2. SYNOPSIS

Name of Sponsor/Company:

Sarepta Therapeutics, Inc.
215 First Street,
Cambridge MA 02142 USA

Phone: +1-617-274-4000

Name of Finished Product:

Eteplirsen injection

Name of Active Ingredient:

Eteplirsen

Title of Study: An Open-Label Safety, Tolerability, and Efficacy Study of Eteplirsen in Patients with Duchenne Muscular Dystrophy who have Completed Study 4658-102

Principal Investigator:

Professor Eugenio Mercuri

Study Number: 4658-102-OLE

Number of Study Center(s) and Countries:

This study was conducted at 4 sites in Italy, France, Belgium, and United Kingdom.

Publications (reference): None

Studied period (years):	**Phase of development:** 2
Study Initiation Date: 26 June 2019 Early Study Termination Date: 31 August 2022	

Objectives and Endpoints

Listed below are the objectives and endpoints that are described in this report.

Primary Objective

- To evaluate the ongoing safety and tolerability of additional treatment with eteplirsen administered once weekly by intravenous (IV) infusion in male Duchenne muscular dystrophy (DMD) patients who have successfully completed the 96-week eteplirsen study: Study 4658-102.

The primary (safety and tolerability) endpoints of the study were:

- Incidence of AEs, serious adverse events (SAEs), and discontinuation from treatment due to AEs
- Incidence of deaths due to AEs
- Incidence of adverse events of special interest (AESIs), including infusion-related reactions, hypersensitivity, and renal events
- Clinically significant laboratory testing, including hematology, coagulation, serum chemistry, and urinalysis

- Clinically significant cardiac function assessments, including electrocardiogram (ECG)
- Clinically significant vital signs
- Clinically significant physical examinations

Methodology:

This was an open-label extension (OLE) study to assess the ongoing safety, tolerability, and efficacy of weekly IV infusions of eteplirsen in DMD patients who have successfully completed Study 4658-102.

Subjects were enrolled into 1 of 2 age cohorts:

- Cohort 1: age 24 to 48 months at baseline for Study 4658-102
- Cohort 2: age 6 months to < 24 months at baseline for Study 4658-102

Subjects had the opportunity to enroll in this study during the last visit of Study 4658-102 (Week 96). After enrollment, subjects were to have received the 30 mg/kg dose of eteplirsen while in this study. The period from Baseline for Study 4658-102-OLE through Week 284 was to be considered the "Treatment Period." Week 284 was to be followed by a 4-week Safety Follow-up Period. However, the Sponsor made the decision to transition subjects enrolled in Study 4658-102-OLE to a post-trial access program or another Sarepta study resulting in prematurely terminating the study. This decision was made in an effort to reduce clinical trial burden on subjects while ensuring continued treatment if desired, pending commercial availability of eteplirsen.

Subjects were allowed to transition to commercial eteplirsen if it was available at any time during the study, without undergoing the Safety Follow-up Period. Home infusion of the study drug may have been available.

Number of Subjects (planned and analyzed):

Planned = 15

Analyzed = 15

Diagnosis and Main Criteria for Inclusion:

Subjects who had successfully completed 96 weeks of treatment in Study 4658-102 were included in this study.

Test Product, Dose and Mode of Administration, Batch Number:

Eteplirsen 30 mg/kg IV infusion.

Duration of Treatment: 284 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Statistical Methods:

Sample size determination: As this study was an OLE study of Study 4658-102, the sample size was predicated on the sample size of Study 4658-102.

Analysis Sets: There was one analysis population, the Safety Analysis Set, which included all subjects who were enrolled in the study and receive at least 1 dose of eteplirsen. This analysis set was used for analyses of all endpoints, unless stated otherwise.

Safety analysis: Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher. An AE was defined as a treatment-emergent adverse event (TEAE) if it developed or worsened in the period from the first dose of study drug to 28 days after the last dose of study drug. A treatment-related TEAE was defined as a TEAE that the Investigator considered related to the study treatment.

Demography and Baseline Characteristics:

Out of the 15 subjects enrolled in the study the majority were White (9 out of 15, 60.0%) and Not Hispanic or Latino (7 out of 15, 46.7%). The overall median age at Baseline was 4 years (range: 2 to 5 years). The overall median time since DMD diagnosis to baseline was 33 months (range: 23 to 46 months).

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Efficacy Results: Not applicable.

Safety Results:

The safety experience in this study is consistent with the known safety profile of eteplirsen. Most of the reported TEAEs were mild. One severe TEAE was observed. Treatment-related TEAEs were reported in 3 subjects (20.0%). All reported treatment-related TEAEs were mild. No protocol-defined treatment emergent AESIs were reported in this study. There was no evidence of renal toxicity in this study.

There was a single SAE in this study, influenza, that was assessed by the Investigator as not related to eteplirsen.

	Cohort 1: Age 24 to 48 months at 4658-102 baseline (N=9)	**Cohort 2: Age 6 to < 24 months at 4658-102 baseline (N=6)**	**Overall (N=15)**
Total Number of Treatment-Emergent Adverse Events by Severity	232	134	366
Mild	226	132	358
Moderate	5	2	7
Severe	1	0	1
Total Number of TEAEs that are Non-Serious	231	134	365
Total Number of TEAEs that are Serious	1	0	1

Subjects with at Least One:			
TEAE	9 (100%)	6 (100%)	15 (100%)
TEAE Possibly/Probably or Definitely Related to Study Drug	2 (22.2%)	1 (16.7%)	3 (20.0%)
Treatment-Emergent Severe Adverse Event	1 (11.1%)	0	1 (6.7%)
Treatment-Emergent Non-Serious Adverse Event	8 (88.9%)	6 (100%)	14 (93.3%)
Treatment-Emergent SAE	1 (11.1%)	0	1 (6.7%)
Treatment-Emergent SAE Possibly/Probably or Definitely Related to Study Drug	0	0	0
TEAE Leading to Discontinuation from Study Drug	0	0	0
TEAE Leading to Death	0	0	0

CONCLUSIONS:

In this open-label extension study of eteplirsen, once-weekly IV infusions at a dose of 30 mg/kg were generally well tolerated in male subjects ages 6 months to 48 months (Cohort 1: age 24 months to 48 months at baseline for Study 4658-102 and Cohort 2: age 6 months to < 24 months at baseline for Study 4658-102) with genotypically confirmed DMD and a deletion mutation amenable to exon 51 skipping. The safety experience in this study was consistent with the known safety profile of eteplirsen. One SAE (influenza) was reported that was determined by the Investigator to be unrelated to study drug. No TEAEs led to death or discontinuation of study drug.

Date and Version of This Report:

03 February 2023, Version 1.0