Amondys 45™ (casimersen) – New orphan drug approval

- On February 25, 2021, the FDA announced the approval of Sarepta's Amondys 45 (casimersen), for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping.
    - This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Amondys 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.
- DMD is a rare genetic disorder characterized by progressive muscle deterioration and weakness. DMD is caused by mutations in the *DMD* gene that results in an absence of dystrophin, a protein found in muscle fiber. The first symptoms are usually seen between three and five years of age and worsen over time.
    - DMD occurs in approximately one out of every 3,600 male infants worldwide; in rare cases, it can affect females.
    - Approximately 8% of patients with DMD have a mutation that is amenable to exon 45 skipping.
- Amondys 45 is designed to bind to exon 45 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. Exon 45 skipping is intended to allow for production of an internally truncated dystrophin protein in patients.
    - This is the first FDA-approved targeted treatment for patients with this type of mutation.
- The efficacy of Amondys 45 was evaluated in an ongoing, double-blind, placebo-controlled study in male DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. Patients received Amondys 45 or placebo. Interim efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, ie, % of normal) at week 48. Interim results are available from 43 evaluable patients who had a muscle biopsy at week 48.

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)	0.81 (0.70)
p-value change from baseline	0.09	< 0.001
Between group mean difference	0.59	
p-value between groups	p = 0.004	

- The FDA concluded that the data submitted by Sarepta demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in patients with DMD. A clinical benefit of the drug, including improved motor function, has not been established. In making this decision,

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the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease, and the lack of available therapy.

  - A placebo-controlled confirmatory trial (ESSENSE) to support the Amondys 45 approval is ongoing and expected to conclude in 2024.

- A warning and precaution for Amondys 45 is renal toxicity.

- The most common adverse reactions (incidence > 20% and ≥ 5% higher than placebo) with Amondys 45 use were upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain.

- The recommended dosage of Amondys 45 is 30 mg/kg administered once weekly as a 35 to 60-minute intravenous infusion.

  - Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio (UPCR) should be measured before starting therapy. Measurement of glomerular filtration rate should be considered prior to initiation of Amondys 45. Monitoring for kidney toxicity during treatment is recommended. Obtain the urine sample prior to infusion of Amondys 45 or at least 48 hours after infusion.

- Sarepta plans to launch Amondys 45 immediately. Amondys 45 will be available as a 100 mg/2 mL single-dose vial.