	0	0	2 (6.7)	0
Other	2 (9.5)	1 (3.2)	6 (21.4)	4 (13.3)	4 (11.1)
Weight, kg					
Mean (SD)	27.4 (5.5)	30.4 (9.2)	30.6 (8.0)	28.0 (7.3)	31.9 (8.8)
Min, max	17.9, 42.3	18.1, 56.7	16.8, 47.4	16.8, 47.4	18.1, 56.7
BMI, kg/m ²					
Mean (SD)	18.4 (2.7)	18.6 (4.3)	18.8 (3.3)	18.2 (2.9)	19.0 (4.2)
Min, max	14.2, 23.7	11.6, 32.2	14.5, 25.3	14.2, 25.1	11.6, 32.2
Baseline QTcF (msec)					
Mean (SD)	381.4 (15.2)	383.5 (17.4)	377.2 (16.2)	382.8 (13.2)	382.8 (15.4)
Median	378.0	387.0	377.5	383.0	385.5
Min, max	356.7, 408.0	344.0, 431.0	349.0, 411.0	356.7, 408.0	347.0, 420.3

BMI, body mass index; max, maximum; min, minimum; QTcF, QT interval corrected for hear rate according to the Fridericia formula; SD, standard deviation.

Categorical analysis

- None of the patients administered golodirsen or casimersen in either period had QTcF intervals >450 msec (**Table 2**)
- ΔQTcF values were generally within accepted thresholds (<30 msec or <60 msec), with few non-recurrent occurrences above these thresholds observed across all groups (**Table 2**)
- Only 1 patient with a ΔQTcF interval >60 msec was observed following administration of casimersen during the double-blind period on week 1 at the end of the infusion (**Table 2**); however, this event did not reoccur within the patient, and ΔQTcF values were <35 msec at all other visits
 - Importantly, the individual QTcF measurement associated with this event was <450 msec
- Although individual instances of ΔQTcF >30 msec (golodirsen, casimersen, and placebo) and >60 msec were observed (casimersen), these events were generally sporadic, non-recurrent within patients, and not consistently aligned with peak drug exposure
- With the exception of 1 patient (casimersen), no patient demonstrated repeated increased categorical QTcF findings across visits
 - Although another patient (casimersen) exhibited increased QTcF values at >1 visit, these findings were not observed at all visits and were not consistently temporally associated with the end-of-infusion timepoint
- Accordingly, these isolated high ΔQTcF values were considered outliers and were excluded from the by-time analysis, as they were not considered reflective of a treatment-related or clinically relevant QT effect

Table 2 Categorical Analysis Results

Endpoint	Visit	Timepoint	Double-blind population		
			Golodirsen n=21 n (%)	Casimersen n=31 n (%)	Placebo n=28 n (%)
QTcF interval >450 msec	Any visit	Any timepoint	0	0	0
ΔQTcF >30 msec	Baseline	NA	0	0	0
	Week 1	1-3 h after end of infusion	0	0	0
	Week 1	End of infusion	0	1 (7.1) ^a	0
	Week 96	1-3 h after end of infusion	1 (7.7) ^b	3 (12) ^c	2 (9.5) ^d
	Week 96	End of infusion	0	5 (20) ^c	2 (9.5) ^d
ΔQTcF >60 msec	Baseline	NA	0	0	0
	Week 1	1-3 h after end of infusion	0	0	0
	Week 1	End of infusion	0	1 (7.1) ^a	0
	Week 96	1-3 h after end of infusion	0	0	0
	Week 96	End of infusion	0	0	0
Open-label population					
Endpoint	Visit	Timepoint	Golodirsen n=21 n (%)	Casimersen n=36 n (%)	
QTcF interval >450 msec	Any visit	Any timepoint	0	0	
ΔQTcF >30 msec	Baseline	NA	0	0	
	Week 1	1-3 h after end of infusion	0	1 (3.3) ^a	
	Week 1	End of infusion	0	2 (6.3) ^f	
	Week 1	Pre dose	0	2 (10.0) ^g	
	Week 48	1-3 h after end of infusion	0	3 (15.8) ^h	
	Week 48	End of infusion	0	3 (15.0) ^g	
ΔQTcF >60 msec	Baseline	NA	0	0	
	Week 1	1-3 h after end of infusion	0	0	
	Week 1	End of infusion	0	0	
	Week 48	1-3 h after end of infusion	0	0	
	Week 48	End of infusion	0	0	

^an=14. ^bn=13. ^cn=25. ^dn=32. ^en=20. ^fn=19. ΔQTcF, change in QTcF from baseline; NA, not applicable; QTcF, QT interval corrected for heart rate according to the Fridericia formula.

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Safety pharmacodynamic sampling collection

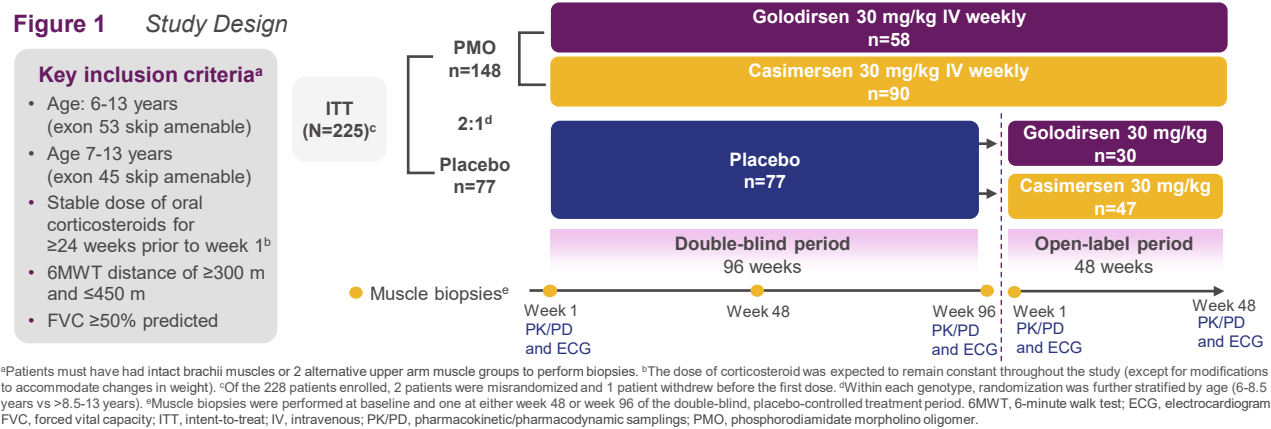
- In ESSENCE, triplicate 12-lead electrocardiograms (ECGs), time-matched to PK concentrations, were obtained during the double-blind period at weeks 1 and 96 and in the open-label period at weeks 1 and 48

Data inclusion criteria

- Only patients with time-matched PK-ECG data were included

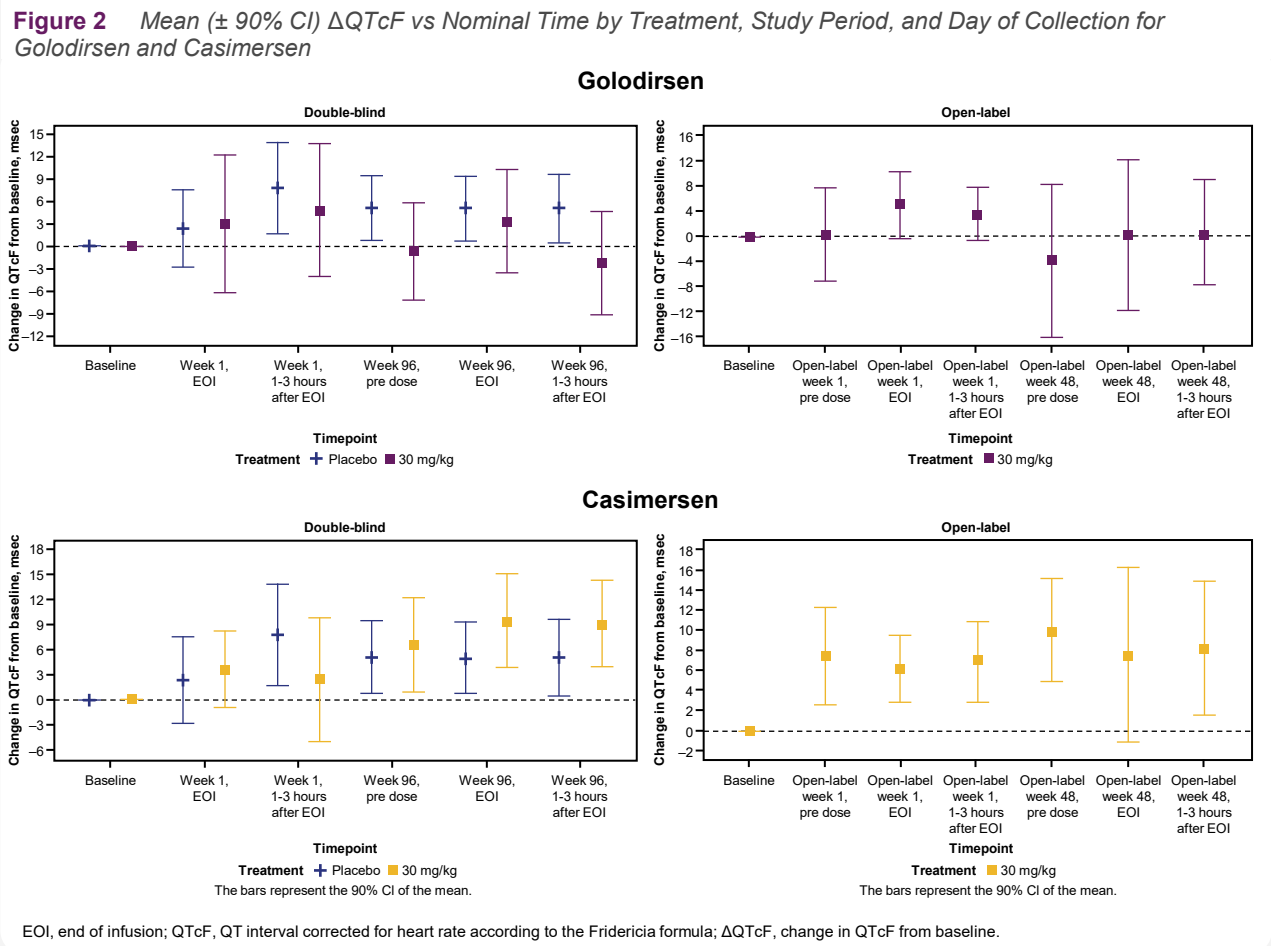
Analyses

- Categorical assessment of absolute QT interval corrected for heart rate according to the Fridericia formula (QTcF) and change from baseline (ΔQTcF) were performed using pre-specified threshold criteria
 - The pre-specified threshold criteria were QTcF interval >450 msec, ΔQTcF interval >30 msec, and ΔQTcF interval >60 msec, as defined in the Food and Drug Administration guidance *Separate for QT/QTc Interval Corrected for Heart Rate (QTc)*
- Analysis of central tendency included ΔQTcF during the double-blind period or open-label period and placebo-corrected change from baseline (ΔΔQTcF) through the double-blind period
- Separately, concentration–QTc (C–QTc) analyses were conducted using linear mixed-effects models



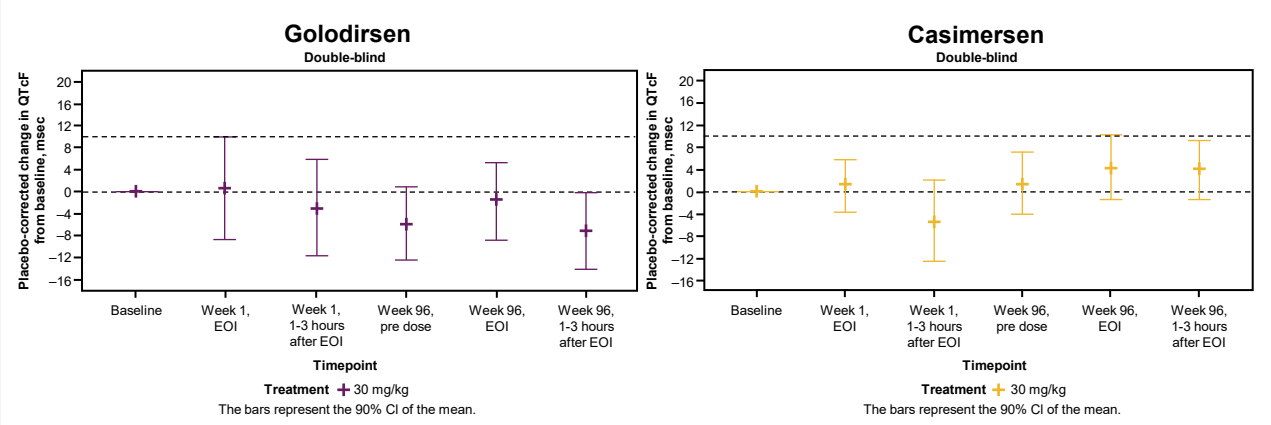
Analysis of central tendency

- For patients receiving golodirsen or casimersen, the upper bound of the two-sided 90% CI for ΔQTcF remained below 20 msec at all evaluable timepoints (**Figure 2**)



- Similarly, the upper bound of the two-sided 90% CI for ΔΔQTcF remained below 10 msec, except for casimersen at the end of the infusion at week 96 (10.12 msec; **Figure 3**); mean values for both golodirsen and casimersen were consistently close to zero across timepoints

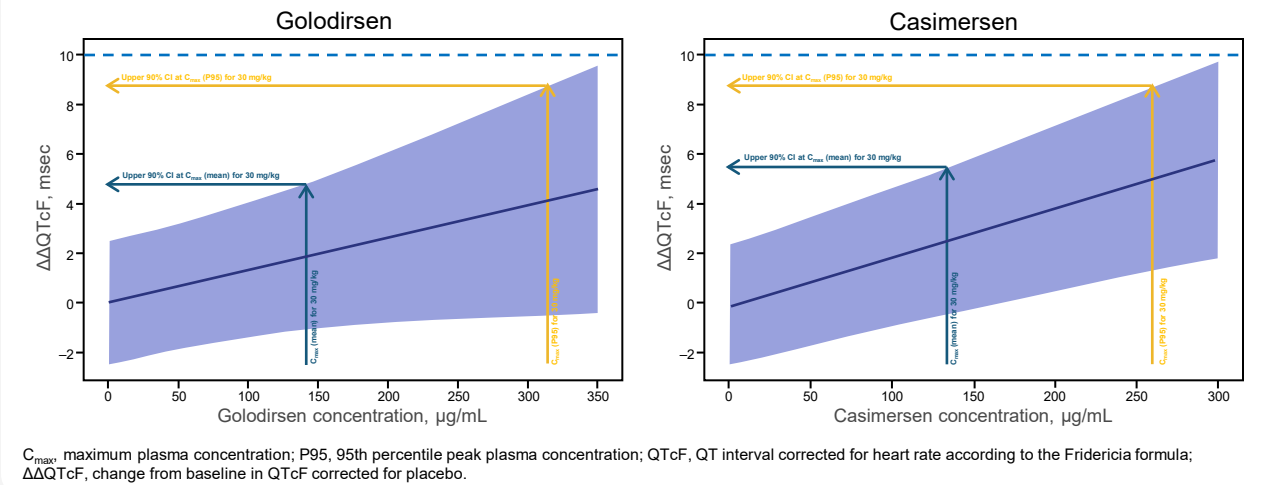
Figure 3 Mean (± 90% CI) ΔΔQTcF vs Nominal Time for Each Compound, by Day of Collection



C–QTc analyses

- C–QTc analyses demonstrated shallow exposure–response relationships with no evidence of concentration-dependent QTc prolongation, and the upper bound of the two-sided 90% CI for model-predicted ΔΔQTcF remained below 10 msec at the 95th percentile of maximum concentration (~8.7 msec for both compounds; **Figure 4**)

Figure 4 Model-Projected Mean With Two-Sided 90% CI of ΔΔQTcF vs Golodirsen or Casimersen Concentration



Conclusions

- Comprehensive ECG, categorical, by-time, and C–QTc analyses did not identify evidence of a clinically meaningful effect of golodirsen or casimersen on cardiac repolarization in patients with DMD
- In the categorical analysis, findings were generally comparable between active-treatment and placebo groups; the observed outlier values occurring infrequently may be reflective of variability in QTc observed in patients with DMD^{7,8}
- A shallow C–QTc slope indicated no meaningful exposure-dependent effect on QTc, supporting a low risk of QT prolongation at clinically high exposures
- Collectively, these findings support the favorable cardiac safety profile of golodirsen and casimersen and indicate no clinically meaningful risk of QTc prolongation in patients with DMD

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