NINDS Contributions to Approved Therapies

NINDS invests in and conducts research across the spectrum of neuroscience and neurology research, from basic studies on fundamental biological mechanisms, to clinical trials to test new treatments in patients. Here, we describe the path leading to the development and approval of one therapy for a neurological disorder, and we highlight contributions enabled by NINDS and NIH support.

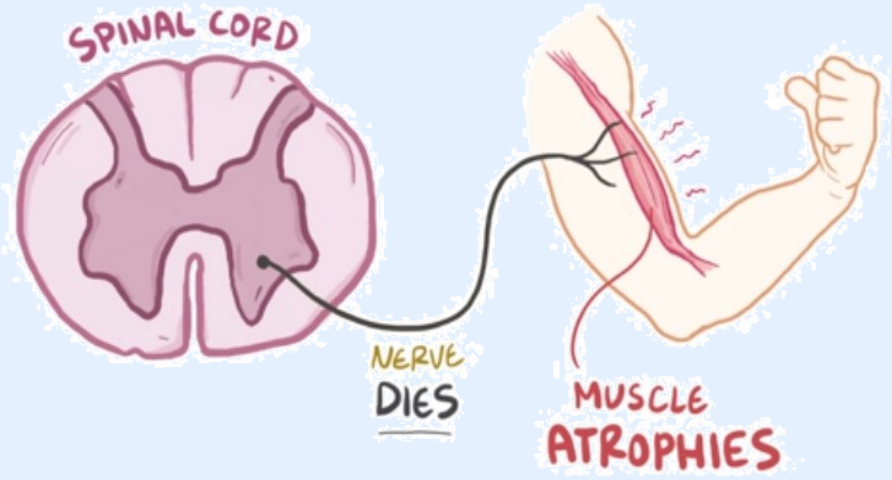
Nusinersen (Spinraza®) for Spinal Muscular Atrophy (SMA)

Overview

Spinal muscular atrophy (SMA) refers to a group of inherited neurological disorders that begin in infancy or childhood and lead to degeneration of spinal motor neurons, the neurons that control skeletal muscles. This degeneration results in weakness, muscle wasting, and in the most severe cases, paralysis and death before two years of age. SMA affects approximately 1 in 10,000 newborns and is a leading genetic cause of death in infants and toddlers. Nusinersen, marketed in the U.S. as Spinraza® (Biogen), is the first therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of SMA.

Nusinersen is an antisense oligonucleotide (ASO) therapy, in which short sequences of nucleotides (the letters in the genetic code) are designed to bind to specific regions of a gene and modify its expression. SMA results from mutations in the gene *SMN1*, which encodes a protein (Survival Motor Neuron, or SMN) important for motor neuron survival. Although a nearly identical gene (*SMN2*) serves as a back-up for *SMN1*, it produces a shortened protein that cannot fully compensate for loss of the protein normally produced from *SMN1*. Nusinersen targets this back-up gene to promote the production of full-length SMN protein.

NINDS and other NIH institutes contributed to nusinersen's development, through support for research that narrowed in on the disease's genetic cause and mechanisms, identified a treatment strategy, and facilitated later stage translational and clinical research. Other sources in the U.S. and internationally also played important roles, including Cure SMA, the Muscular Dystrophy Association, and the SMA Foundation. Beyond its impact for SMA, nusinersen's success signals the potential for ASO therapies to correct gene defects in other neurological disorders.



Excerpt from "Spinal muscular atrophy" by Open.Osmosis.org licensed under CC BY-SA 4.0

Learn more at: https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies

Nusinersen (Spinraza®)—SMA Development Timeline

1995 — Researchers identify the gene (*SMN1*) associated with SMA, as well as a nearly identical gene (*SMN2*). They find that RNA transcripts from *SMN2* lack one protein-coding segment (exon 7).

1997 — Studies show that *SMN2* copy number and SMN protein levels correlate inversely with disease severity. NIH

1999 — The first clinical trial of nusinersen (Spinraza®) begins.

2000-2009 — Researchers determine the protein produced from truncated *SMN2* transcripts is unstable, explaining why *SMN2* can only partially offset mutations in SMN1. NIH NINDS

2001-2003 — Researchers report that antisense oligonucleotides (ASOs) targeting *SMN2* can promote translation of full-length SMN protein. NIH

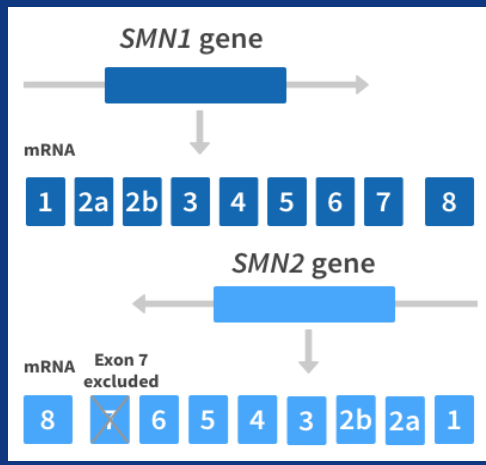
2006 — Researchers identify a regulatory element in the *SMN2* gene that will become the specific target of nusinersen. NIH NINDS

2008-2010 — Researchers first describe the ASO that will become nusinersen and demonstrate successful treatment in SMA mouse models. NIH

2011

2016

- Phase 3 clinical trials testing nusinersen in infants and children with SMA show that treatment significantly improves motor function. Ongoing studies, including one treating infants prior to symptom onset, add to evidence of nusinersen's disease-modifying effects.
- FDA approves nusinersen (Spinraza®) for the treatment of SMA.



A single nucleotide difference between the *SMN1* and *SMN2* genes leads to exon 7 skipping. NIH NINDS