M173

Safety and Tolerability of Eteplirsen in Patients 6–48 Months Old With DMD Amenable to Exon 51 Skipping: An Open-Label Extension Study

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Background

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked, neuromuscular disease caused by mutations in the dystrophin gene[1]
- Irreversible muscle damage is present at birth in patients with DMD, resulting in progressive functional decline[2–7]
- Initiating treatment early before significant muscle degeneration has occurred may improve clinical outcomes[8–10]
- Eteplirsen is indicated for the treatment of patients with DMD who have a confirmed mutation in the dystrophin gene amenable to exon 51 skipping[6,11]
- Previous studies in patients >4 years of age indicate eteplirsen is well tolerated and attenuates pulmonary and ambulatory decline compared with mutation-matched natural history cohorts[6,11–14]
- Data from Study 4658-102, the first clinical trial of eteplirsen in patients with DMD aged 6 to 48 months, supported the safety and tolerability of eteplirsen at the approved 30 mg/kg dose up to 96 weeks in boys as young as 6 months old[15]
- Here, we report the results from the open-label extension (OLE) portion of Study 4658-102 (up to >3 years; 162 weeks) for patients treated with eteplirsen for up to ~5 years (258 weeks)

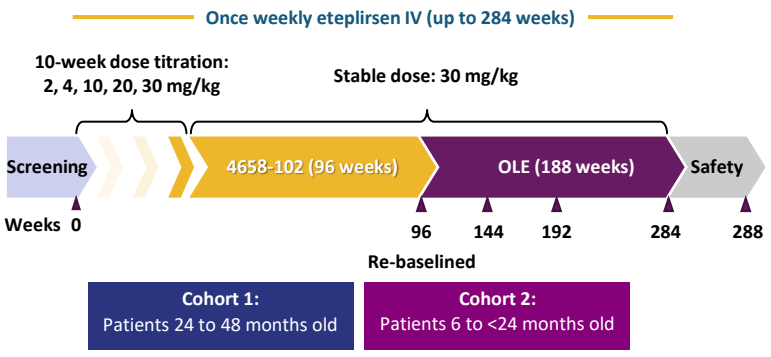
Objective

To assess long-term safety and tolerability of eteplirsen in boys aged 6 to 48 months with DMD who completed the phase 2 dose escalation trial (Study 4658-102; NCT03218995)[15]

Methods

Patients who completed Study 4658-102 were enrolled in the OLE for an additional 192 weeks (**F1**)

F1 *Study Design of 4658-102 OLE*



IV=intravenous; OLE=open-label extension.

Study population

- Male patients with genotypically confirmed *DMD* deletion mutation amenable to exon 51 skipping
- Aged 6 to 48 months

Study endpoints

- Safety and tolerability (primary) up to 192 weeks post–parent study end

Results

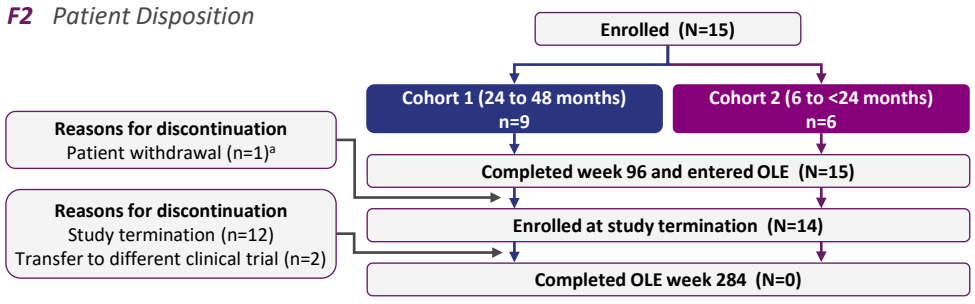
- 15 patients were enrolled in Study 4658-102-OLE (**F2**)
- The study was terminated by the sponsor to reduce the clinical trial burden on the patients while ensuring continued treatment if desired
- Mean (SD) age of patients at OLE baseline was 3.7 (1.10) years (range, 2–5 years) (**T1**)
- From the start of the OLE study, patients received a mean (SD) of 108.5 (37.1) eteplirsen infusions and were on eteplirsen for a mean (SD) of 120.1 (35.79) weeks
- At OLE baseline, 4/15 patients (26.7%, cohort 1) were receiving corticosteroids
- During the OLE study, 11 patients in total received steroids for treatment of DMD, with a median time of 50 days to steroid initiation; 46.7% received continuous and 26.7% received intermittent steroids; 8 patients received deflazacort and 3 patients received prednisolone

Safety during OLE study

- Eteplirsen was well tolerated in patients as young as age 6 months, with no new safety signals; no kidney toxicity was observed up to 162 weeks of treatment, and there was no discernible difference between cohorts 1 and 2 (**T2**)
  - Most treatment-emergent adverse events (TEAEs) were mild or moderate and reduced in frequency and severity compared with the parent study
  - All patients experienced ≥1 TEAE, with the most common being consistent with those commonly seen in pediatric populations: cough, pyrexia, rhinorrhea, and nasopharyngitis
  - 3 patients experienced treatment-related TEAEs (swelling at port site, chromaturia, abnormal urine albumin/creatinine ratio), and all were mild in severity; 1 serious TEAE (influenza; cohort 1) was reported, which was unrelated to treatment
  - No treatment-related hypersensitivity TEAEs were reported
  - No treatment-related discontinuations or deaths were observed
- 13 (86.7%) patients experienced ≥1 adjudicated infusion-related reaction (IRR)*
  - 12 were mild in severity and 1 was moderate (nasal congestion)
- Of the boys who received an implanted port (9/15), no port-related serious bloodstream infections were observed, consistent with Study 4658-102, and no new AEs associated with ports were reported during the OLE study

*IRRs were defined as events reported with a start during or within 24 hours after an infusion that were medically reviewed by a pharmacovigilance specialist and physician to determine if they met the criteria for an IRR.

F2 *Patient Disposition*



[a]Withdrew from the study for reasons not related to the efficacy or safety of eteplirsen. OLE=open-label extension.

T1 *Baseline Characteristics at Start of OLE Study*

Characteristic[a]	Cohort 1 Age 24 to 48 Months (n=9)	Cohort 2 Age 6 to <24 Months (n=6)	Total (N=15)
Age, years	4.4 (0.73)/3, 5	2.7 (0.52)/2, 3	3.7 (1.10)/2, 5
Height, cm	107.6 (7.12)/99.0, 118.0	92.4 (5.12)/87.0, 99.0	101.5 (9.87)/87.0, 118.0
Weight, kg	20.3 (4.63)/15.0, 28.9	15.3 (2.58)/13.0, 19.8	18.3 (4.61)/13.0, 28.9
BMI, kg/m^2	17.4 (2.53)/14.3, 22.6	17.8 (1.41)/16.0, 20.2	17.6 (2.10)/14.3, 22.6
Mutation, n (%)			
45–50	3 (33.0)	1 (16.7)	4 (26.7)
48–50	0	1 (16.7)	1 (6.7)
49–50	2 (22.2)	2 (33.3)	4 (26.7)
50	0	1 (16.7)	1 (6.7)
52	4 (44.4)	1 (16.7)	5 (33.3)
Time since DMD diagnosis, months	34.7 (6.34)/26.0, 46.0	29.8 (7.99)/23.0, 41.0	32.7 (7.20)/23.0, 46.0
Duration of eteplirsen from start of 4658-102, weeks	229.5 (36.14)	197.8 (28.27)	216.8 (35.92)
Median (min, max)	247.9 (157, 258)	204.0 (157, 230)	218.7 (157, 258)
Duration of eteplirsen from start of 4658-102 OLE, weeks	132.7 (36.18)	101.2 (27.92)	120.1 (35.79)
Median (min, max)	150.1 (60, 162)	107.3 (60, 133)	122.7 (60, 162)
Corticosteroid type, n (%)			
Deflazacort	3 (33.3)	0	3 (20.0)
Prednisone	1 (11.1)	0	1 (6.7)
No corticosteroids taken	5 (55.6)	6 (100)	11 (73.3)
Corticosteroid frequency, n (%)			
Continuous	3 (33.3)	0	3 (20.0)
Intermittent	1 (11.1)	0	1 (6.7)
Corticosteroids started, n (%)			
Prior to eteplirsen initiation	2 (22.2)[b]	0	2 (13.3)
At eteplirsen initiation	0	0	0
After eteplirsen initiation	2 (22.2)[c]	0	2 (13.3)
Duration of steroids at start of 4658-102 OLE, months	18.5 (11.25)[d]		18.5 (11.25)[d]
Median (min, max)	23.0 (1.8, 26.2)	0	23.0 (1.8, 26.2)

[a]Data are mean (SD)/min, max unless otherwise stated. [b]Mean duration of corticosteroid use was 2.5 months. [c]Corticosteroids were started ~14 and 21 months after study entry. [d]n=4. DMD=Duchenne muscular dystrophy; OLE=open-label extension.

T2 *Summary of TEAEs During OLE Study*

Patients With ≥1, n (%)	Cohort 1 Age 24 to 48 Months (n=9)	Cohort 2 Age 6 to <24 Months (n=6)	Total (N=15)	Parent Study Total (N=15)
Any TEAE	9 (100)	6 (100)	15 (100)	15 (100)
Related to study drug	2 (22.2)	1 (16.7)	3 (20.0)[a]	3 (20.0)[b]
Serious	1 (11.1)	0	1 (6.7)[c]	1 (6.7)[d]
Leading to discontinuation	0	0	0	0
Number of TEAEs by severity				
Mild	226	132	358	399
Moderate	5	2	7	17
Severe	1	0	1[c]	0
TEAEs in ≥50% of all patients				
Cough	6 (66.7)	6 (100)	12 (80.0)	13 (86.7)
Pyrexia	4 (44.4)	5 (83.3)	9 (60.0)	12 (80.0)
Rhinorrhea	6 (66.7)	3 (50.0)	9 (60.0)	7 (46.7)
Nasopharyngitis	4 (44.4)	4 (66.7)	8 (53.3)	12 (80.0)
Rhinitis[e]	4 (44.4)	2 (33.3)	6 (40.0)	8 (53.3)

[a]Catheter site swelling, chromaturia, abnormal urine albumin/creatinine ratio; all were mild in severity and resolved without intervention. [b]Vomiting, localized edema, flushing; all were mild in severity and resolved without intervention. [c]Influenza, unrelated to study drug. [d]Mild bronchiolitis, unrelated to study drug. [e]Rhinitis is defined as inflammation of the nasal membranes characterized by symptoms of sneezing, nasal congestion, and clear nasal discharge, whereas rhinorrhea refers to clear nasal discharge. OLE=open-label extension; TEAE=treatment-emergent adverse event.

Key Findings

These data support the safety and tolerability of eteplirsen at the approved 30 mg/kg dose in patients as young as 6 months old

Conclusions

Safety in the OLE portion of Study 4658-102, a phase 2, dose-escalation trial of boys with DMD aged 6 to 48 months who were amenable to exon 51 skipping, was consistent with the parent trial and the known safety profile of eteplirsen

Eteplirsen was well tolerated in this young patient population, with no treatment-related discontinuations

There were no new safety signals for up to 162 weeks of treatment in the OLE study and no evidence of kidney toxicity

TEAEs were mild or moderate and reduced in frequency and severity compared with the parent study 102; no serious TEAEs were related to treatment

Infusion-related reactions were considered an important identified risk; all instances of infusion-related reactions in the OLE study were nonserious and were consistent with those reported in the parent study

Acknowledgments & Disclosures

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