

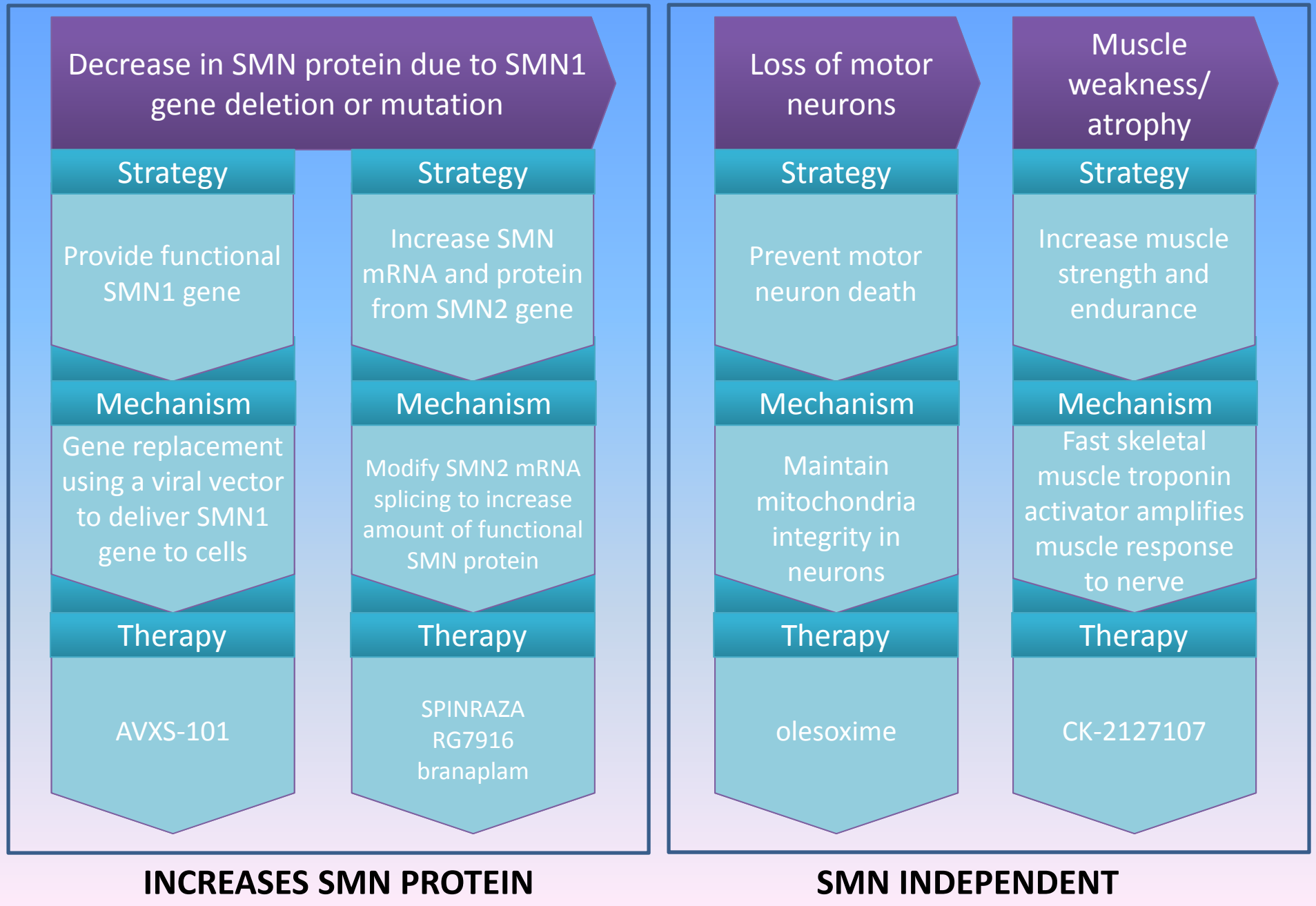
SMA Therapeutics: A Comparative Overview of Drugs Approved and in Development







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Targets for Therapeutic Intervention in SMA



	 AVXS-101	 SPINRAZA® (nusinersen)	 branaplam	 RG7916	 olesoxime	 CK-2127107
Mechanism	Increases SMN			SMN Independent		
Strategy	SMN Gene Replacement	SMN2 Splicing Modifier		Neuroprotectant	Muscle Activator	
Drug Type	Gene Therapy	ASO	Small Molecule			
Delivery Method	IV	Intrathecal	Oral			
Dosing	One Time	3 Loading Doses Then Once Every 4 Months	Once Weekly	Once Daily		Twice Daily
Body Distribution	Systemic	CNS Only	Systemic			
Current Target Population	Type I	Approved All Types	Type I	Type I-III	Type II-III	Type II-IV

Drug	Clinical Safety Profile
AVXS-101 (AveXis)	Results from a Phase 1 study in SMA Type I patients demonstrate that AVXS-101 appears to be well-tolerated, with a favorable safety profile ¹ .
SPINRAZA (Biogen)	SPINRAZA demonstrated a favorable safety profile in Phase 1-3 clinical trials ^{2,3} . For additional safety information please see SRINRAZA prescribing information ⁴ .
RG7916 (Roche)	Clinical studies in healthy volunteers and SMA patients demonstrated that RG7916 was safe and well-tolerated at all doses studied ^{5,6} .
branaplam (Novartis)	A Phase 1/2 study in Type I SMA patients is currently underway that tests the safety of branaplam (LMI070) ⁷ .
olesoxime (Roche)	In a Phase 2 clinical trial in Type 2 and non-ambulatory Type 3 SMA patients, olesoxime was found to be safe at the doses studied for the duration of the trial ⁸ .
CK-2127107 (Cytokinetics)	Five Phase 1 studies of CK-2127107 have been completed and there were no safety concerns based on data from exposure in healthy volunteers ⁹ .

Drug	Patient Population and Developmental Status
AVXS-101 (AveXis)	Phase 1 study in Type I patients is ongoing ¹⁰ ; plans to initiate a Phase 1 study via intrathecal delivery in Type II patients and a pivotal trial in Type I patients via intravenous delivery ¹ . Some patients may not be eligible for gene transfer therapy due to preexisting antibodies for the AAV9 virus ^{10,11,12} .
SPINRAZA (Biogen)	Approved for all SMA Type patients in U.S., E.U., Japan and Canada following a sham-controlled trial. Expanded access program for Type I patients is available ^{13,14,15} .
RG7916 (Roche)	Currently being tested in Phase 2 trials in patients with Type I, II, III ¹⁶ .
branaplam (Novartis)	Currently being tested in Phase 1/2 trial in Type I patients ⁷ .
olesoxime (Roche)	Phase 2 trial in Type II and III patients was completed ⁸ .
CK-2127107 (Cytokinetics)	Currently being tested in Phase 2 trial in Type II, III, IV patients ¹⁷ .

Glossary

SMN Upregulating

Drug acts through a mechanism to increase SMN protein levels. SMA is caused by the reduced levels of SMN protein.

SMN Independent

Drug acts through a mechanism that does not increase SMN protein levels.

SMN Gene Replacement

AXVS-101 uses a non-pathogenic adeno-associated virus (AAV9) containing the SMN1 transgene¹⁸. The virus is designed to deliver the gene to cells and provides constitutive, long-term SMN expression¹⁹.

SMN2 Splicing Modifier

SPINRAZA, RG7916, and branaplam all modulate the splicing of SMN2 RNA to increase the inclusion of exon 7 and results in an increase in the amount of functional SMN protein produced from the SMN2 transcript^{20,21,22,23}.

Neuroprotectant

Neuroprotectants protect against neuronal injury or degradation. Olexosime is a neuroprotectant. Its mechanism of action is not fully understood but it likely acts on mitochondrial proteins by preventing excessive permeability of the mitochondrial membrane under stress conditions^{8,24}. Olesoxime does not upregulate SMN levels.

Glossary

Muscle Activator

CK-2127107 is a fast skeletal muscle troponin activator (FSTA) that amplifies the response of certain muscle fibers in response to motor neuron input²⁵. CK-2127107 does not upregulate SMN levels.

IV

Intravenous delivery is a route of administration of drugs through a vein.

Intrathecal

Intrathecal administration is a route of administration for drugs into the cerebrospinal fluid that surrounds spinal cord and brain via a lumbar puncture performed in the lower back. It may result in side effects such as headache, back pain, and transient or persistent cerebrospinal fluid leakage. In some cases, scoliosis could hinder the success of intrathecal delivery and may require special imaging during the procedure²⁶. Intravenous (IV), inhaled, or local anesthesia/sedation is routinely used for lumbar punctures, and the administration is performed in a hospital or clinic setting. ASOs have difficulty crossing the blood-brain barrier into the central nervous system (CNS) where motor neurons reside^{27,28}.

Oral

Oral delivery is a route of administration where a drug is taken through the mouth.

Gene Therapy

Gene therapy is an experimental technique to treat or prevent disease by inserting a gene into a patient's cells²⁹.

Glossary

ASO

An antisense oligonucleotide is a short nucleic acid polymer (usually of 25 nucleotides or fewer) that binds to the specific RNA sequence of a gene target. ASOs are produced by chemical synthesis.

Small Molecule

A small molecule is a low molecular weight organic compound that can bind to and alter the activity or function of proteins, DNA, or RNA. Most therapeutic drugs are small molecules. Small molecules are produced by chemical synthesis.

Systemic

Systemic means the drug is distributed throughout the entire body, including the CNS, rather than restricted to a single organ/tissue. RG7916, branaplam, olexosime, AVXS-101, and CK-2127107 have systemic distribution^{1,5,7,8,17,23,30}.

CNS Only

CNS only means that the drug is mainly distributed in the central nervous system (brain and spinal cord). Distribution of SPINRAZA is mainly restricted to CNS.

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