Safety, Tolerability, And Pharmacokinetics of Casimersen In Patients With Duchenne Muscular Dystrophy

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Abstract: Duchenne muscular dystrophy (DMD) is caused by mutations in the DMD gene resulting in the absence of dystrophin. Casimersen is a phosphorodiamidate morpholino oligomer designed to bypass frameshift DMD mutations and produce internally truncated, yet functional, dystrophin protein in patients amenable to exon 45 skipping. Our primary study objective was to evaluate safety and tolerability of casimersen; the secondary objective was to characterize the plasma pharmacokinetics.

INRODUCTION: - In DMD, frameshift or nonsense mutations in the DMD gene prevent the production of functional dystrophin, resulting in progressive, life-shortening disease. Management of DMD has involved a multidisciplinary approach to treat symptoms and modify disease progression; however, there is no cure for the disease [4] Antisense therapy using chemically engineered antisense oligonucleotides (ASOs) complementary to specific mRNA is a prominent method for treating neuromuscular disorders like Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) [5,6]. ASOs can be used for RNA degradation, suppression of translation, or modulation of splicing [6]. Standard-of-care therapy for DMD includes the long-term use of glucocorticosteroids [7] One approach that has been investigated in the development of therapies for DMD has been to target restoration of the production of functional dystrophin, including using exon skipping. [4,8,9]. The approval, granted under the US FDA's Accelerated Approval Program, was based on an observed increase in dystrophin production in skeletal muscle in patients treated with casimersen [10]. Dystrophic muscle is not able to recover enough to overcome this loss, gradually leading to fibrotic remodelling and the replacement of muscle with fat [11] In addition to muscle weakness and loss of ambulation, DMD patients develop respiratory and cardiac weakness, requiring palliative care [12] An increase in dystrophin production is considered reasonably likely to predict clinical benefit; however, clinical benefit, including improved motor function, is yet to be established [13]. Continued approval of casimersen in the treatment of DMD may be contingent on verification of a clinical benefit in confirmatory trials. [10]

Features and properties of casimersen

Alternative names	Amondys 45; SRP-4045
Class	Antisense oligonucleotides; phosphorodiamidate morpholino oligomers
Mechanism of Action	Binds to exon 45 of dystrophin pre-mRNA; restores the open-reading frame (by skipping exon 45) resulting in the production of an internally truncated but functional dystrophin protein
Route of Administration	Intravenous infusion
Pharmacodynamics	Increases dystrophin levels in muscle tissues of patients with Duchenne muscular dystrophy
Pharmacokinetics	Exposure is approximately dose proportional over dose range of 4–30 mg/kg; little to no accumulation with once-weekly dosing; elimination half-life = 3.5 h; excretion is mostly (> 90%) via the urine as unchanged drug
Most common Adverse Effect	Upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain
WHO ATC code	M09A-X (Other drugs for disorders of the musculo-skeletal system)
ATC codes	
EphMRA ATC codes	M5X (All other musculoskeletal products

Table. 1

Key clinical trials of casimersen in Duchenne muscular dystrophy

Drug(s)	Phase	Status	Locations (S)	Sponsor (Collaborator)	Identifer (S)
Casimersen, golodirsen, placebo	III	Ongoing/recruiting	Multinational	Sarepta Therapeutics	NCT02500381; ESSENCE
Golodirsen, Casimersen	III	Enrolling by invitation	Multinational	Sarepta Therapeutics	NCT03532542
Casimersen, eteplirsen, golodirsen	II	Enrolling by invitation	USA	Kevin Flanigan (Sarepta Kevin Flanigan (Sarepta)	NCT04179409; SRPT-Dup US-001

Placebo, Casimersen	I /II	Completed	USA	Sarepta Therapeutics	NCT02530905

Table. 2

DMD therapies examined

Manufacturer	Type	Name	Technology	FDA regulatory status
Sarepta therapeutics	Gene	SRP-9001	AAVrh74	Phase III
Pfizer	Gene	PF-06939926	AAV9	Phase III
Solid biosciences	Gene	SGT-001	AAV9	Phase I/IIa
Sarepta therapeutics	Exon-skipping	Eteplirsen	PMO	Approved
Sarepta therapeutics	Exon-skipping	SRP-5051	PMO	Phase II
Sarepta therapeutics	Exon-skipping	Golodirsen	PMO	Approved
Sarepta therapeutics	Exon-skipping	Casimersen	PMO	Approved
Nippon Shinyaku	Exon-skipping	NS-089/NCNP-02	PMO	Phase I/II
Nippon Shinyaku	Exon-skipping	Viltolarsen	PMO	Approved

Table .3

Pharmacodynamics: - Casimersen is designed to bind to exon 45 of the DMD gene pre-mRNA resulting in exclusion (or skipping) of this exon during mRNA processing [10]. In patients with genetic mutations that are amenable to exon 45 skipping, the action of casimersen is intended to allow for production of an internally truncated but functional dystrophin protein that can compensate for the lack of functional dystrophin in patients with DMD [10]

Pharmacokinetics: - Casimersen exposure is approximately dose proportional over the tested dose range of 4–30 mg/kg [14] Following a single IV dose, peak plasma concentrations are reached at the end of the infusion [10] Little to no accumulation of casimersen is observed with once-weekly dosing [14]

Current Status: - Casimersen received its first approval on 25 February 2021, in the USA (under the US FDA Accelerated Approval Program), for the treatment of DMD in confirmed mutation of the DMD gene that is amenable to exon 45 skipping [ ]. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

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