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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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Objective

To assess long-term safety and tolerability of eteplirsen in boys aged 6 to 48 months with Duchenne muscular dystrophy (DMD) who completed the phase 2 dose escalation trial (Study 4658-102; NCT03218995)[1]

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

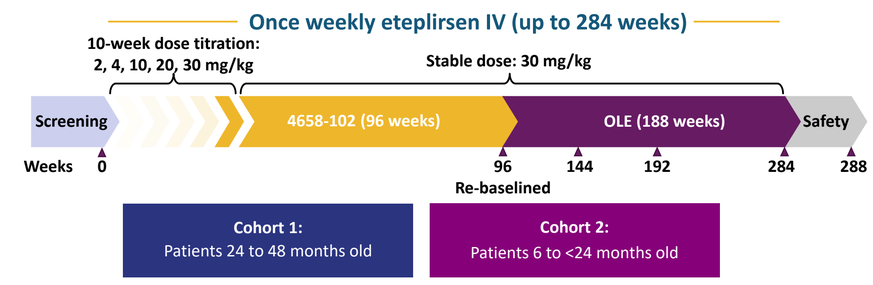
- Safety in the OLE portion of Study 4658-102, a phase 2, dose-escalation trial of boys with DMD aged 6 to 48 months who were amenable to exon 51 skipping, was consistent with the parent trial and the known safety profile of eteplirsen
- Eteplirsen was well tolerated in this young patient population, 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 non-serious and were consistent with those reported in the parent study

BACKGROUND

- DMD is a fatal, X-linked, neuromuscular disease caused by mutations in the dystrophin gene[2]
- Irreversible muscle damage is present at birth in patients with DMD, resulting in progressive functional decline[3–8]
- Initiating treatment early before significant muscle degeneration has occurred may improve clinical outcomes[9–11]
- Eteplirsen is indicated for the treatment of patients with DMD who have a confirmed mutation in the dystrophin gene amenable to exon 51 skipping[7,12]
- 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[7,12–15]
- 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[1]
- 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)

METHODS

Study Design of 4658-102 OLE



IV=intravenous; OLE=open-label extension.

Study population

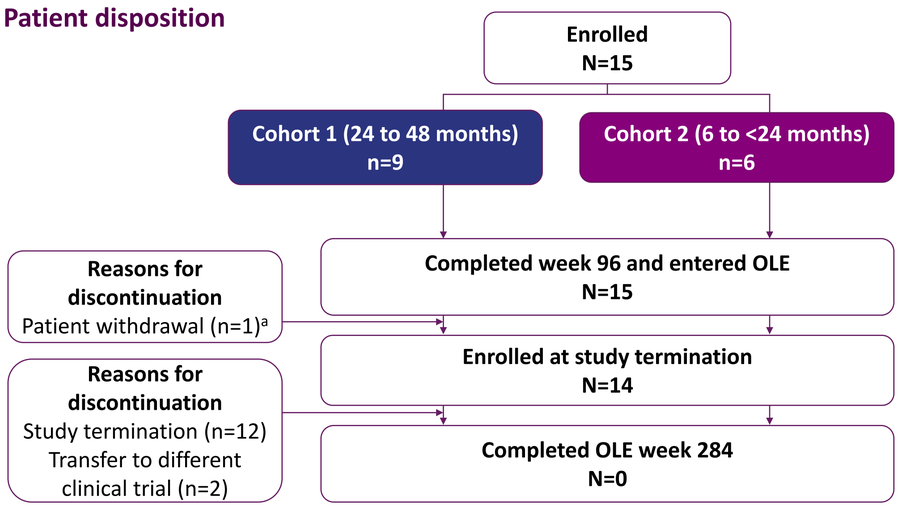
- Male patients with genotypically confirmed DMD deletion mutation amenable to exon 51 skipping
- Aged 6 to 48 months

Study endpoints

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

RESULTS

Patient disposition



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

- 15 patients were enrolled in Study 4658-102-OLE
- The study was terminated by the sponsor to reduce the clinical trial burden on the patients while ensuring continued treatment if desired

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/m²	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]	0	18.5 (11.25)[d]
Median (min, max)	23.0 (1.8, 26.2)		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.

- Mean (SD) age of patients at OLE baseline was 3.7 (1.10) years (range, 2–5 years)
- 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 discernable difference between cohorts 1 and 2
  - 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

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)

*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. [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.

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