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

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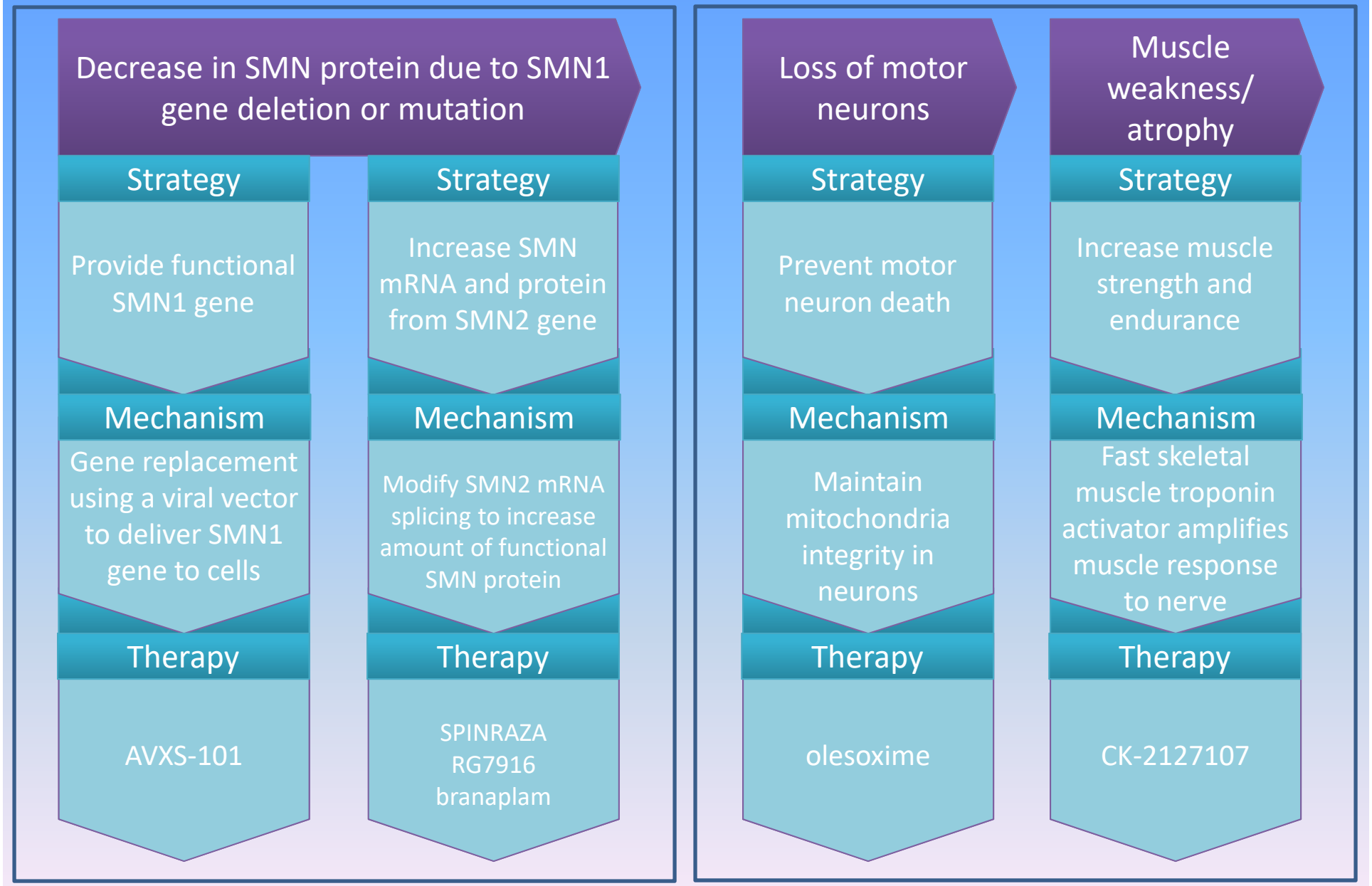
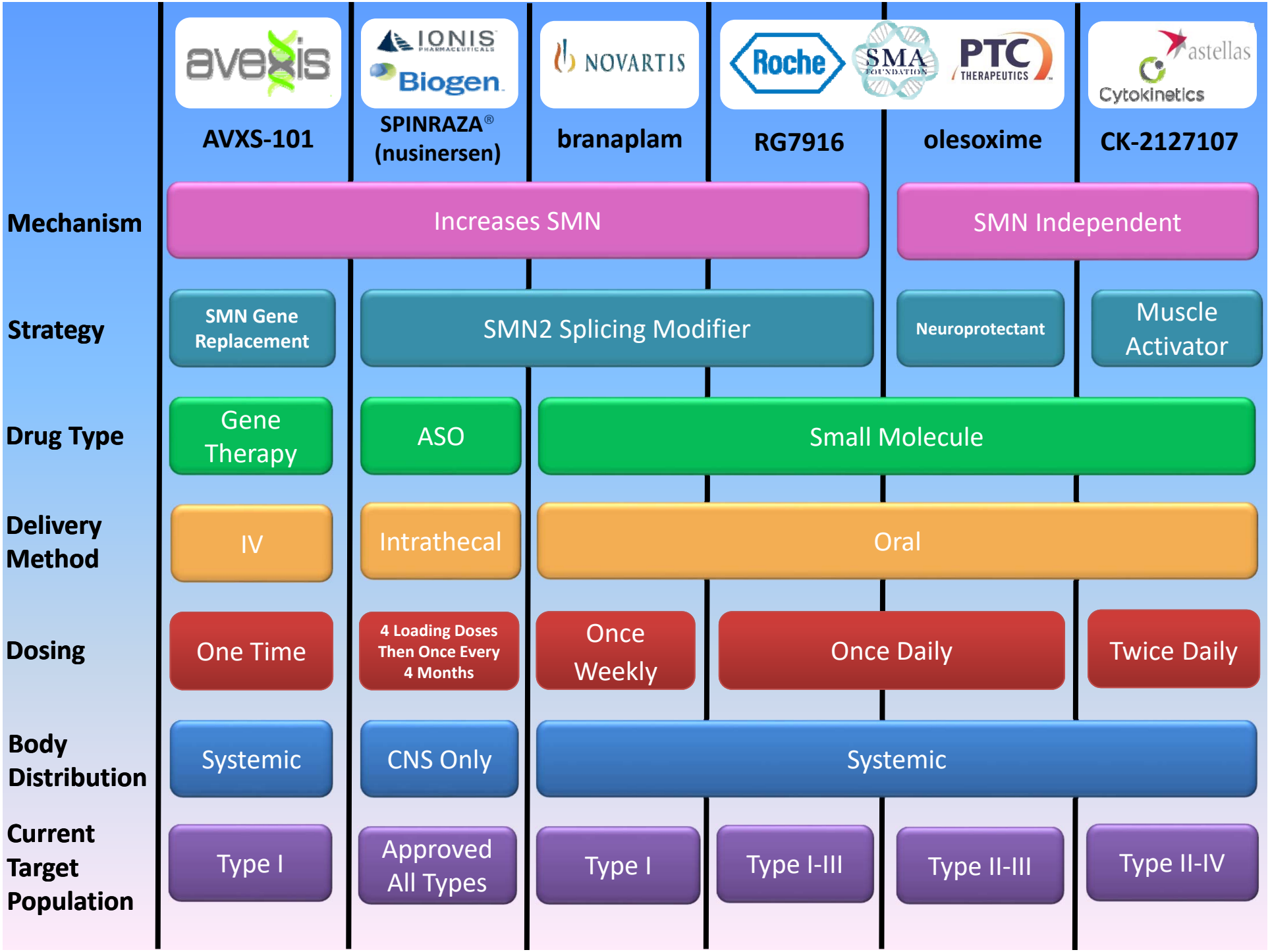
Targets for Therapeutic Intervention in SMA




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
4 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 transgene[18]. The virus is designed to deliver the gene to cells and provides constitutive, long-term SMN expression[19].
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 input[25]. 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 procedure[26]. 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 cells[29].

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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