Considerations for the selection of disease-modifying treatments in SMA: A case-based discussion

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Agenda

- Treatment selection for a 3-month-old infant
- Treatment selection for a 3-year-old child
- Treatment selection for an 18-year-old young adult

Overview of the mechanisms of action, indications and adverse events for currently approved treatments for SMA

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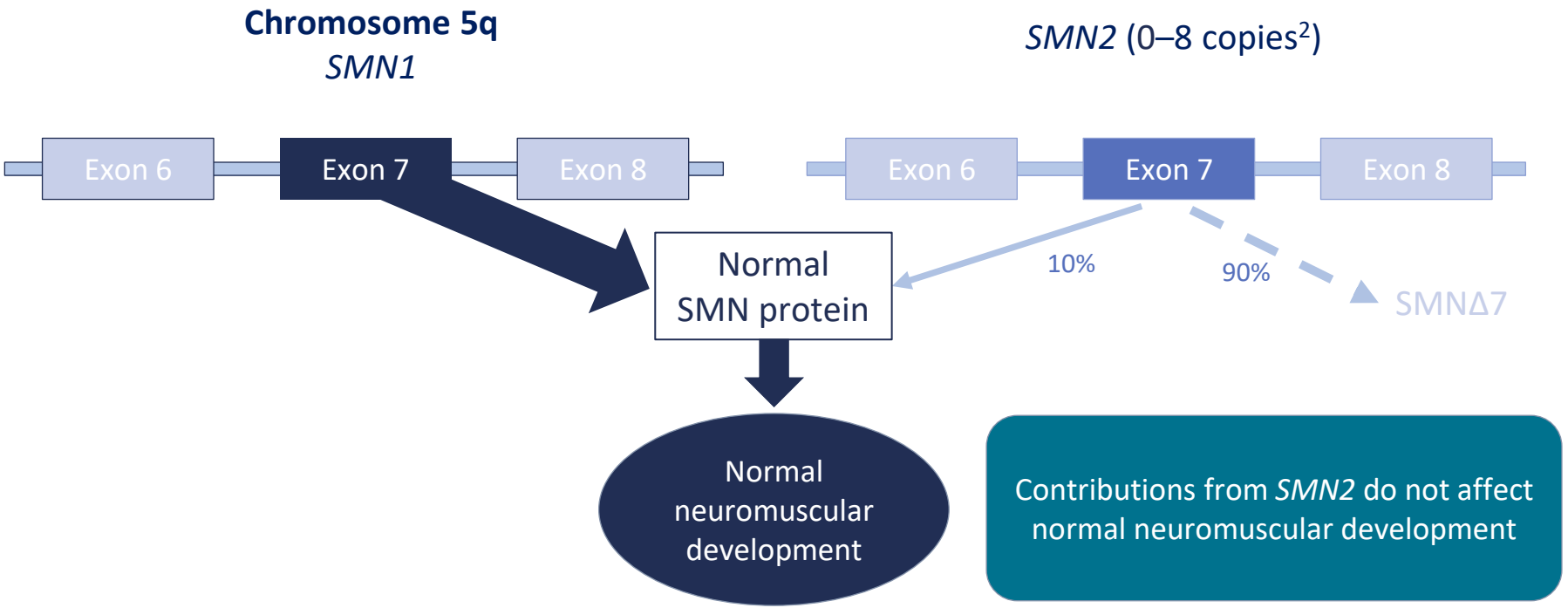
The genetics behind normal neuromuscular physiology[1]



SMN, survival motor neuron.

1. Schorling DC, et al. *J Neuromuscul Dis*. 2020;7:1–13; 2. Butchbach MER, et al. *Front Mol Biosci*. 2016;3:7.

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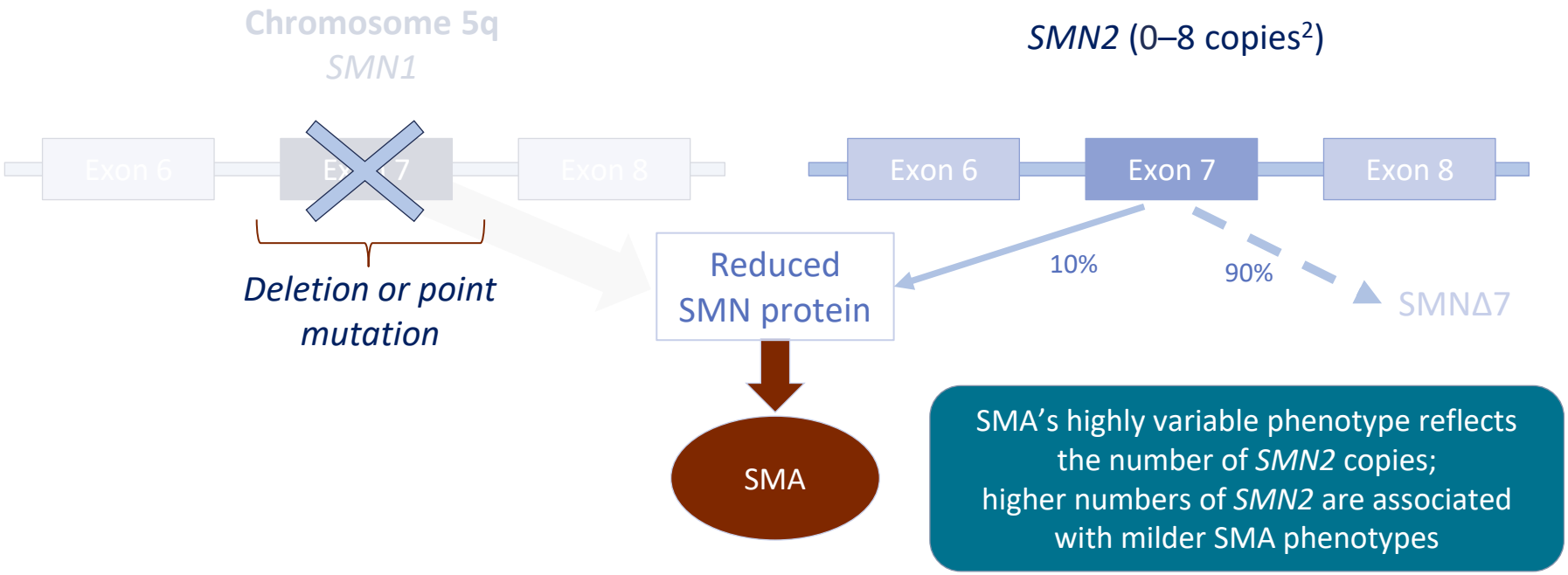
The genetics behind SMA pathophysiology[1]

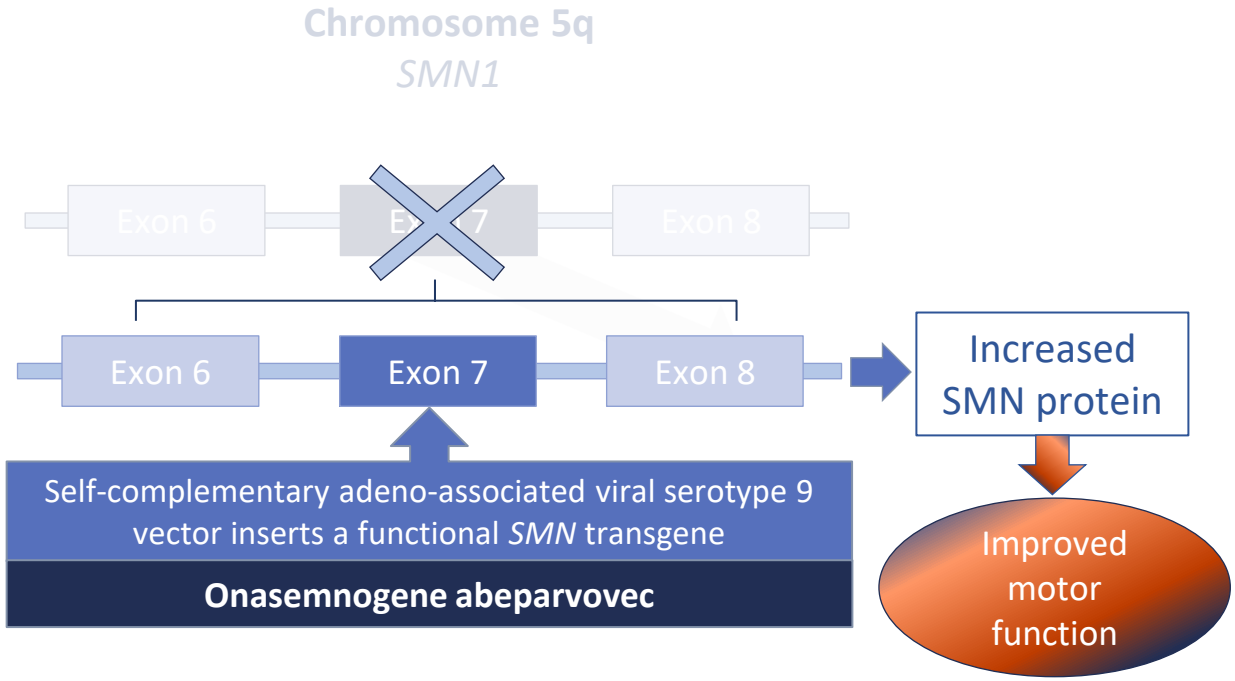


SMA's highly variable phenotype reflects the number of *SMN2* copies; higher numbers of *SMN2* are associated with milder SMA phenotypes

SMA, spinal muscular atrophy; SMN, survival motor neuron.

1. Schorling DC, et al. *J Neuromuscul Dis*. 2020;7:1–13; 2. Butchbach MER, et al. *Front Mol Biosci*. 2016;3:7.

Approved treatments: Mechanisms of action[1,2]



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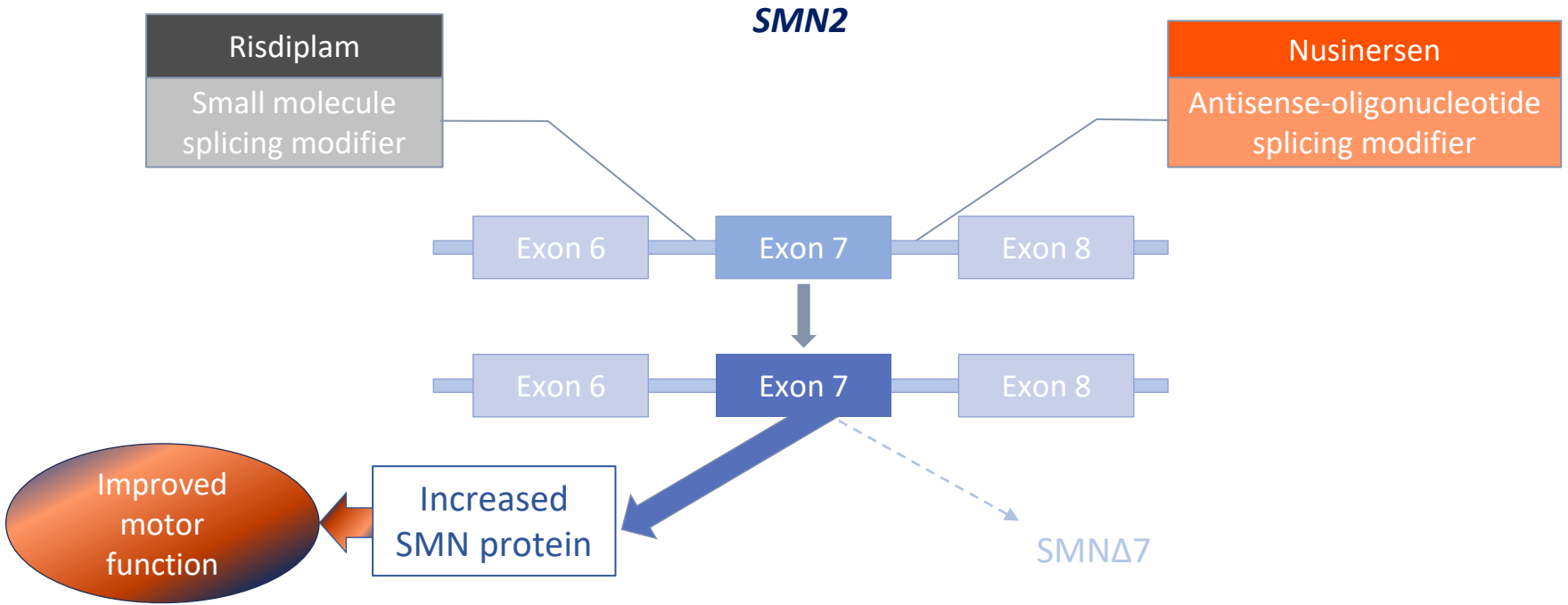
2. EMA. Onasemnogene abeparvovec. Summary of product characteristics. Available at: www.ema.europa.eu/en/medicines (accessed 28 March 2022).

Approved treatments: Mechanisms of action



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Approved treatments: EU indications

Antisense-oligonucleotide Nusinersen[1] (approved May 2017)	**Gene therapy** Onasemnogene abeparvovec[2] (approved May 2020)	**Small molecule** Risdiplam[3] (approved March 2021)
For patients with 5q SMA	For patients with 5q SMA* and: • A clinical diagnosis of Type 1, **or** • ≤3 copies of the *SMN2* gene **Dosing is provided for patients weighing 2.6–21 kg*	For patients ≥2 months old with: • A clinical diagnosis of 5q SMA Types 1–3, **or** • 1–4 *SMN2* copies
 Intrathecal bolus injection, four loading doses (days 0, 14, 28, 63) Maintenance dose every 4 months	 Single-dose intravenous infusion	 Orally, once a day after a meal at approximately the same time each day

There are regional variations in the indications for the three therapeutic agents for SMA

EU, European Union; SMA, spinal muscular atrophy; SMN, survival motor neuron.

1. EMA. Nusinersen. Summary of product characteristics. Available at: www.ema.europa.eu/en/medicines (accessed 28 March 2022);
2. EMA. Onasemnogene abeparvovec. Summary of product characteristics. Available at: www.ema.europa.eu/en/medicines (accessed 28 March 2022);
3. EMA. Risdiplam. Summary of product characteristics. Available at: www.ema.europa.eu/en/medicines (accessed 28 March 2022).

Special considerations for each treatment

Nusinersen[1]

Procedure-related common AEs

- Headache
- Vomiting
- Back pain

- Risk of AEs from lumber puncture
  - Sedation maybe required
  - Potential exposure to fluoroscopy
  - Difficulties administering to patients with scoliosis
- Risks associated with ASOs
  - Thrombocytopenia and coagulation abnormalities
  - Renal toxicity
- Hydrocephalus

Onasemnogene abeparvovec[2]

Common AEs

- Thrombocytopenia
- Vomiting
- Hepatotoxicity
- Pyrexia
- Hepatic enzyme increase

Before administration, test for:

- AAV9 antibody, liver function, creatine, blood count and troponin
- Immunomodulatory regimen is required if the patient is AAV9-positive

Risdiplam[3]

Common and very common AEs

- Diarrhoea, nausea, mouth ulcers
- Rash
- Headache
- Pyrexia
- Urinary tract infection
- Arthralgia

Potential risks:

- Embryo-foetal toxicity
- Retinal toxicity
- Male fertility effects

AAV9, adeno-associated virus serotype 9; AE, adverse event; ASO, antisense oligonucleotide.

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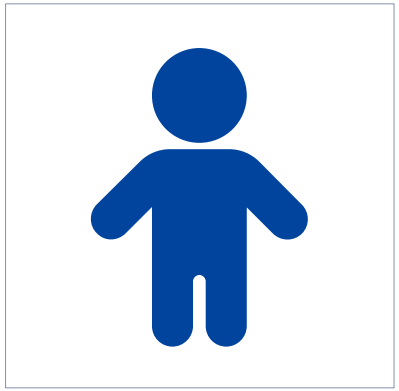
Case 1: Treatment of an infant <6 months old

- Three-month-old infant girl with hypotonia, reduced spontaneous movements and other clinical signs of SMA
- Genetic testing has confirmed SMA with 2 copies of the *SMN2* back-up gene

SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Case 2: Treatment of a 3-year-old child



- Three-year-old boy who has been genetically identified with SMA 5q, with 3 copies of the *SMN2* back-up gene
- The child is walking, but he now keeps falling; he is finding it difficult to get up off the floor and is also getting tired standing without support

SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Case 3: Treatment of an older patient

- A young adult aged 18 years of age
- She is complaining of extreme fatigue when doing anything physical
- She has had a number of falls recently and is thinking about using a stick to help prevent them
- Genetic tests reveal that she has 5q SMA with 4 copies of *SMN2*

SMA, spinal muscular atrophy; SMN, survival of motor neuron.