Eteplirsen (Exondys 51; Sarepta Therapeutics, Inc.**)**
FDA Approval Date: 9/19/2016

New Drug Review: Vyondys 53 (golodirsen). IPD Analytics. 2021.
Exondys 51 (eteplirsen) injection, for intravenous use [package insert]. Cambridge, MA. Sarepta Therapeutics, Inc. 2021.

Exondys 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Methods	**Study 1** ● N=12 ● Mean age ~9.4 years, mean 6MWT at baseline of 363 meters, and were on a stable dose of corticosteroids. ● 4 patients: 30 mg/kg q week, 4 patients: 50 mg/kg q week, 4 patients: placebo for 24 weeks. **Study 2** ● N=12, same patients from study 1 for an additional 4 years ● 6 patients 30 mg/kg q week, 6 patients 50 mg/kg q week. **Study 3** ● N=13 ● Mean age ~8.9 years and were on a stable dose of corticosteroids for at least 6 months. ● 30 mg/kg q week for 48 weeks.
Endpoints	Primary Endpoint - dystrophin production Secondary Endpoints - 6-minute walk test (6MWT)
Results	**Study 1** ● No difference in change in 6MWT **Study 2** ● Average dystrophin protein level after 180 weeks was 0.93% of the level in healthy adults. ● No evidence of clinical benefit. **Study 3** ● Pre-treatment dystrophin level = 1.16% $\pm$ 0.12% of the dystrophin levels in healthy adults and 0.44% $\pm$ 0.43% after 48 weeks of treatment ($p<0.05$). ● Median increase after 48 weeks was 0.1%.
Conclusion	The FDA concluded that this data based on skeletal muscle biopsy demonstrated an increase in dystrophin production and is reasonably likely to predict clinical benefit. Any clinical benefit, including improved motor function has not been established.

A study to compare safety and efficacy of a high dose of eteplirsen in Duchenne Muscular Dystrophy (DMD) patients (MIS51ON). Clinicaltrials.gov.

CONFIRMATORY TRIAL

Objectives	Evaluate the safety and efficacy of a high dose eteplirsen in patients with Duchenne Muscular Dystrophy with deletion mutations amenable to exon 51 skipping.
Methods	Part 1 is open-label, dose escalation, while part 2 is double-blind, dose finding and dose comparison; randomized

	Inclusion Criteria - 7 to 13 years old, male, established clinical diagnosis of DMD and an out-of-frame deletion mutation of the DMD gene amenable to exon 51 skipping, achieved a mean 6-minute walk test (6MWT) distance ≥ 300 and <450 meters, intact right and left biceps muscles or alternative upper arm muscle group, been on a stable dose or dose equivalent of oral corticosteroids for at least 12 weeks prior to randomization, stable pulmonary function (FVC ≥ 50% of predicted and no requirement for nocturnal ventilation). Exclusion Criteria - use of any pharmacologic treatment (besides corticosteroids) within 12 weeks prior to randomization, current or previous treatment with gene therapy or any other experimental treatment for DMD, previous treatment with Ezutromid in the last 1 week prior to first dose or Drisapersen in the last 36 weeks prior to first dose, major surgery within 3 months prior to randomization, presence of any other significant neuromuscular or genetic disease, presence of any known impairment of renal function and/or clinically significant illness, or has evidence of cardiomyopathy. Experimental Part 1: patients received high dose level 1 of eteplirsen once weekly for at least 4 weeks, followed by high dose level 2 of eteplirsen once weekly for at least 4 weeks. Active comparator Part 2: patients will receive eteplirsen 30 mg/kg once weekly for up to 144 weeks. Experimental Part 2: patients will receive high dose level 1 of eteplirsen once weekly before the selection of high dose occurs and then the selected high dose once weekly for up to 144 weeks. Experimental Part 2: patients will receive high dose level 2 of eteplirsen once weekly before the selection of high dose occurs and then the selected high dose once weekly for up to 144 weeks.
Endpoints	Primary Endpoint - ● Part 1 and 2 (dose finding): incidences of adverse events (AEs). ● Part 2 (dose finding): dystrophin expression in biopsied muscle tissue, pharmacokinetic (PK) plasma concentration, tissue concentration from biopsied muscle tissue. ● Part 2 (dose comparison): change from baseline in the North Star Ambulatory Assessment (NSAA) total score. Secondary Endpoints - ● Part 2 (dose comparison): total distance walked during 6-minute walk test (6MWT), time to complete walk/run (stairs and time to rise), annual rate in decline of forced vital capacity percent predicted (FVC %), time to loss of ambulation (LOA), skeletal muscle dystrophin expression, and incidence of adverse events (AEs).
Results	Interim results have not been released yet.
Conclusion	Study is estimated to be completed in 2026.