Presented at the 17th International Congress on Neuromuscular Diseases; July 5 –9, 2022; Brussels, Belgium

eP04.06.04

Safety, Tolerability, and Pharmacokinetics of Eteplirsen in Patients 6–48 Months Old With Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

Eugenio Mercuri,[1] Andreea M Seferian,[2] Laurent Servais,[2-4] Nicolas Deconinck,[5,6] Herb Stevenson,[7] Lilly East,[7] Wenfei Zhang,[7] Sameer Upadhyay,[7] Francesco Muntoni[8,9]

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Study 4658-102 was the first clinical trial of eteplirsen in patients aged 6–48 months, the youngest population of patients with DMD in a clinical trial to date

The safety experience in this study was consistent with the known safety profile of eteplirsen

Eteplirsen was well tolerated in this young patient population with no evidence of kidney toxicity

Eteplirsen pharmacokinetics were consistent between both cohorts and aligned with expectations based on previous clinical experience in boys with DMD aged older than 4 years

These data support the safety and tolerability of eteplirsen in patients as young as 6 months old

Please scan QR code for full study details

REFERENCES, DISCLOSURES, & ACKNOWLEDGEMENTS

DMD=Duchenne muscular dystrophy.

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Background

- Progressive and irreversible muscle damage begins at birth in patients with DMD due to the absence of dystrophin protein[1,2]
- Motor development in patients aged ≤7 years often masks muscle degeneration, commonly leading to delayed diagnosis, while those aged >7 years tend to exhibit progressive deterioration and declining ambulatory function[3-7]
- Initiating treatment early before significant muscle degeneration has occurred may improve clinical outcomes[8-10]
- Eteplirsen is indicated to treat patients with DMD who have a mutation in the dystrophin gene amenable to exon 51 skipping[6,11]
- Previous studies in patients aged >4 years indicate eteplirsen is well tolerated and attenuates pulmonary and ambulatory decline compared with mutation-matched natural history cohorts[6,11-14]

DMD=Duchenne muscular dystrophy.

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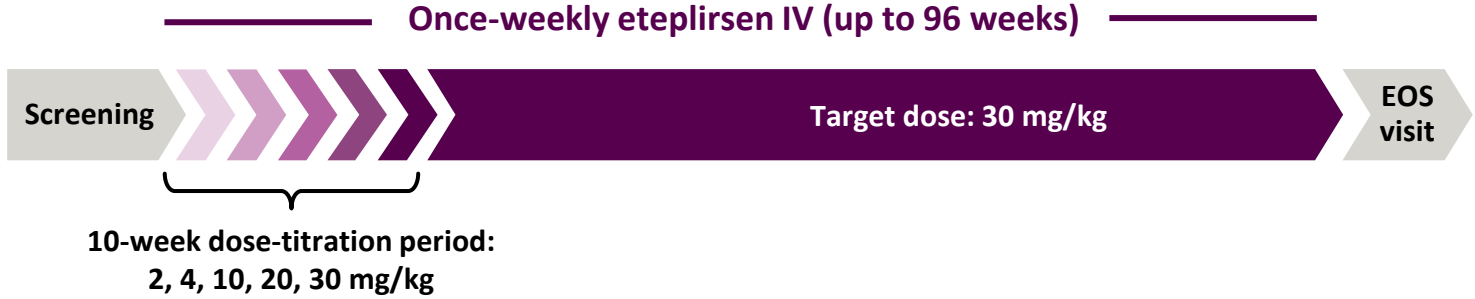
Study Design

Study 4658-102 is a phase 2, multicenter, open-label, dose-escalation study in the youngest population of patients with DMD in a clinical trial to date



Study population

- Male patients aged 6–48 months with DMD amenable to exon 51 skipping
  - **Cohort 1**: Aged 24 to 48 months
  - **Cohort 2**: Aged 6 to <24 months
- Enrollment for Cohort 2 began after the first 3 Cohort 1 patients completed ≥12 infusions and all available safety data were reviewed

Study endpoints

- **Primary**: Safety and tolerability
- **Secondary**: Pharmacokinetics

DMD=Duchenne muscular dystrophy; EOS=end of study; IV=intravenous.

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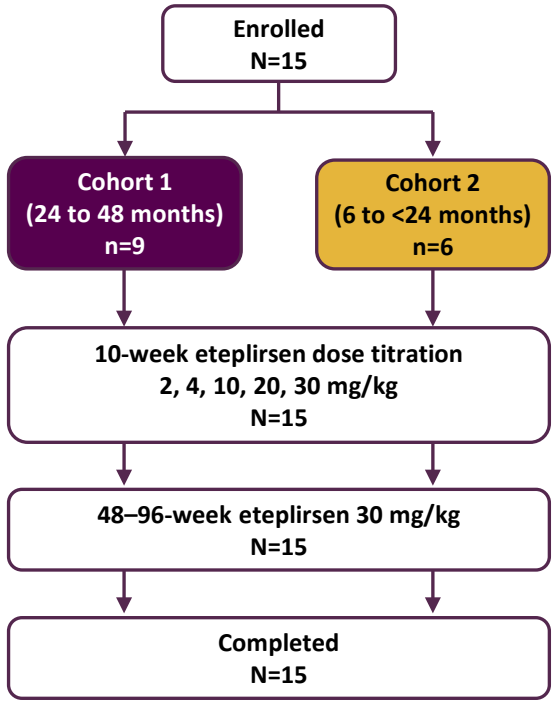
Patient disposition



Baseline characteristics

Characteristic	Cohort 1 Age 24 to 48 months (n=9)	Cohort 2 Age 6 to <24 months (n=6)	Total (N=15)
Age, months	36.8 (8.2)	16.0 (7.1)	28.5 (12.9)
Height/length, cm	96.6 (6.4)	77.1 (6.1)	88.8 (11.6)
Weight, kg	16.3 (2.7)	10.6 (2.4)	14.0 (3.8)
BMI, kg/m^2	17.4 (1.8)	17.5 (1.7)	17.4 (1.7)
Time since DMD diagnosis, months	12.3 (6.7)	7.8 (8.0)	10.5 (7.3)
Corticosteroid type, n (%)			
Deflazacort	2 (22.2)	0	2 (13.3)
Prednisone	0	0	0
No corticosteroids taken	7 (77.8)	6 (100)	13 (86.7)
Corticosteroid frequency, n (%)			
Continuous	2 (22.2)	0	2 (13.3)
Intermittent	0	0	0

Treatment exposure

- Patients received a mean of 93.1 eteplirsen infusions (Cohort 1, 94.6; Cohort 2, 90.8); mean of 85.1 infusions at the 30 mg/kg dose
- 9/15 (60%) patients had an implantable venous access device port placed during the study
  - **Cohort 1**: 4 patients had ports placed on study days -5, 65, 135, and 259
  - **Cohort 2**: 5 patients had ports placed on study days -5, -13, 16, 104, and 209
- Mean time on eteplirsen was 96.5 weeks (1.85 years), representing a total of 27.8 patient-years[a] of eteplirsen exposure (N=15)

Values are mean (SD) unless otherwise noted. [a]Patient-years on eteplirsen is calculated as: (last treatment date – first treatment date + 7)/365.25.
DMD=Duchenne muscular dystrophy; BMI=body mass index.

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Eteplirsen was well tolerated in patients aged as young as 6 months, with no new safety signals after 96 weeks of treatment and no discernable differences between Cohort 1 and 2

- All TEAEs were mild or moderate in severity
  - All patients experienced ≥1 TEAE, with the most common (≥50% of patients) consistent with those commonly seen in pediatric populations
- 3 patients experienced treatment-related TEAEs (vomiting, localized edema, flushing), all mild in severity
- 1 serious TEAE, mild bronchiolitis, was reported in Cohort 2 and unrelated to treatment
- Shifts from baseline in serum chemistry values were not clinically significant
- There were no IVAD-related serious bloodstream infections reported
  - 4 events associated with IVADs were reported (catheter site eczema, catheter site swelling, procedural pain, and dermatitis contact), all mild in severity and unrelated to treatment
- There were no treatment-related discontinuations or deaths, and no kidney toxicity was observed

Summary of TEAEs

Participants with ≥1 TEAE, n (%)	Cohort 1 Age 24 to 48 months (n=9)	Cohort 2 Age 6 to <24 months (n=6)	Total (N=15)
Any TEAE	9 (100)	6 (100)	15 (100)
TEAE related to study drug	2 (22.2)	1 (16.7)	3 (20.0)
Serious TEAE	0	1 (16.7)	1 (6.7)
Serious TEAE related to study drug	0	0	0
TEAE leading to discontinuation	0	0	0
TEAE leading to death	0	0	0
Number of TEAEs by severity			
Mild	234	165	399
Moderate	5	12	17
Severe	0	0	0

IVAD=implanted venous access device; TEAE=treatment-emergent adverse event.

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Additional safety details

- 80% of patients experienced ≥1 adjudicated infusion-related reaction[a]
- All were mild in severity and most (43/44) were assessed as unrelated to study drug by the investigator
- The most common (≥20% of patients) were rhinorrhea, diarrhea, cough, vomiting, and pyrexia
- No adverse events of thrombocytopenia, hepatotoxicity, anaphylaxis, severe allergic reactions, or severe complement-mediated inflammation events were reported
- No kidney toxicity was observed; screening for kidney toxicity yielded a single laboratory abnormality, deemed unrelated to treatment (Cohort 2)
  - Laboratory abnormality: Patient had low creatinine clearance (59.8 mL/min) at screening and week 24 prior to eteplirsen administration (56.9 mL/min); clearance values were otherwise normal throughout the study, and the patient completed the study

TEAEs occurring in ≥50% of patients

Participants with TEAE by preferred term, n (%)	Cohort 1 Age 24 to 48 months (n=9)	Cohort 2 Age 6 to <24 months (n=6)	Total (N=15)
Pyrexia	7 (77.8)	6 (100)	13 (86.7)
Cough	7 (77.8)	5 (83.3)	12 (80.0)
Nasopharyngitis	7 (77.8)	5 (83.3)	12 (80.0)
Vomiting	8 (88.9)	4 (66.7)	12 (80.0)
Diarrhea	5 (55.6)	3 (50.0)	8 (53.3)
Rhinitis	4 (44.4)	4 (66.7)	8 (53.3)

[a]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 infusion-related criteria.
TEAE=treatment-emergent adverse event.

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Pharmacokinetic characteristics of eteplirsen were consistent between both cohorts and aligned with expectations based on clinical experience in the older population

- T_{max} of eteplirsen was estimated to be 0.4–0.6 hours after dosing, consistent across both cohorts and all dose levels
- C_{max} and AUC_{last} values increased with increasing dose level through 20 mg/kg and remained similar to the pharmacokinetic exposure parameters of 30 mg/kg at weeks 10 and 24
- Variability was high across all dose levels, with overall geometric CV% values ranging from 82.8% to 136% for C_{max} and 41.7% to 113% for AUC_{last}
- At 30 mg/kg, eteplirsen exposure was consistent between cohorts, with Cohort 1 C_{max} and AUC_{last} values 1.1–1.5-fold of those observed in Cohort 2
- Urine pharmacokinetic parameters support that urinary excretion is time-independent and a major pathway of eteplirsen clearance

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AUC_{last}=area under the curve from time 0 to last quantifiable concentration; C_{max}=maximum plasma concentration; CV=coefficient of variance; T_{max}=time of C_{max}.

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Key plasma and urine eteplirsen pharmacokinetic parameters

Parameter	Cohort 1					Cohort 2				
	2 mg/kg (Week 2)	10 mg/kg (Week 6)	20 mg/kg (Week 8)	30 mg/kg (Week 10)	30 mg/kg (Week 24)	2 mg/kg (Week 2)	10 mg/kg (Week 6)	20 mg/kg (Week 8)	30 mg/kg (Week 10)	30 mg/kg (Week 24)
C_{max}, µg/mL – geo. mean (geo. CV%)	n=8 9.67 (75.9%)	n=9 46.5 (72.3%)	n=9 63.3 (123%)	n=9 93.7 (55.5%)	n=8 78.2 (92.2%)	n=5 4.22 (120%)	n=6 17.2 (192%)	n=6 85.0 (67.6%)	n=6 63.8 (124%)	n=6 59.7 (82.7%)
T_{max}, h – median (range)	n=8 0.58 (0.17–2.67)	n=9 0.58 (0.47–4.25)	n=9 0.78 (0.50–2.75)	n=9 0.58 (0.50–1.48)	n=8 0.63 (0.42–6.83)	n=5 0.58 (0.42–0.67)	n=6 0.72 (0.58–3.32)	n=6 0.73 (0.53–1.17)	n=6 0.92 (0.50–2.75)	n=6 0.72 (0.58–1.83)
AUC_{last}, µg*h/mL – geo. mean (geo. CV%)	n=8 13.8 (118%)	n=9 56.1 (57.2%)	n=9 92.1 (94.7%)	n=9 119 (30.8%)	n=8 100 (42.5%)	n=5 6.13 (73.1%)	n=6 27.8 (113%)	n=6 81.4 (89.6%)	n=6 85.0 (114%)	n=6 89.6 (43.8%)
$Ae_{(0\text{-}4h)}$, µg – mean (SD)	n=3 7720 (9060)	n=7 56,000 (73,300)	n=6 102,000 (108,000)	n=8 263,000 (209,000)	n=7 239,000 (140,000)	n=3 1430 (1390)	n=6 28,700 (24,100)	n=5 65,600 (47,900)	n=6 94,700 (68,500)	n=4 147,000 (132,000)
$Fe_{(0\text{-}4h)}$, % – mean (SD)	n=3 27.2 (33.8)	n=7 32.2 (40.9)	n=6 32.1 (31.0)	n=8 50.9 (35.2)	n=7 52.5 (33.4)	n=3 6.81 (7.07)	n=6 29.7 (27.7)	n=5 35.2 (26.6)	n=6 33.6 (27.9)	n=4 45.5 (41.4)

$Ae_{(0\text{-}4h)}$=amount of unchanged drug excreted in urine 0–4h after dosing; AUC_{last}=area under the curve from time 0 to last quantifiable concentration; C_{max}=maximum plasma concentration; CV=coefficient of variance; $Fe_{(0\text{-}4h)}$=fraction of drug excreted in urine 0–4h after dosing; geo.=geometric; T_{max}=time of C_{max}.

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Conclusions

- This was the first clinical trial of eteplirsen in patients aged 6–48 months, the youngest population of patients with DMD in a clinical trial to date
- The safety experience in this study was consistent with the known safety profile of eteplirsen
- Eteplirsen was well tolerated in this young patient population with no evidence of kidney toxicity
  - All treatment-emergent adverse events were mild or moderate, and none led to death or discontinuation of study drug
- Infusion-related reaction is an important identified risk; all infusion-related reactions were nonserious and consistent with those previously reported
- Eteplirsen pharmacokinetics were consistent between both cohorts and aligned with expectations based on previous clinical experience in boys with DMD aged older than 4 years

DMD=Duchenne muscular dystrophy.

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Safety, Tolerability, and Pharmacokinetics of Eteplirsen in Patients 6–48 Months Old With Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

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OVERVIEW

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REFERENCES, DISCLOSURES, & ACKNOWLEDGMENTS

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