2. SYNOPSIS

Name of Sponsor/Company:
Sarepta Therapeutics, Inc.

Name of Finished Products:
AMONDYS 45 and VYONDYS 53

Name of Active Ingredients:
Casimersen and Golodirsen

Title of Study: Long-term, Open-label Extension Study for Patients with Duchenne Muscular Dystrophy Enrolled in Clinical Trials Evaluating Casimersen or Golodirsen

Principal Investigator: PPD

Study Number:
SRP-4045-302

Number of Study Center(s) and Countries:
This study was conducted at 51 centers with 171 subjects enrolled and treated in Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Israel, Italy, Poland, Spain, Sweden, United Kingdom, and the United States of America.

Publications (reference): None

Studied period (years):	**Phase of development:** 3
Study Initiation Date: 02 August 2018 Early Study Termination Date: 26 July 2023	

Objectives and Endpoints

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

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of long-term treatment with 30 mg/kg casimersen or golodirsen	• Subject incidence of serious adverse events (SAEs)

Methodology:

This was a multicenter, open-label extension (OLE) study to assess the long-term safety and efficacy of golodirsen or casimersen in subjects with Duchenne muscular dystrophy (DMD) amenable to treatment by skipping exons 53 or 45. Subjects were eligible to transfer into this study only after completing the original studies, evaluating golodirsen (4053) or casimersen (4045). Every effort was made to ensure that the subject did not experience any interruption in dosing of golodirsen or casimersen during the transition from the original study to this study. Subjects continued to receive 30 mg/kg of either golodirsen or casimersen once weekly by intravenous (IV) infusion, depending upon their genotype, starting at Week 1 of this study, and continuing up to 144 weeks. This study was terminated before all subjects reached the last protocol-defined end of study visit. Early study termination resulted in subjects either being transitioned to a post-trial access program, to another study, or declining further treatment.

Adverse events (AEs), concomitant medications, and the use of any physiotherapeutic interventions (including assisted ventilation) were collected throughout the study. Renal function blood tests were collected once every 12 weeks; clinical laboratory tests were collected once every 12 weeks through 48 weeks, and thereafter, once every 24 weeks; vital signs were collected weekly; and 12-lead electrocardiogram (ECG) was collected at 48, 96, and 144 weeks.

Number of Subjects (planned and analyzed):

The planned number of subjects was based on the number of subjects enrolled in the qualifying studies evaluating golodirsen or casimersen in subjects with DMD amenable to skipping either exon 53 or exon 45.

A total of 171 subjects amenable to exon 53 (n=74) or exon 45 (n=97) skipping were enrolled and included in the safety analysis population.

Diagnosis and Main Criteria for Inclusion:

Subjects who had successfully completed a clinical study evaluating golodirsen or casimersen, per protocol and were between 7 and 23 years of age, inclusive, at enrollment.

Test Product, Dose and Mode of Administration:

Golodirsen or casimersen: 30 mg/kg weekly via IV infusion.

Duration of Treatment: 144 weeks

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

Statistical Methods:

Sample size determination: As this was an OLE study, the sample size was predicated on the sample size in the original studies evaluating golodirsen and casimersen.

Analyses of primary endpoints: There was 1 analysis population, the Safety Analysis Set, which included all subjects who were enrolled in the study and receive at least 1 dose of study treatment (golodirsen or casimersen).

Safety analysis: Safety analyses were descriptive in nature.

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Efficacy Results: Not applicable

Safety Results:

Most subjects in the golodirsen group (90.5%) and casimersen group (97.9%) experienced at least 1 TEAE and most were mild in severity. Severe TEAEs were reported in <20% of subjects in both groups. Treatment-related AEs were reported in 20.3% and 17.5% of subjects in the golodirsen and casimersen groups, respectively. Treatment-emergent SAEs were reported in 16.2% of subjects in the golodirsen and 22.7% of subjects in the casimersen groups. There were no treatment-emergent treatment related SAEs. The TEAEs leading to discontinuation of study drug in 1 subject treated with casimersen and leading to death in 1 subject treated with golodirsen were assessed as unrelated to study drug and related to the subject's underlying disease. Rhabdomyolysis meeting the confirmed AESI criteria was reported in 5 subjects treated with golodirsen and in 4 subjects treated with casimersen. All events were mild in severity, except for 1 event that was moderate. Two events of rhabdomyolysis in 1 subject treated with casimersen and 2 events of chromaturia in 1 subject treated with golodirsen were considered related to study drug.

	Golodirsen (N=74) n (%)	**Casimersen (N=97) n (%)**
Number of TEAEs	863	938
Mild	735	784
Moderate	108	116
Severe	20	38
Number of Treatment-Emergent SAEs	15	42
Subjects with at least one:		
TEAE (by Maximum Severity)	67 (90.5%)	95 (97.9%)
Mild	66 (89.2%)	95 (97.9%)
Moderate	32 (43.2%)	37 (38.1%)
Severe	14 (18.9%)	19 (19.6%)
Treatment-Emergent, Treatment-Related AE	15 (20.3%)	17 (17.5%)
Treatment-Emergent Severe Adverse Event	14 (18.9%)	19 (19.6%)
Treatment-Emergent SAE	12 (16.2%)	22 (22.7%)
Treatment-Emergent, Treatment-Related SAE	0	0
TEAE Leading to Discontinuation of Study Drug	0	1 (1.0%)
TEAE Leading to Death	1 (1.4%)	0

CONCLUSIONS:

In this OLE study of golodirsen or casimersen, once-weekly IV infusions at a dose of 30 mg/kg were generally well tolerated in male subjects between 7 and 23 years of age with genotypically confirmed DMD and a deletion mutation amenable to exon 53 or exon 45 skipping. The safety experience in this study was consistent with the known safety profiles of golodirsen and casimersen.

Date and Version of This Report:

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