1. SYNOPSIS

Name of Sponsor/Company: Sarepta Therapeutics, Inc.	
Name of Finished Product: vesleteplirsen (SRP-5051)	
Name of Active Ingredient: SRP-5051	
Title of Study: An Open-Label Extension Study for Patients with Duchenne Muscular Dystrophy Who Participated in Studies Of SRP-5051	
Principal Investigator: Study 5051-102 did not have a single principal investigator; see Note to File. **Investigators:** Refer to Appendix 16.1.4 for complete list of Investigators.	
Study center(s): The study was conducted at 8 sites in the US and 1 site in Canada. Patients were enrolled at 7 sites in the US and 1 site in Canada.	
Publications (reference): Section 15	
Studied period (years): Date first patient enrolled: 12 December 2018 Date last patient completed: 25 August 2021	**Phase of development:** 1/2
Objectives: *Primary:* To evaluate the AE profile of repeat Q4W administration of SRP-5051 *Secondary:* • To determine the PK of SRP-5051 following repeat Q4W administration • To evaluate additional safety and tolerability of repeat Q4W administration of SRP-5051	
[redacted]	

Methodology:

This Phase 1/2, multicenter, open-label, long-term extension (LTE) study evaluated patients who had completed other studies administering SRP-5051. The study planned to assess the safety, tolerability, and pharmacokinetics (PK) of SRP-5051 administered Q4W for approximately 144 weeks in patients with DMD who had deletion mutations amenable to exon 51-skipping treatment.

Patients in Study 5051-102 completed 3 study periods: Screening, Treatment and Observation, and Safety Follow-up.

Number of patients (planned and analyzed):
Planned: Up to 60 patients were planned to enroll in this LTE study upon completing a Phase 1 (ie, the completed Study 5051-101) or Phase 2 (eg, the ongoing Study 5051-201) study of SRP-5051, [redacted]

Analyzed: 15 patients were analyzed.
The Sponsor made the decision to terminate the study; the last patient last visit date was 25 August 2021. All participants from Study 5051-102 were made eligible to enroll in Study 5051-201 Part B.

Diagnosis and main criteria for inclusion:

The patient:

1. Had completed a study in which SRP-5051 was administered.
2. Had not subsequently received treatment with any investigational therapy for DMD.
3. If sexually active, agreed to use a male condom during such activity for the entire duration of the study and for 90 days after the last dose. The sexual partner must have also used a medically acceptable form of contraceptive during this time frame.
4. Was willing to provide informed consent or informed assent (if applicable) and had (a) parent(s) or legal guardian(s) who were willing to provide informed consent for the patient to participate in the study.
5. Was able to understand and comply with all the study requirements and, if under 18 years of age, had as (a) parent(s) or legal guardian(s) who was able to understand and comply with all the study requirements.

Test product, dose and mode of administration:
SRP-5051 injection; 100 mg/vial
SRP-5051 at a dose of 1.0, 2.0, 4.0, 6.0, 10.0, or 20.0 mg/kg was administered via IV infusion over 60 ± 5 minutes.

Duration of treatment:
Planned for up to 144 weeks.

Reference therapy, dose and mode of administration, batch number:
Not applicable

Criteria for evaluation:
Pharmacokinetics:
Plasma concentrations
Safety:
- Adverse events (including TEAEs, SAEs, AESIs, and clinical laboratory abnormalities)
- Vital signs
- Physical examinations
- Clinical laboratory tests
- Electrocardiograms

Statistical methods:
The Safety Set included all patients who received the study drug. The dose group was designated according to the actual dose level received. The PK Set included all patients who received the study drug and had evaluable PK data. The Serum Magnesium Set was defined as patients who have serum magnesium collected on or after 01 September 2020 (when systematic monitoring of hypomagnesemia in 5051-102 started).

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:
The maximum mean concentration in each dose group was observed at the end of infusion. The mean plasma concentration at the end of infusion increased with increasing dose. The mean plasma concentrations at the end of infusion increased from 7053.33 to 156333.33 for dose range of 1 to 20 mg/kg.

SAFETY RESULTS:

The safety results in Study 5051-102, designed as a long-term extension study to offer continued SRP-5051 dosing to DMD patients who had completed other SRP-5051 studies, provided safety data in 15 patients treated with doses of SRP-5051 of 1 mg/kg, 2 mg/kg, 4 mg/kg, 6 mg/kg, 10 mg/kg, and 20 mg/kg.

Notwithstanding the new detection of hypomagnesemia as a safety signal, SRP-5051 was well tolerated overall in patients with DMD amenable to exon 51 skipping, as supported by the following observations:

- Except for TEAEs leading to fatal outcomes (none of them related to SRP-5051), each of the other categories of TEAEs (related, severe, serious, leading to interruption or to discontinuation) occurred mostly with [redacted] patients in the highest dose level (20 mg/kg), in a dose dependent manner.
- The most frequent TEAE was hypomagnesemia, [redacted] Hypomagnesemia was accompanied by transient and moderate symptoms in a single patient. No cardiac effects were associated with hypomagnesemia. Mostly with magnesium supplementation, hypomagnesemia was reversible within a median of 26 days from the first identification.
- Based on the laboratory analyses, Grade 4 hypomagnesemia (not life-threatening) not related to SRP-5051 was reported [redacted] Grade 3 hypomagnesemia was reported [redacted] without clinical consequences. Other clinically meaningful electrolyte abnormalities consisted of Grade 3 hypokalemia.
- ECG findings and laboratory parameters (urinalysis, serum chemistry besides hypomagnesemia, and hematology) throughout the study consisted of either normal results or not clinically significant abnormalities that were not dose dependent. Transient renal tubular injury changes observed via urinalyses and urine biomarkers did not affect renal function parameters.

CONCLUSIONS:

SRP-5051 at doses between 1 and 20 mg/kg was overall tolerated in patients with DMD amenable to exon 51 skipping, with the new detection of hypomagnesemia as a safety signal. Hypomagnesemia was detected, manageable, and reversible without clinical consequences.

Following the identification of hypomagnesemia as a safety signal, all treatment in Study 5051-102 was voluntarily halted. While treatment was halted, the Sponsor made the decision to terminate the

study; the last patient last visit date was 25 August 2021. All participants from Study 5051-102 were made eligible to enroll in Study 5051-201 Part B.

In ongoing and future clinical studies, the Sponsor is currently adopting an intensified safety monitoring strategy and a comprehensive risk mitigation plan to minimize the risk of hypomagnesemia and transient renal tubular injury. [redacted]

With the adoption of these precautions, further development of SRP-5051 is warranted for the treatment of patients with DMD with genetic mutations amenable to exon 51-skipping therapy.

Date of the report:
23 August 2022