Spinal Muscular Atrophy (SMA)

Novartis and AveXis combine, aiming to transform the care of SMA, the #1 genetic cause of infant mortality[1]

Novartis

Novartis has completed the acquisition of the clinical-stage gene therapy company AveXis, Inc.

- The acquisition accelerates the Novartis strategy to pursue high-efficacy, first-in-class therapies and to deliver transformative innovation in areas of high unmet medical need.
- It provides another gene therapy platform, in addition to our CAR-T platform for cancer, and broadens our leadership in neuroscience.
- Together, we aim to advance a growing pipeline of gene therapies across therapeutic areas, including other SMA types, cancer, and blindness.

AveXis, Inc.

AveXis, headquartered in Bannockburn, Illinois, is a clinical-stage gene therapy company-dedicated to developing and commercializing novel treatments for patients and families affected by rare and life-threatening neurological genetic diseases.

- The lead AveXis product candidate, **AVXS-101**, has potential to be the first-ever one-time gene replacement therapy for spinal muscular atrophy (SMA), a disease which results in early death or lifelong disability.[1]
- The company has established a fully-operational, state-of-the-art manufacturing facility to support current and future commercial demand.

> We are delighted to add the AveXis leading gene therapy technology to our company and to welcome our AveXis colleagues to Novartis. Together, we now have the potential to bring to children the first one-time gene- based treatment for the devastating disease, spinal muscular atrophy
>
> **– Vas Narasimhan, CEO Novartis**

What is Spinal Muscular Atrophy (SMA)?

SMA is an inherited neurodegenerative disease caused by a defect in a single gene, the survival motor neuron (*SMN1*). It leads to a loss of motor neurons, resulting in progressive muscle weakness and paralysis.[1]

#1 **Genetic cause of infant death.[1]**

<2 **Not many with SMA Type 1 survive beyond 2 years.[1]**

1/10K **1 in 10,000 live births are affected by all types of SMA.[2]**

SMA Type 1 typically presents within the first 6 months of life and those affected[1]
- never sit without support
- have difficulty breathing and swallowing
- never crawl or walk

90% **More than 90% will die or need permanent ventilation support by the age of 2.[3]**

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The genetics behind SMA

Human DNA has about 20,000 genes. SMA is caused by a mutation in the *SMN1* gene, which prevents the body from making enough SMN protein. Without sufficient SMN protein, nerve cells die. The result: a debilitating, and often fatal, muscle weakness called SMA.[1]

Gene therapy is an experimental technique that replaces the defective genes that are responsible for disease development and encode a therapeutic protein necessary for normal cellular function.

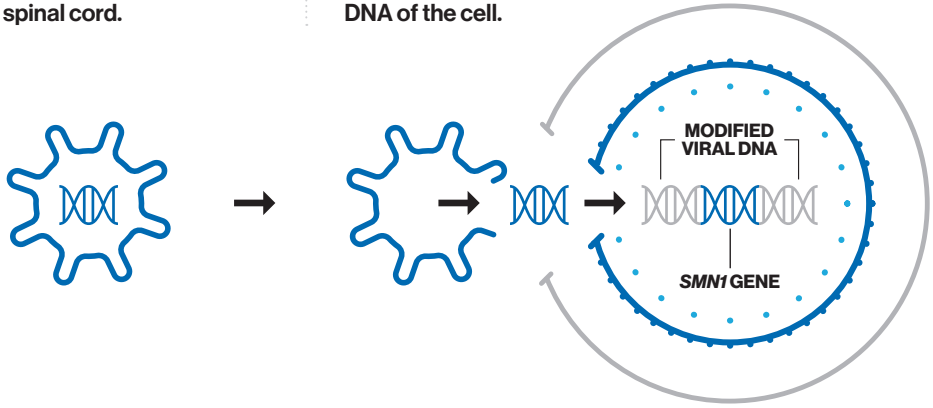
How does it work?

The major steps of gene therapy are[4,5]

Step 1
A modified noninfectious and nonpathogenic adeno-associated Virus is administered to the patient either intravenously or into the spinal cord.

Step 2
The virus enters neurons and forms a DNA satelite called an episome that is delivered into the nucleus and does not integrate into the normal DNA of the cell.

Step 3
The episome is transcribed and translated to produce the missing *SMN1* protein that is required for the health and survival of the neurons.



Looking ahead

AveXis has expanded its clinical research to include additional types of SMA and other novel potential gene therapy treatment approaches.

VISION	ESTABLISH →	EXPAND →	BUILD →
Leader in rare and life-threatening neurological genetic diseases	Foundational presence in SMA Type 1	Development of AVXS-101 into SMA Type 2	Pipeline of gene therapy treatments

Stressing the importance of the acquisition, Paul Hudson, CEO, Novartis Pharmaceuticals, said,

Novartis and AveXis bring truly complementary capabilities behind a shared purpose: transforming the care of patients with life-threatening neurological genetic diseases...

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AveXis has built a team with exceptional depth of expertise and experience, a clinically proven gene delivery platform, manufacturing and R&D capabilities, while Novartis has been for 70 years a leader in Neuroscience, building on a global footprint and its extensive experience in bringing transformational medicines to the clinic stage.

– Paul Hudson, CEO, Novartis Pharmaceuticals

In addition to SMA, AveXis is also exploring novel gene therapy treatment approaches for Rett syndrome and a genetic form of amyotrophic lateral sclerosis (ALS) caused by mutations in the superoxide dismutase 1 (*SOD1*) gene.

RETT SYNDROME (RTT)

Rare, neurodevelopmental disorder predominantly affecting girls, characterized by slowed growth, loss of normal movement and coordination, and loss of communication skills.[6]

Caused by an X-linked dominant mutation in the **methyl CpG binding protein 2 (*MECP2*) gene**, which results in problems with MECP2 protein production **critical for brain development**[6]

1 in 10,000-15,000 girls affected[6]

Onset of signs and symptoms begin between **6-18 months of age**[6]

RTT typically results in **significant disability** that can include autistic-like behaviors, breathing irregularities, feeding and swallowing difficulties, growth retardation, and seizures.[6]

SOD1 AMYOTROPHIC LATERAL SCLEROSIS (ALS)

ALS (Lou Gehrig's Disease) is a progressive disease leading to significant disability, including muscle weakness, that results in loss of the ability to speak, eat, move, and eventually breathe.[9] In most cases the cause of ALS is not known, but in about 5%-10% of cases, a genetic cause can be identified. One of these causes is a mutation in *SOD1*.

Caused by **mutations in the gene that produces the copper zinc superoxide dismutase 1** (*SOD1*) enzyme.[7]

40-70 years

Onset usually occurs in people between **40 and 70 years of age** with a median age of diagnosis of 55.[8,9]

Genetic ALS affects **1,000-2,000 people in the U.S.**, 12%–20% caused by mutations in *SOD1*.[7]

3-5 years

Typically results in death within 3-5 years of diagnosis.[7,9]

1. Farrar M., et al. Annals of Neurology. Emerging Therapies and Challenges in Spinal Muscular Atrophy. December 2016. 2. National Organization for Rare Disorders (NORD). Spinal Muscular Atrophy. http://rarediseases.org/rare-diseases/spinal-muscular-atrophy/ Accessed March 7, 2018. 3. Darras B.T., et al. Spinal Muscular Atrophy. Chapter 25 - Natural History of Spinal Muscular Atrophy. October 2016. 4. Global Genes. A Guide to Gene Therapy. https://globalgenes.org/wp-content/uploads/2016/03/Guide-to-Gene Therapy_DIGITAL_spread-1.pdf Accessed April 19, 2018. 5. NIH. How does gene therapy work? https://ghr.nlm.nih.gov/primer/therapy/procedures Accessed April 19, 2018. 6. National Institute of Neurological Disorders and Stroke. Rett Syndrome Fact Sheet. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Rett-Syndrome-Fact-Sheet. Accessed April 9, 2018. 7. National Institute of Neurological Disorders and Stroke. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/ Amyotrophic-Lateral-Sclerosis-ALS- Fact-Sheet. Accessed April 25, 2018. 8. ALS Association. Facts You Should Know. http://www.alsa.org/about-als/facts-you-should-know.html. Accessed April 25, 2018. 9. Chen S., et al. Molecular Neurodegeneration. Genetics of amyotrophic lateral sclerosis: an update. August 2013.

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