Presented virtually at the Muscular Dystrophy Association Clinical & Scientific Conference, March 13–16, 2022, Nashville, TN

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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Objective

To evaluate the safety, tolerability, and pharmacokinetics of eteplirsen treatment in male patients with Duchenne muscular dystrophy (DMD) aged 6–48 months who have a confirmed mutation of the DMD gene amenable to exon 51 skipping in Study 4658-102 (NCT03218995)

Key Takeaway

The safety and pharmacokinetic results from Study 4658-102 contribute to the body of evidence supporting the early use of eteplirsen in boys with DMD

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 (TEAEs) 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 older than 4 years of age

BACKGROUND

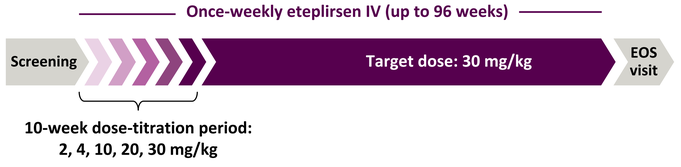
- Progressive and irreversible muscle damage begins at birth in patients with DMD due to the absence of dystrophin protein[1,2]
- Motor development in patients ≤7 years of age often masks muscle degeneration, commonly leading to delayed diagnosis, while those >7 years of age tend to exhibit progressive 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 >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]

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 6–48 months of age with DMD amenable to exon 51 skipping
  - Cohort 1: aged 24–48 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

EOS=end of study; IV=intravenous.

RESULTS

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
- 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)

[a]Patient years on eteplirsen is calculated as (last treatment date – first treatment date + 7)/365.25.

Safety

Eteplirsen was well tolerated in patients as young as 6 months of age, with no new safety signals after 96 weeks of treatment and no discernable difference 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 treatment-related discontinuations or deaths, and no kidney toxicity was observed

Please scan QR code for additional safety details.

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

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)

Pharmacokinetics

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 at 30 mg/kg on 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

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%)
$Ae_{(0-4h)}$, 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)
$Fe_{(0-4h)}$, % – 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)

$Ae_{(0-4h)}$=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; $Fe_{(0-4h)}$=fraction of drug excreted in urine 0–4h after dosing; geo.=geometric; T_{max}=time of C_{max}.

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ACKNOWLEDGMENTS & DISCLOSURES

The authors and Sarepta Therapeutics, Inc., thank the patients and their families. Study 4658-102 (NCT03218995) was funded by Sarepta Therapeutics, Inc. Editorial support was provided by Paraskevi Briassouli, PhD, of Eloquent Scientific Solutions, and was funded by Sarepta Therapeutics, Inc. **Disclosures: EM** has received consultant fees from Sarepta Therapeutics, Inc. **AMS** has no conflicts to disclose. **LS** has participated on advisory boards for Sarepta Therapeutics, Inc. **ND** has participated on advisory boards for Sarepta Therapeutics, Inc. **HS, LE, WZ, and SU** are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. **FM** has received consultant fees and speaker honoraria from Sarepta Therapeutics, Inc. Presented previously at the 2021 World Muscle Society Virtual Congress, September 20–24, 2021 and the British Paediatric Neurology Association (BPNA) Virtual Annual Conference, January 19–21, 2022.