Casimersen (Amondys 45; Sarepta Therapeutics, Inc.)
FDA Approval Date: 02/25/2021

Golodirsen (Vyondys 53; Sarepta Therapeutics, Inc.)
FDA Approval Date: 12/12/2019

Study of SRP-4045 and SRP-4053 in Participants with Duchenne Muscular Dystrophy (DMD) (ESSENCE). Clinicaltrials.gov.
New Drug Review: Amondys 45 (casimersen). IPD Analytics. 2021.
New Drug Review: Vyondys 53 (golodirsen). IPD Analytics. 2021.
Center For Drug Evaluation and Research Application (211970Orig1s000) Summary Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000SumR.pdf.

Objectives	Evaluate the efficacy and safety of SRP-4045 (Amondys 45) and SRP-4053 (Vyondys 53) compared to placebo in participants with DMD with out-of-frame deletion mutations amenable to skipping exon 45 and exon 52, respectively.
Methods	Double-blind, placebo-controlled, multi-center, open-label extension, randomized trial. Inclusion Criteria - 6 to 13 years, male, genetically confirmed DMD with genetic deletion amenable to exon 45 or 53 skipping, stable dose of oral corticosteroids for at least 24 weeks prior to week 1 and the dose is expected to remain constant throughout the study, intact right and left biceps or 2 alternative upper muscle groups, mean 6MWT ≥300 meters and ≤450 meters, and stable pulmonary function (FVC ≥ 50% predicted). Exclusion Criteria - treatment with gene therapy at any time, previous treatment with SMT C1100 within1 week prior to week 1 and previous treatment with PRO045, PRO053, or PRO051 within 24 weeks prior to week 1, current or previous treatment with any other experimental treatment within 12 weeks prior to week 1, major surgery within 3 months prior to week 1, or presence of other clinically significant illness. Patients were randomized (2:1 allocation) to receive once weekly (IV) infusions of 30 mg/kg SRP-4045 or 30 mg/kg SRP-4053 or placebo for up to 96 weeks. This will be followed by an open-label extension period in which all participants will receive open-label active treatment for 48 weeks.
Endpoints	Primary Endpoint - Change in 6 Minute Walk Test (6MWT) from Baseline (to week 48) Secondary Endpoints - Total distance walked during 6MWT at week 144, Dystrophin Protein levels (western blot) at weeks 48 or 96, dystrophin intensity levels (immunohistochemistry), participants ability to rise independently from the floor (North Star Ambulatory Assessment), time to loss of ambulation (LOA), NSAA total score at week 96 and 144, and forced vital capacity percent (FVC%) predicted at week 96 and 144. Safety - adverse events (AE's), laboratory tests, electrocardiograms (ECGs), echocardiograms (ECGs), vital signs and physical examinations.
Results	**Amondys 45 - Interim results** Baseline Characteristics ● 43 evaluable male patients with DMD who have confirmed DMD gene amenable to exon 45 skipping (n = 27 in Amondys 45, n = 16 in placebo group) ● Patients who provided muscle biopsy data had a median age of 9 year and 85% were white.

Efficacy

Dystrophin Levels (% of normal) at Baseline and at Week 48 from Muscle Biopsy		
	Placebo (n=16)	Amondys 45 (n=27)
Baseline Mean (SD)	0.54 (0.79)	0.93 (1.67)
Week 48 Mean (SD)	0.76 (1.15)	1.74 (1.97)
Change from Baseline Mean (SD)	0.22 (0.49) p = 0.09	0.81 (0.70) p <0.001
Between-group Mean Difference	0.59, p= 0.004	

- Patients who received Amondys 45 showed a significantly greater increase in dystrophin protein levels from baseline to Week 48 compared to those who received placebo.

Safety

- Kidney toxicity was not observed in the Amondys 45 clinical studies, but it was observed in nonclinical studies. Kidney toxicity, including potentially fatal glomerulonephritis have been observed after administration of some antisense oligonucleotides.
- Common side effects
    - Upper respiratory tract infection, cough, fever, headache, joint pain, and throat pain.
- Other adverse effects (5%<10%)
    - Ear pain, nausea, ear infection, post traumatic pain, dizziness, and light-headedness.

Vyondys 53

Baseline Characteristics

- n=25, no randomized control group
- Median age ~ 8 years

Efficacy

- Patients who received Vyondys 53 demonstrated a mean increase in truncated dystrophin quantification by western blot relative dystrophin levels from 0.10% of normal at baseline to 1.02% after 48-59 weeks, with a mean change of 0.92% (p<0.001).
- Median change from baseline was 0.88%.

Safety

- Common side effects
    - Headache, pyrexia, and gastrointestinal symptoms.

Conclusion

Amondys 45 demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in patients with DMD who have confirmed mutation of the dystrophin gene amenable to exon 45 skipping. A clinical benefit, including improved motor function has not been established.

Vyondys 53 observed an increase in dystrophin in skeletal muscle in patients with DMD who have confirmed mutation of the dystrophin gene amenable to exon 53 skipping. It is unknown whether that increase is clinically significant or if it results in an improvement in functional outcome.

This study is ongoing, and it remains blinded to collect additional safety and efficacy data. It is expected to conclude in 2024 as the confirmatory trial for Amondys 45 and Vyondys 53.