Cytokinetics

ABOUT

SMA

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a genetic neuromuscular disease that affects the part of the nervous system that controls voluntary muscle movement. It is caused by a mutation of the survival motor neuron 1 (SMN1). In a healthy person, this gene produces a protein that is essential to the function of the nerves that control muscles. Without it, those nerve cells cannot function properly and eventually die, leading to debilitating muscle function and often fatal muscle weakness.

There are four primary types of SMA based on age of onset and the manifestation of the disease:[1,2,3]

- **Type 1**, also known as Werdnig-Hoffmann disease, is the most common and most severe form of SMA, and the leading genetic cause of death for infants.
- **Type 2** is diagnosed in children between the ages of 6 months and 2 years. The symptoms are less severe than Type I but become more noticeable in older children.
- **Type 3**, also known as Kugelberg-Welander disease or juvenile SMA, is the mildest form of childhood SMA and typically does not shorten life expectancy.
- **Type 4** is very rare, usually appearing after age 35 with mild to moderate symptoms.

PREVALENCE OF SMA

SMA accounts for approximately 1 in 11,000 babies, and about 1 in every 50 Americans is a genetic carrier. Around sixty percent of all cases of SMA are Type 1. SMA can affect any race or gender.[1,2,3]

SYMPTOMS AND PROGNOSIS OF SMA

Symptoms and life expectancy vary from mild to severe, depending on the type of SMA. The most severe symptoms include severely reduced muscle tone and impaired breathing. The long-term prognosis for patients varies depending on the type of SMA and the degree of respiratory impairment.[4]

DIAGNOSING SMA

A For 95% of SMA Types 1, 2 and 3 a diagnosis of SMA can be confirmed by a blood test designed to identify genetic defects in the SMN1 gene. Other diagnostic tests may include electromyography, nerve conduction velocity studies, muscle biopsy and other lab tests.[3]

TREATING SMA

There is no cure to SMA. Currently there is one FDA-approved treatment for SMA, Spinraza® (*nusinersen*), an antisense oligonucleotide that targets SMN2, often referred to as the SMA "backup gene," causing it to make more complete SMN protein. In addition, treatment consists of managing symptoms and preventing complications, which may include physical therapy, muscle relaxants, heat application to relieve muscle pain and assistive devices such as supports, braces, orthotics or wheelchairs. Some individuals require additional therapy for speech, chewing and swallowing, and may require a feeding tube or assisted ventilation. Proper nutrition is also essential to maintaining weight and strength.[3]

ABOUT *RELDESEMTIV*

In collaboration with Astellas, Cytokinetics is developing *reldesemtiv*, a next-generation fast skeletal muscle troponin activator (FSTA) as a potential treatment for people living with SMA and amyotrophic lateral sclerosis (ALS). *Reldesemtiv* slows

SMA TYPE	SEVERITY	PERCENT OF PREVALENT POPULATION	AGE OF ONSET	SYMPTOMS	HIGHEST FUNCTION	LIFE EXPECTANCY
Type 1 (Infantile)	Severe	~10%	0-6 months	Very weak; difficulty breathing, sucking and swallowing	Unable to sit	<2 years
Type 2 (Intermediate)	Intermediate	~34%	6-18 months	Respiratory complications are common	Sits but unable to stand or walk independently	>2 years
Type 3 (Juvenile)	Mild	~45%	>18 months	Stands and walks	Can stand and walk, but with mobility issues later in life	Near normal
Type 4 (Adult)	Mildest	~11%	Adult onset	Mild motor impairment	Able to walk, with gradual weakness and mobility issues later in life	Normal

the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers, which sensitizes the sarcomere to calcium, leading to an increase in skeletal muscle contractility. It has been granted orphan drug designation by the U.S. Food and Drug Administration (FDA) for the potential treatment of SMA.

Reldesemtiv has been the subject of five Phase 1 clinical trials in healthy volunteers, which evaluated safety, tolerability, bioavailability, pharmacokinetics, and pharmacodynamics.

Reldesemtiv was the subject of a Phase 2, hypothesis-generating clinical study in SMA which showed increases in the distance patients could walk in six minutes, a validated measure of endurance consistent with the mechanism of action in patients treated with *reldesemtiv*.

Reldesemtiv was also the subject of FORTITUDE-ALS, a Phase 2 clinical trial in ALS. The trial did not achieve statistical significance for its primary endpoint of change from baseline in slow vital capacity after 12 weeks of dosing, but all patients on all doses of *reldesemtiv* declined less than patients on placebo for SVC and ALSFRS-R with clinically meaningful differences emerging over time.

Cytokinetics, Inc.
280 East Grand Avenue
South San Francisco, CA 94080
650 624 3000
cytokinetics.com

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