Identifying, diagnosing and treating patients with later-onset SMA

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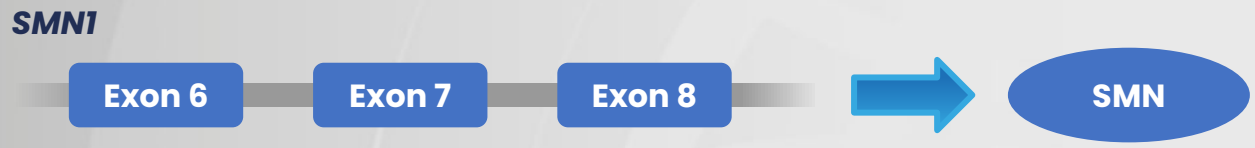
Diagnosis of SMA in older adolescent and adult populations

Genetic pathophysiology of SMA

SMA is an autosomal recessive inherited disease



SMA, spinal muscular atrophy; SMN, survival motor neuron.
Schorling DC, et al. *J Neuromuscul Dis*. 2020;7:1–13.

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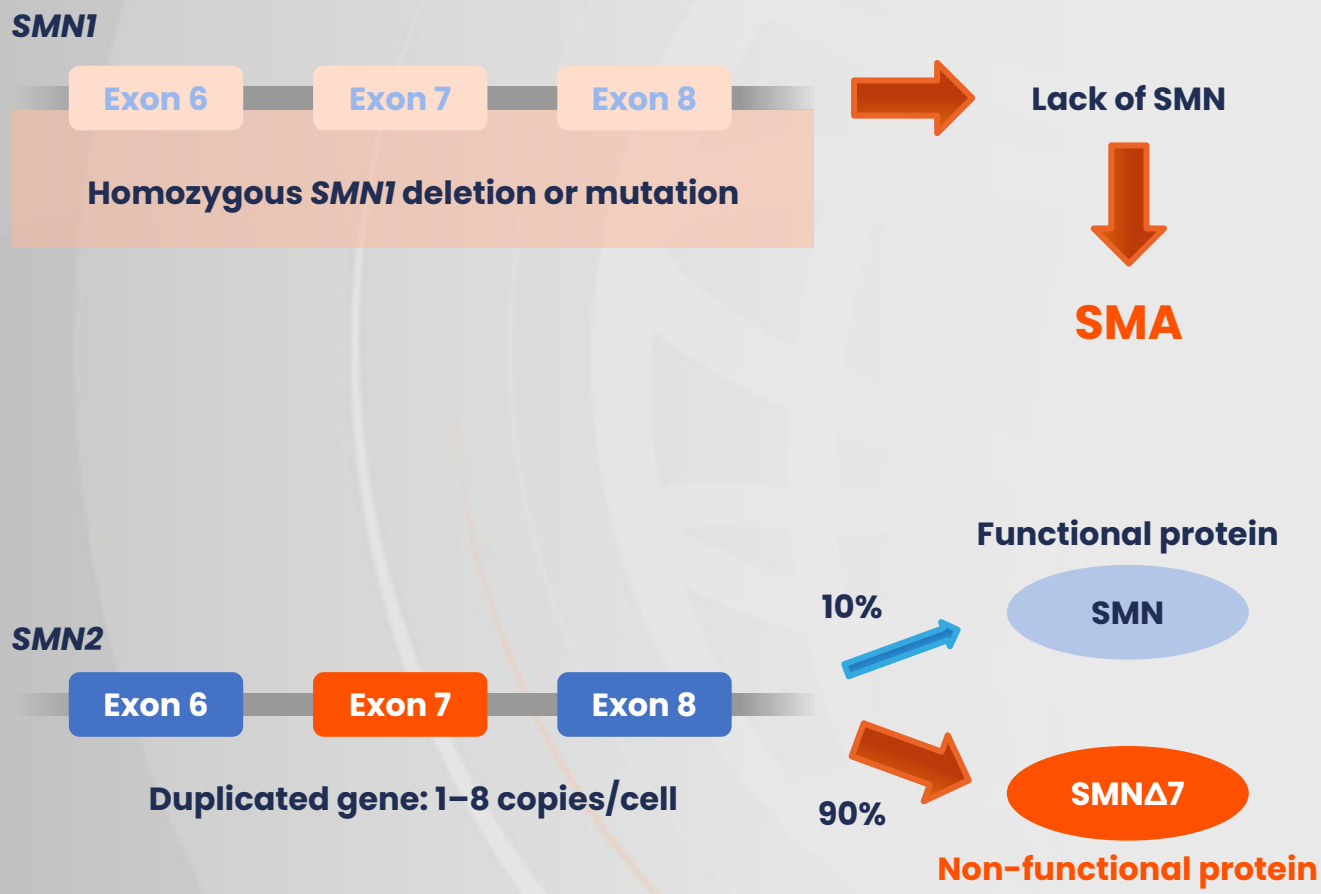

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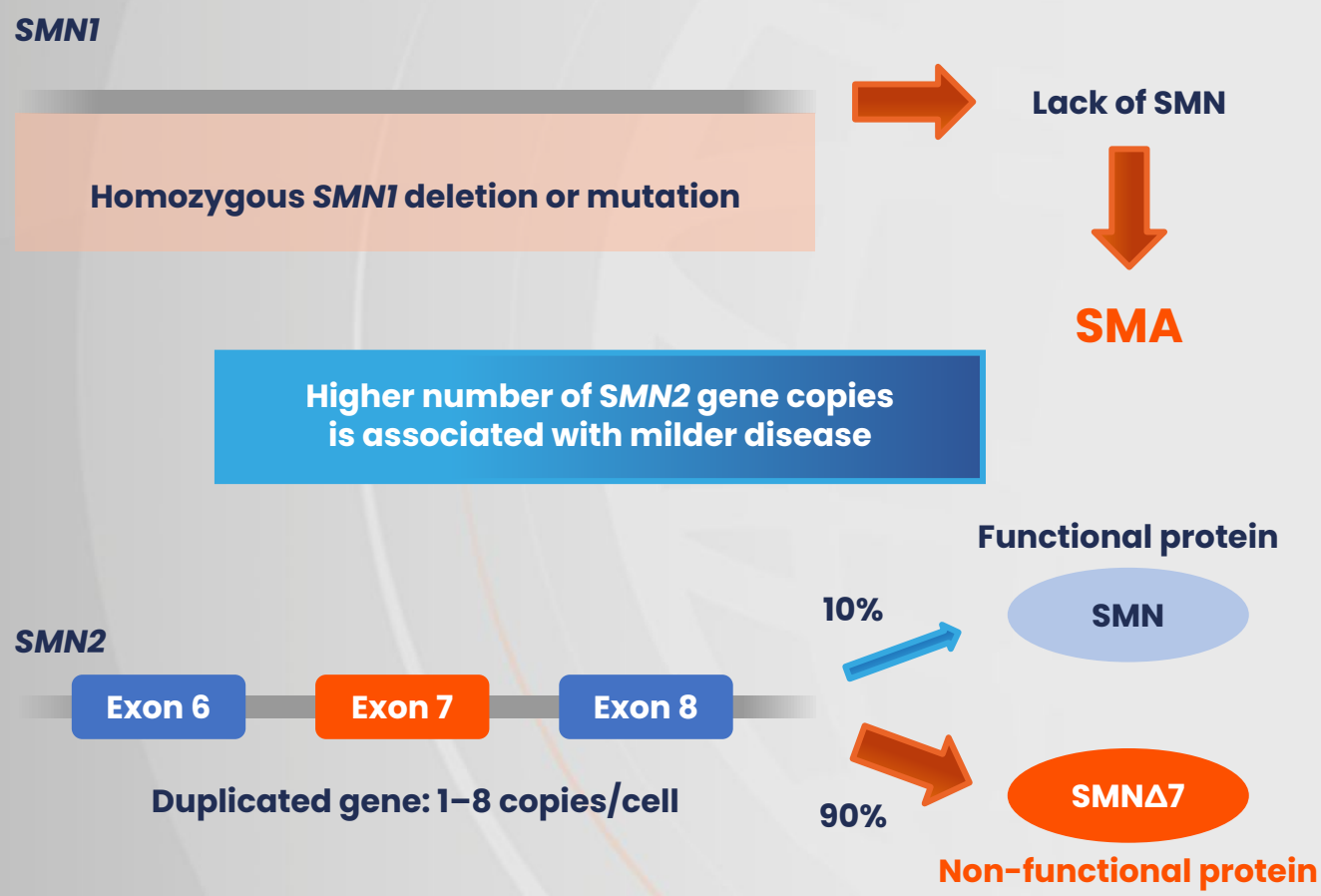

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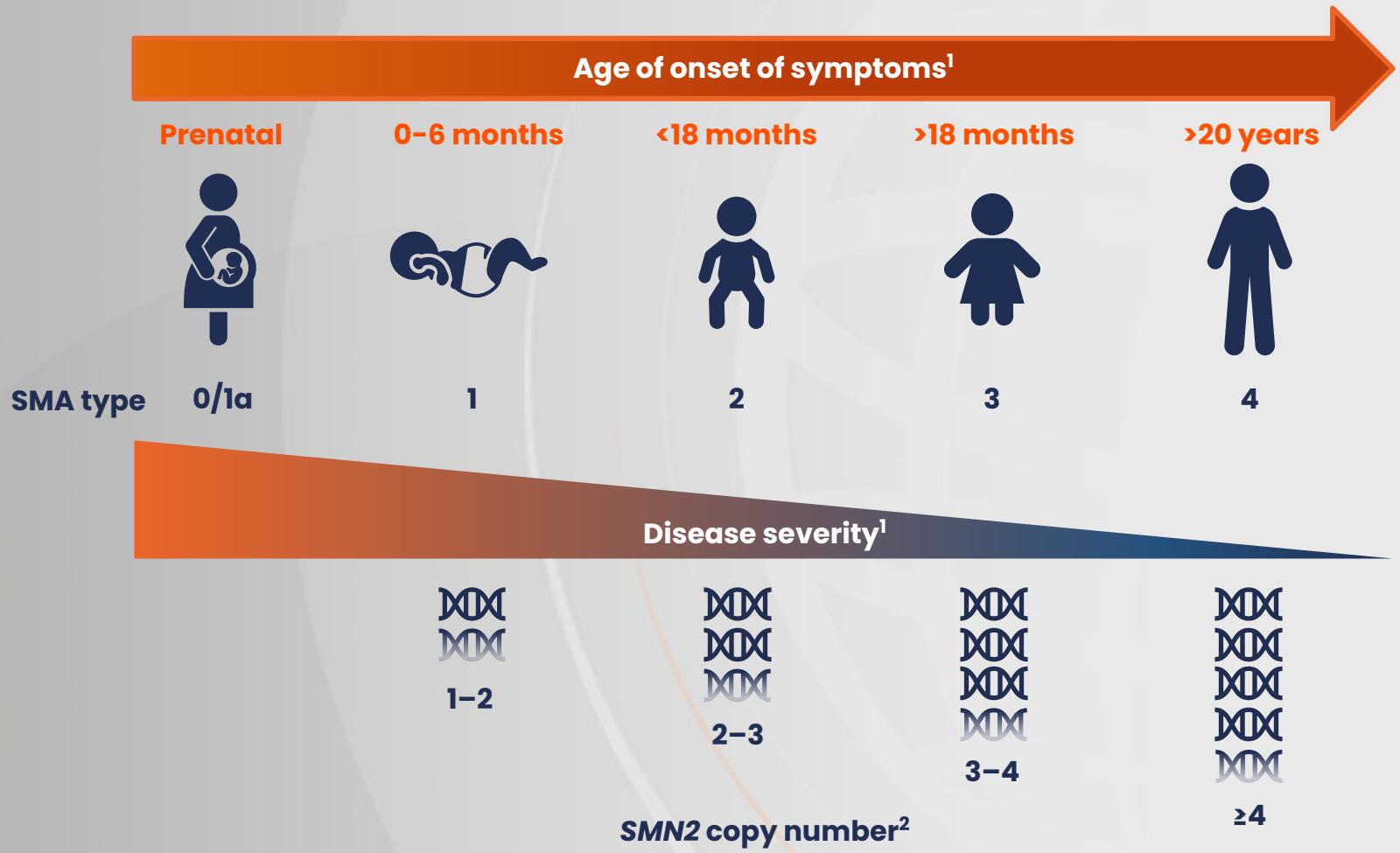
SMA types: Age of onset, disease severity and clinical features



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1. Smeriglio P, et al. *J Pers Med*. 2020;10:75; 2. Schorling DC, et al. *J Neuromuscul Dis*. 2020;7:1–13.

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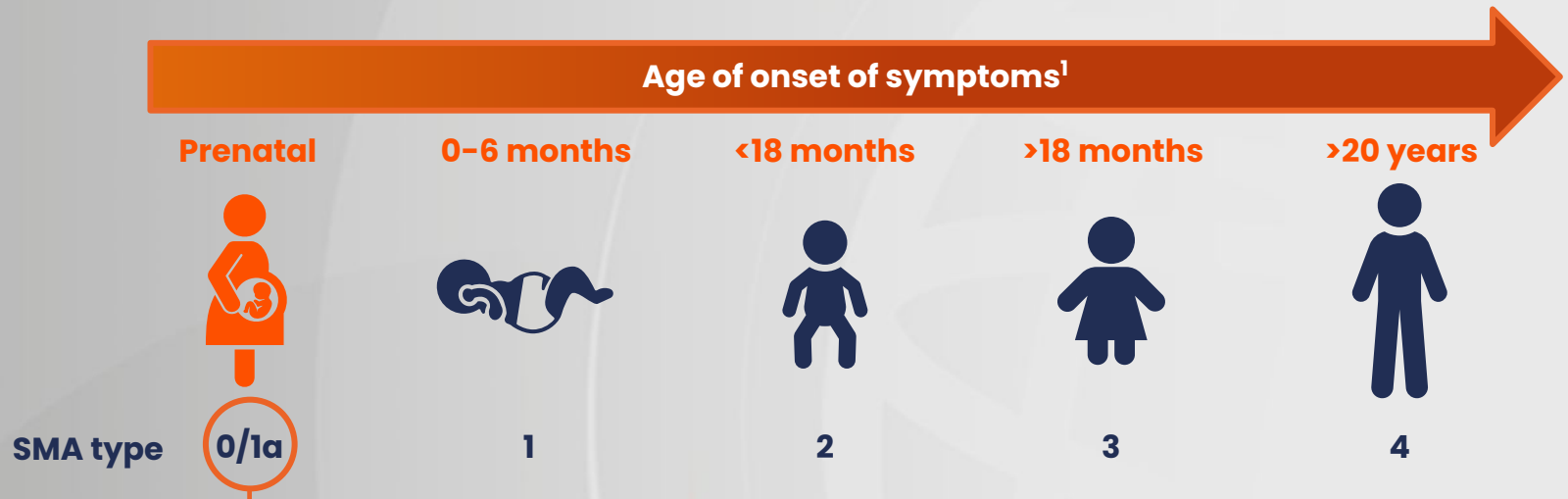

Clinical presentation	
• Respiratory assistance required[1]	
Life expectancy	**Prevalence**
• <1 month[1]	• <1% of cases[2]

SMA, spinal muscular atrophy.

1. Smeriglio P, et al. *J Pers Med*. 2020;10:75; 2. Keinath MC, et al. *Appl Clin Genet*. 2021;14:11–25; 3. Pera MC, et al. *PLoS ONE*. 2020;15:e0230677; 4. Sharawat IK, et al. *BMJ Case Rep*. 2019;12:e230618; 5. Schorling DC, et al. *J Neuromuscul Dis*. 2020;7:1–13.

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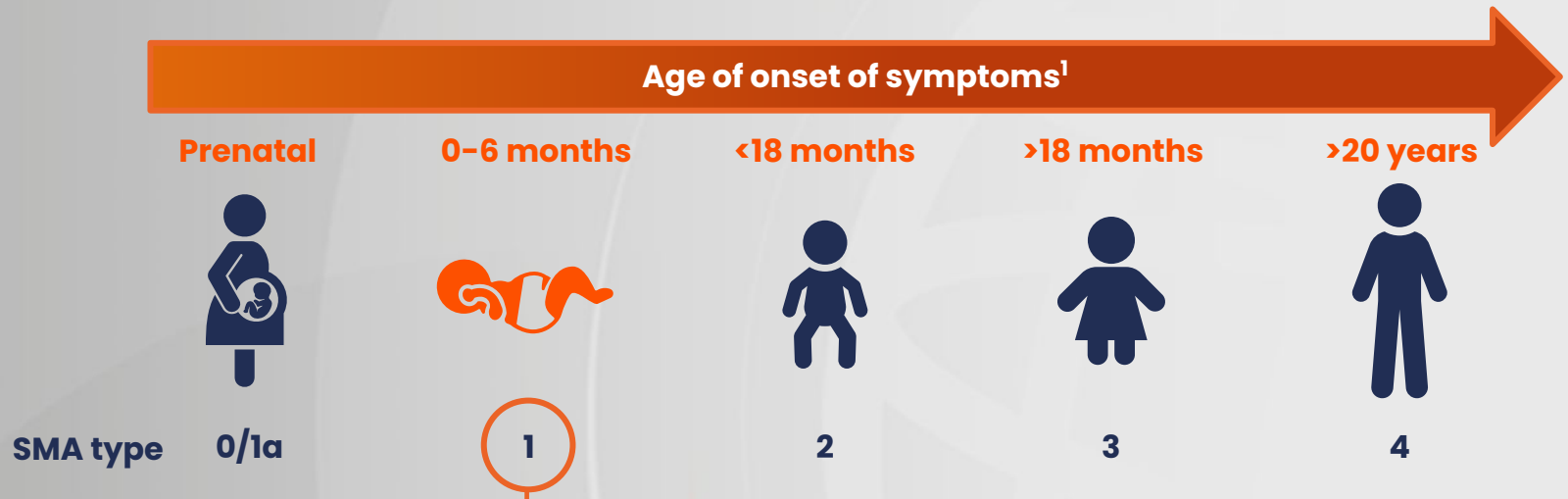

Clinical presentation

- General hypotonia, difficulty breathing and swallowing, tongue fasciculations[3]
- Cannot sit independently, absence of head control, inability to roll over[1,3]

Life expectancy	Prevalence
• <2 years[1]	• ~45% of cases[2]

SMA, spinal muscular atrophy.

1. Smeriglio P, et al. *J Pers Med*. 2020;10:75; 2. Keinath MC, et al. *Appl Clin Genet*. 2021;14:11–25; 3. Pera MC, et al. *PLoS ONE*. 2020;15:e0230677; 4. Sharawat IK, et al. *BMJ Case Rep*. 2019;12:e230618; 5. Schorling DC, et al. *J Neuromuscul Dis*. 2020;7:1–13.

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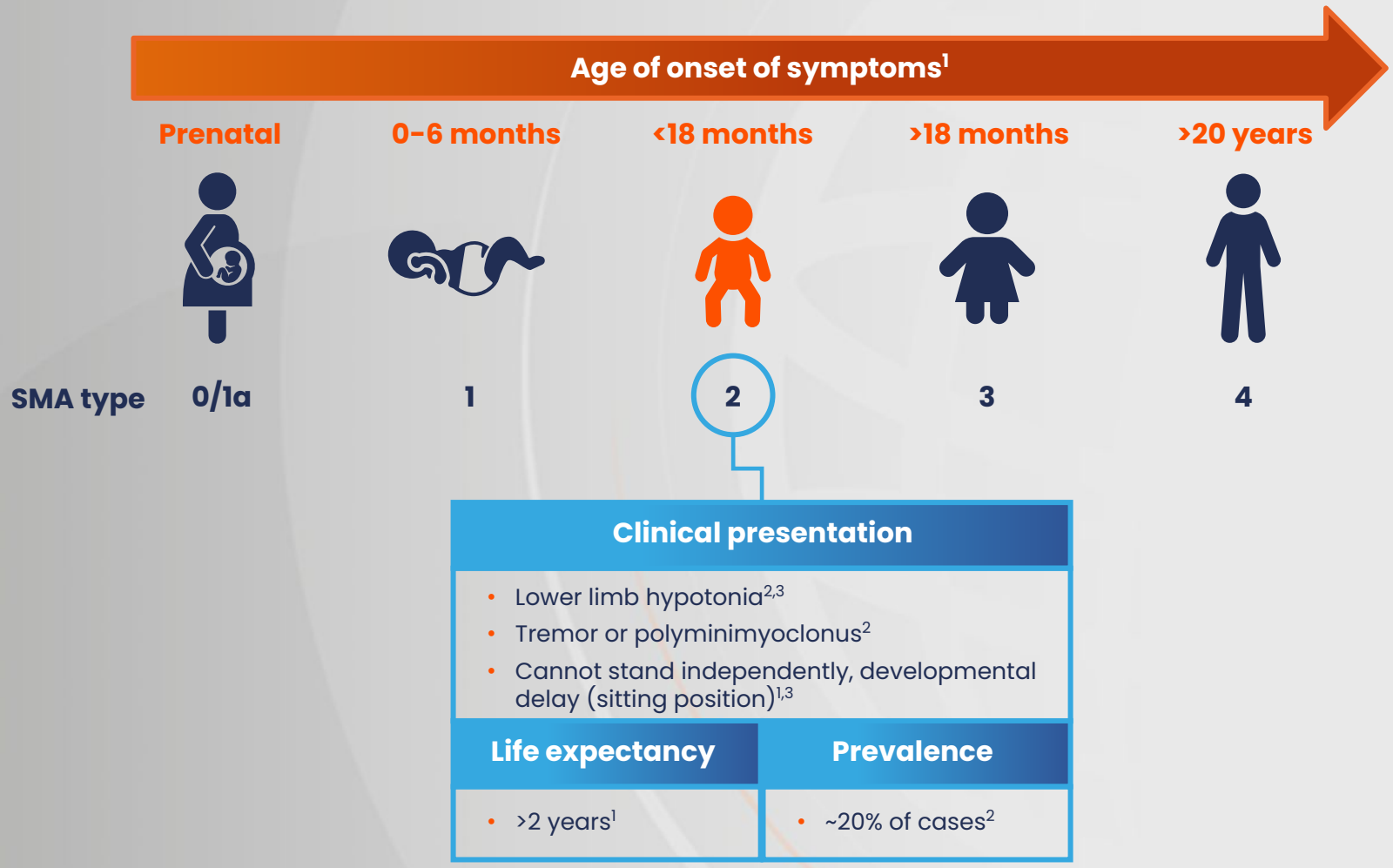

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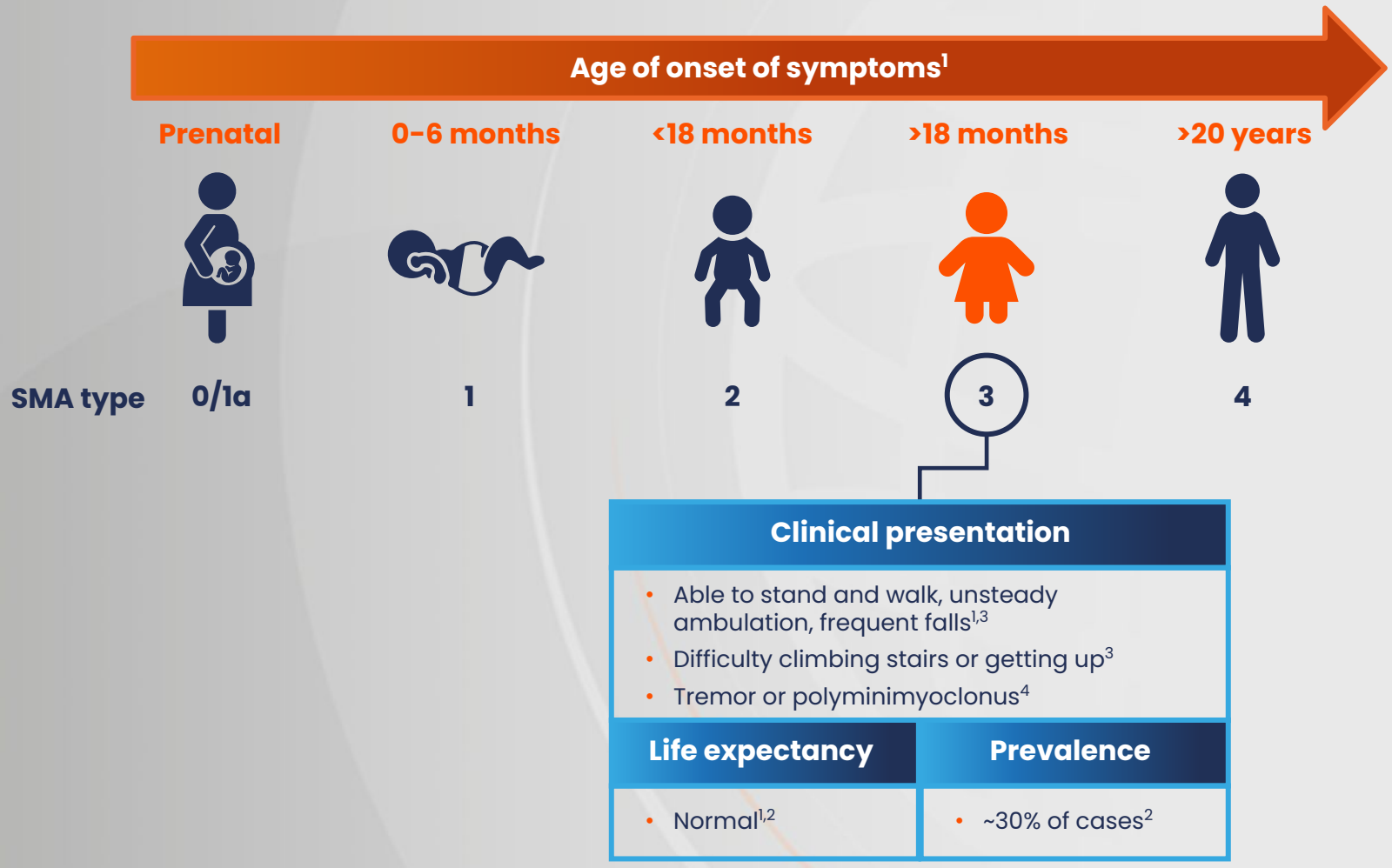

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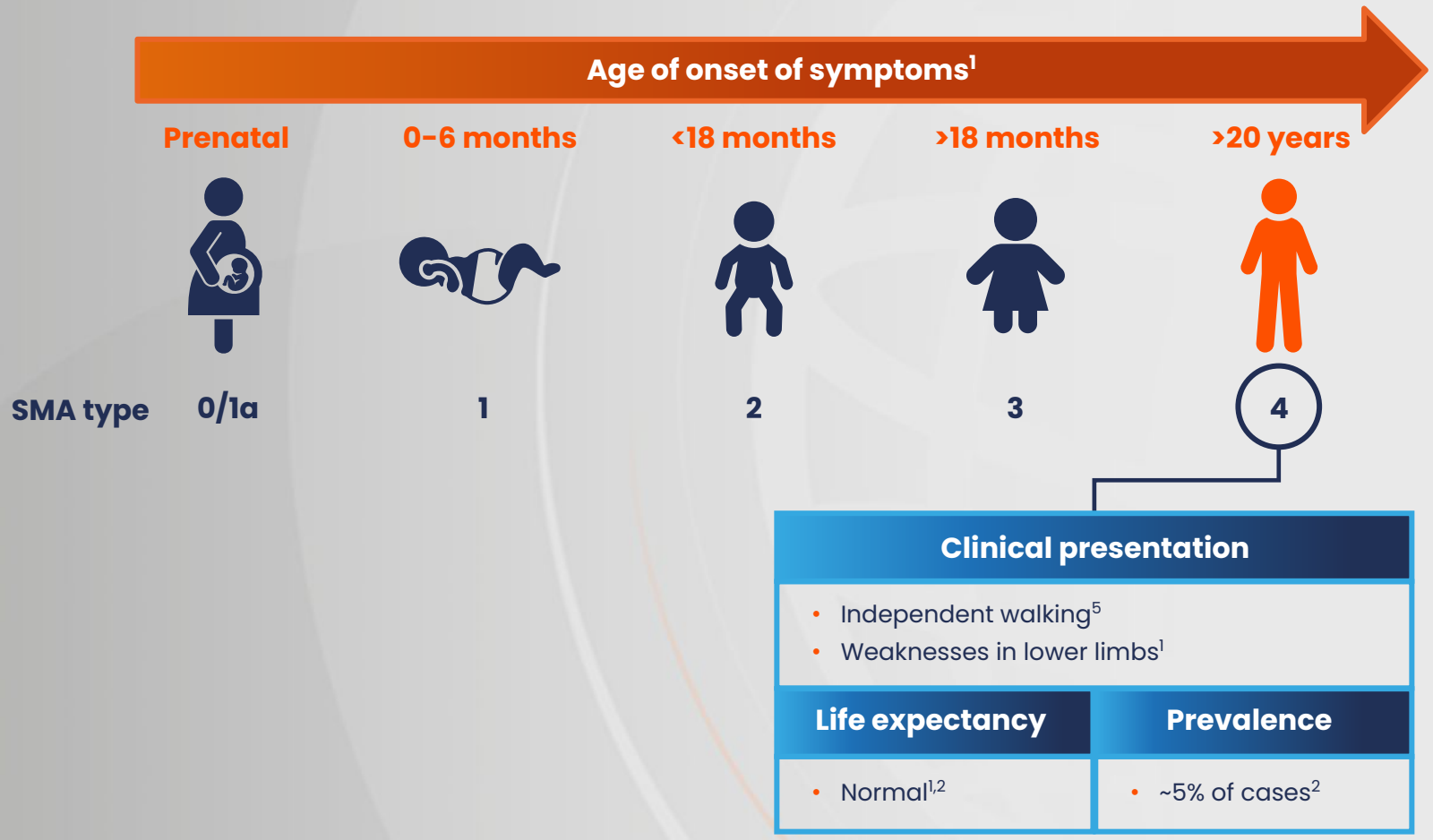

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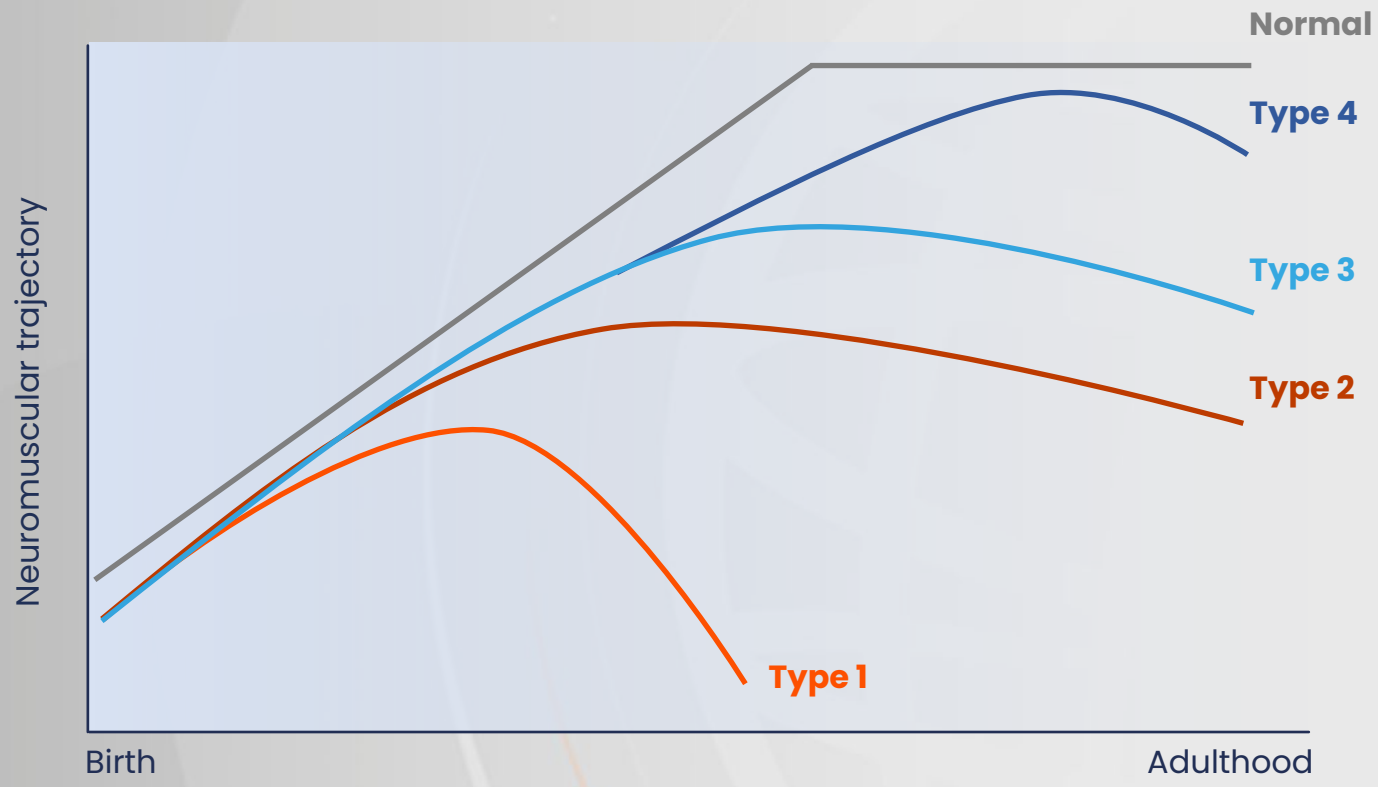
The importance of early diagnosis in SMA



- **Early diagnosis** may expedite early initiation of treatment before substantial motor neuron loss occurs
- **Effective and early treatment** may allow patients to more closely follow normal development trajectories

SMA, spinal muscular atrophy.
Figure adapted from Serra-Juhe C, Tizzano EF. *Eur J Hum Genet*. 2019:27:1774–82.

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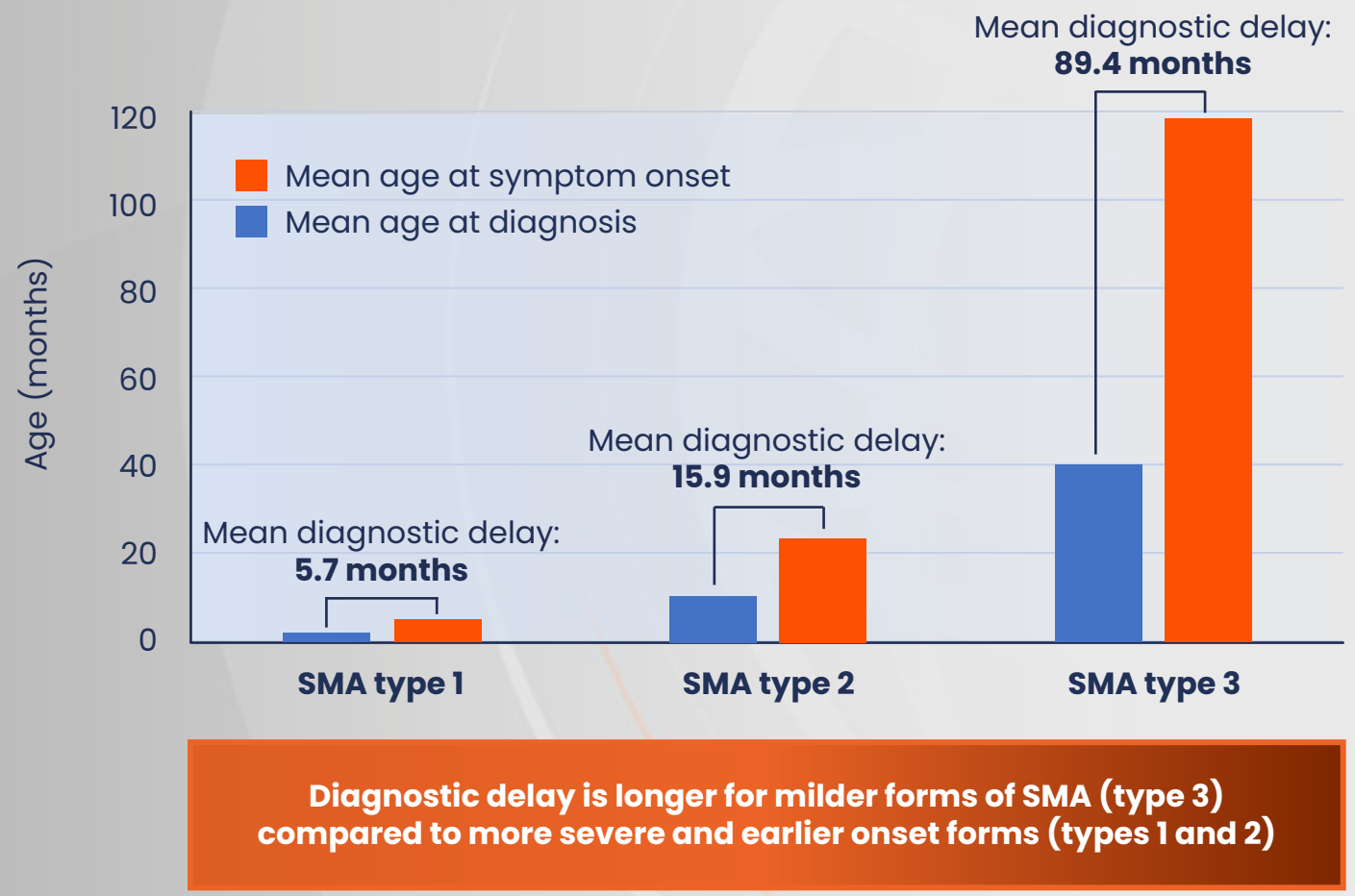
Time to diagnosis for SMA depending on disease type

Cure SMA 2018 survey: Large, US-based patient-reported database for people affected with SMA (N=760)



Diagnostic delay is longer for milder forms of SMA (type 3) compared to more severe and earlier onset forms (types 1 and 2)

SMA, spinal muscular atrophy.

Belter et al. *J Neuromuscul Dis.* 2021;8:109-23.

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Diagnostic delay in patients with milder, later-onset SMA

Factors that may lead to a delayed diagnosis in later-onset SMA

Parental and provider 'wait and see' attitude (milder and less specific symptoms in patients aged >3 years)

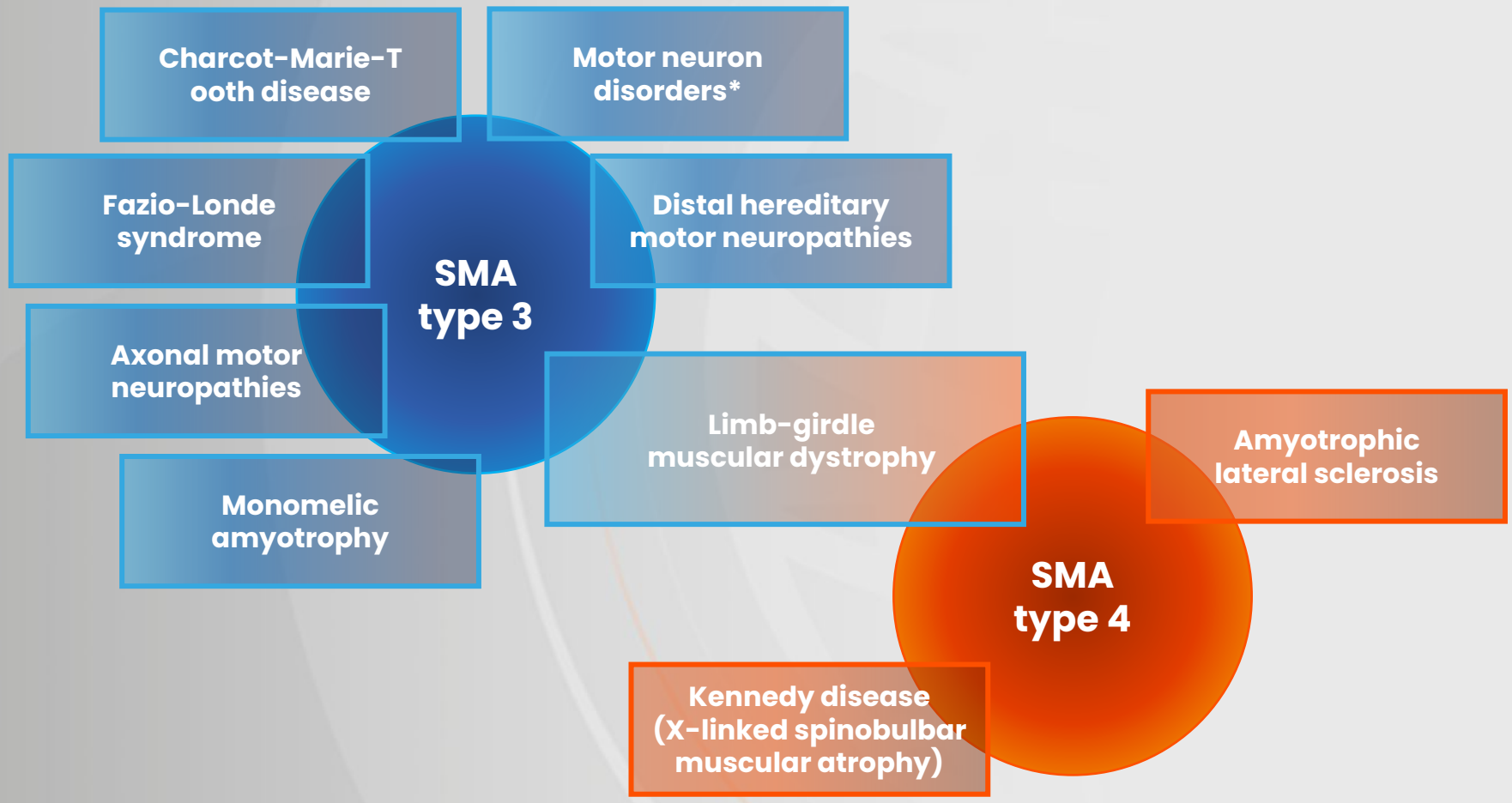
Delayed referral to specialist

Higher number of investigations prior to diagnosis

SMA, spinal muscular atrophy.

Pera MC, et al. *PLoS ONE*. 2020;15:e0230677.

Overlap of later-onset SMA with other neuromuscular diseases



*Non-5q form of SMA, late-onset hexosaminidase A deficiency.
SMA, spinal muscular atrophy.
Salort-Campana E, Quijano-Roy S. *Arch Pediatr*. 2020;27:7S23–8.

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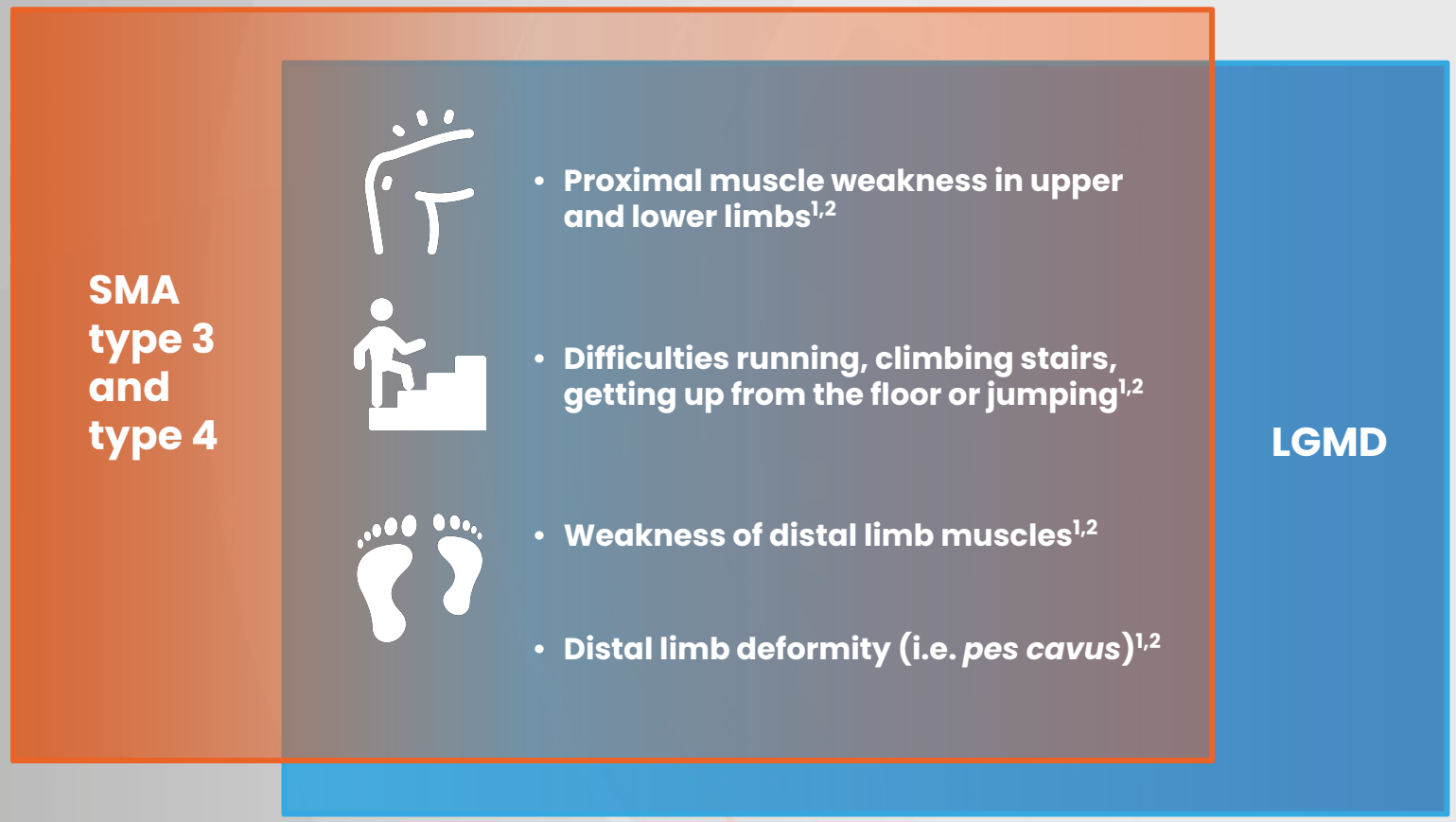
SMA and LGMD: Overlapping symptoms



LGMD, limb-girdle muscular dystrophy; SMA, spinal muscular atrophy.

1. Salort-Campana E, Quijano-Roy S. *Arch Pediatr*. 2020;27:7S23–8; 2. Boito CA, et al. *Arch Neurol.* 2005;62:1894–9.

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Differential diagnosis of later-onset SMA phenotypes

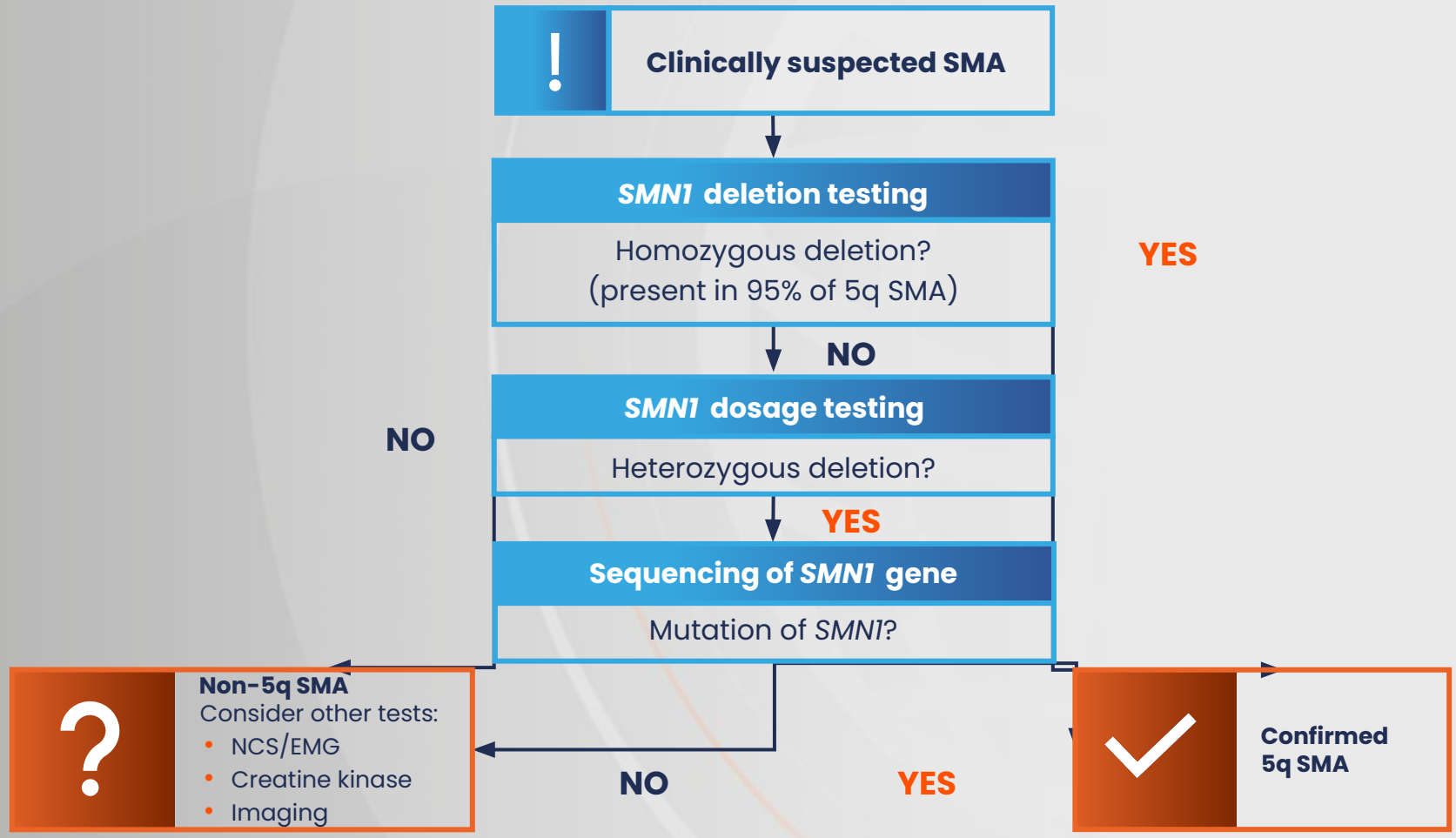
Pattern of disease	
SMA • Predominant proximal muscle involvement	**Distal hereditary motor neuropathies** • Insidious onset • Slowly progressive • Symmetrical weakness • Prominent distal involvement
Topography	
SMA • Symmetrical, lower and upper limb involvement	**ALS and Kennedy disease (X-linked spinobulbar muscular atrophy)** • Asymmetric, bulbar, upper limbs
Nerve conduction studies	
SMA • Usually conserved conduction velocities, but may be reduced • SMA type 4 phenotypically close to Charcot-Marie-Tooth disease	**Charcot-Marie-Tooth disease** • Reduced conduction velocities • Reduced sensory responses • Distal atrophy • Less severe phenotype than SMA type 2

ALS, amyotrophic lateral sclerosis; SMA, spinal muscular atrophy.

Salort-Campana E, Quijano-Roy S. *Arch Pediatr*. 2020;27:7S23–8.

The diagnostic journey for SMA

Molecular testing has replaced EMG and muscle biopsy as the standard diagnostic tool for SMA



EMG, electromyography; NCS, nerve conduction study; SMA, spinal muscular atrophy; SMN, survival motor neuron.
Adapted from Arnold WD, et al. *Muscle Nerve.* 2015;51:157–67.

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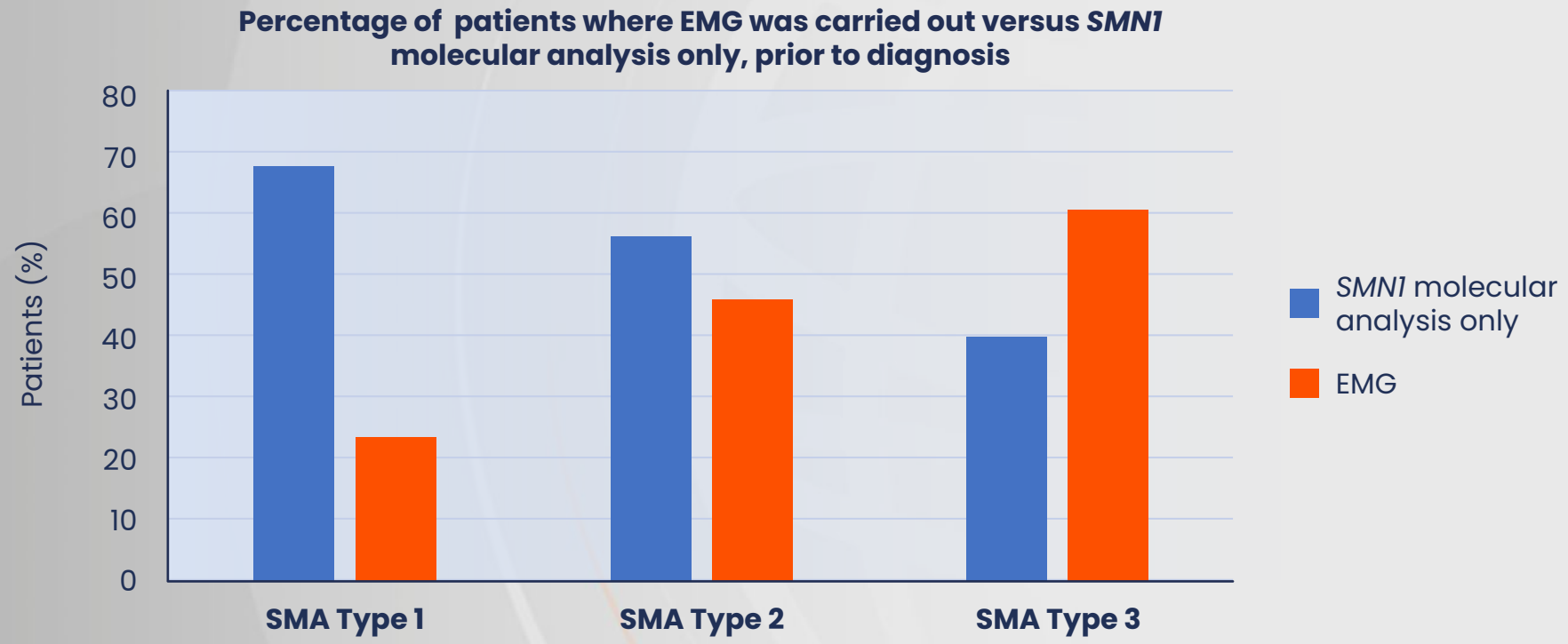
The diagnostic journey for SMA

Study from five tertiary Italian neuromuscular centers involved in the diagnosis and follow-up of SMA patients from 1996 onwards



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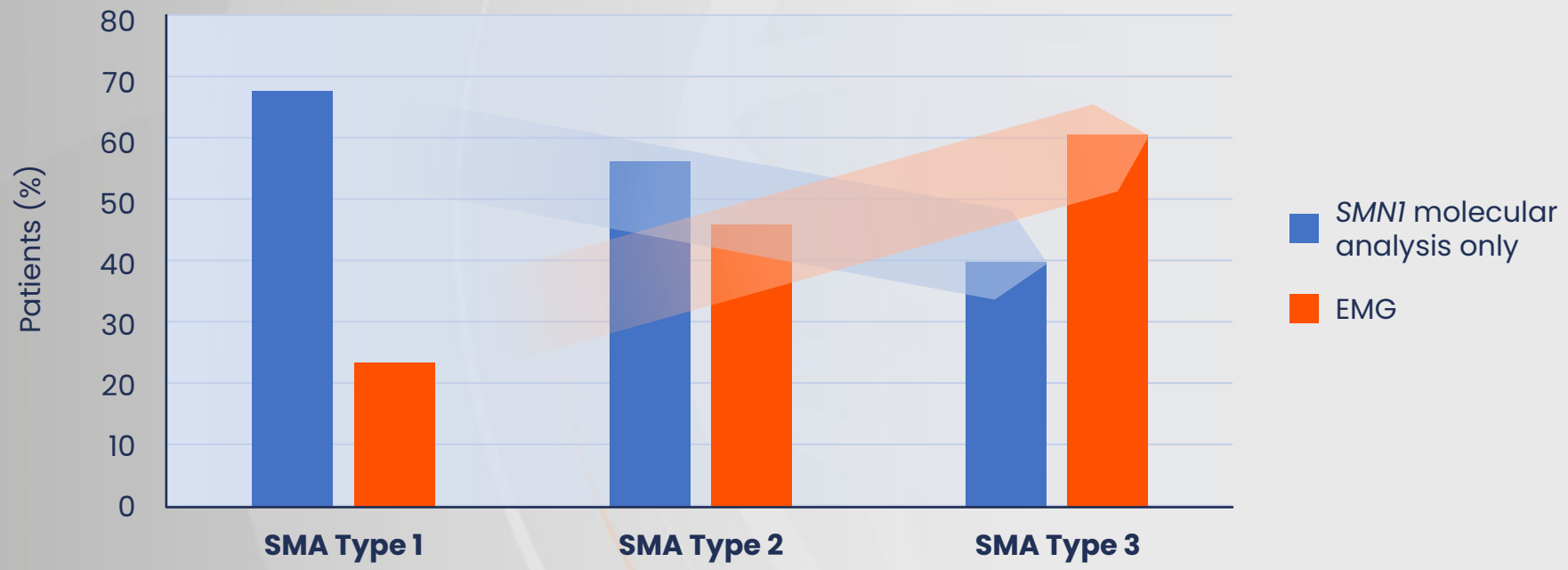
Study from five tertiary Italian neuromuscular centers involved in the diagnosis and follow-up of SMA patients from 1996 onwards

Percentage of patients where EMG was carried out versus *SMN1* molecular analysis only, prior to diagnosis



- EMG is usually not performed for the diagnosis of SMA type 1
- Diagnostic tools other than molecular *SMN1* testing are often still used in the diagnostic process of milder, later-onset SMA

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

Pera MC, et al. *PLoS ONE*. 2020;15:e0230677.

Conclusions

The challenges and importance of prompt and early diagnosis of later-onset SMA

It can be difficult to diagnose milder forms of SMA, with less severe symptoms that may overlap with other conditions

Adolescents and adults may face a relatively long diagnostic journey compared with children with more severe forms of SMA

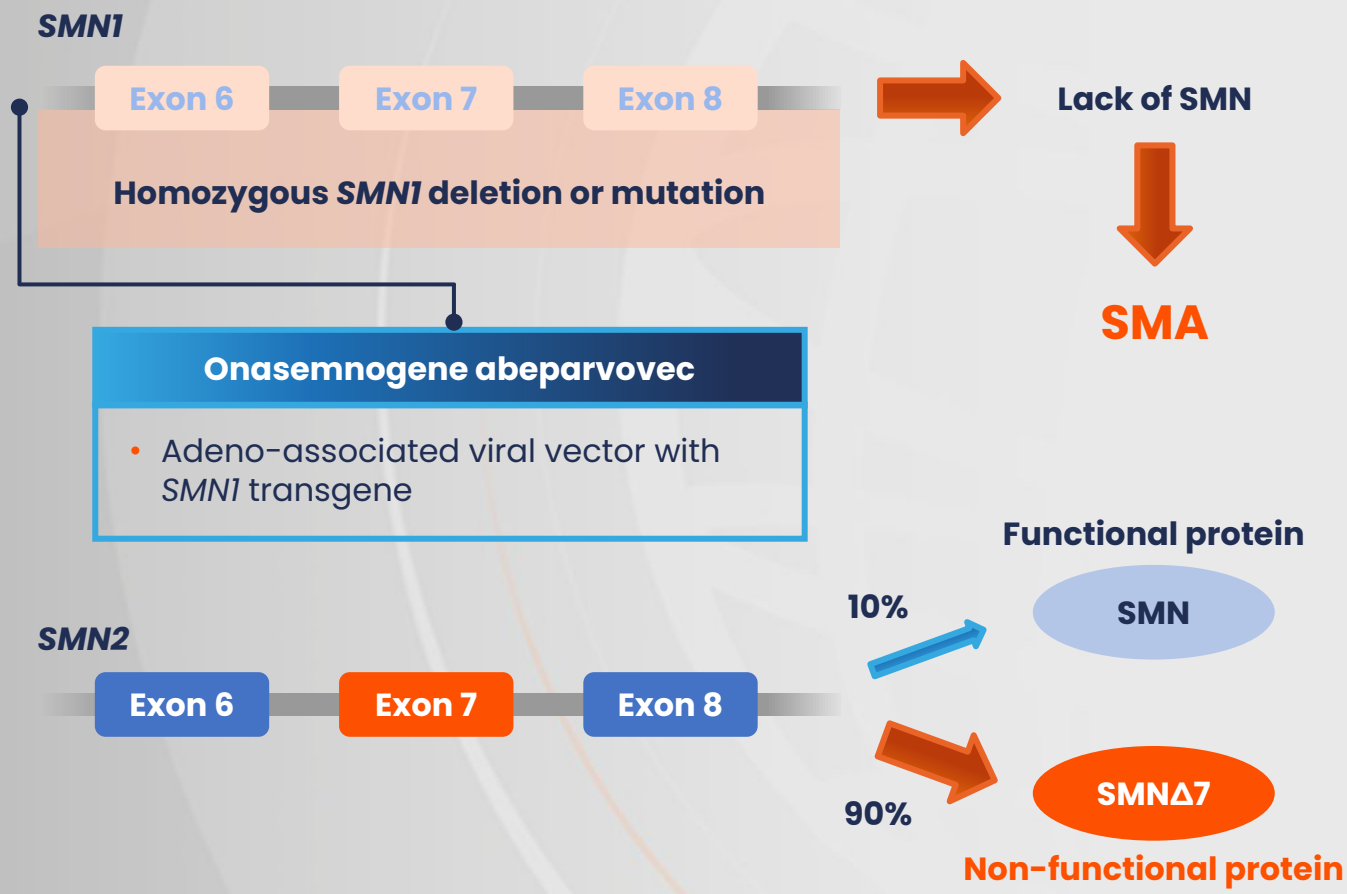
It is important to refer patients for genetic testing as quickly as possible to achieve early diagnosis and allow early treatment which will ultimately improve patient outcomes

SMA, spinal muscular atrophy.

Overview of DMTs and available data on their use in patients with later-onset SMA

Approved therapies for SMA: Mechanism of action

Onasemnogene abeparvovec: *SMN1* gene replacement therapy



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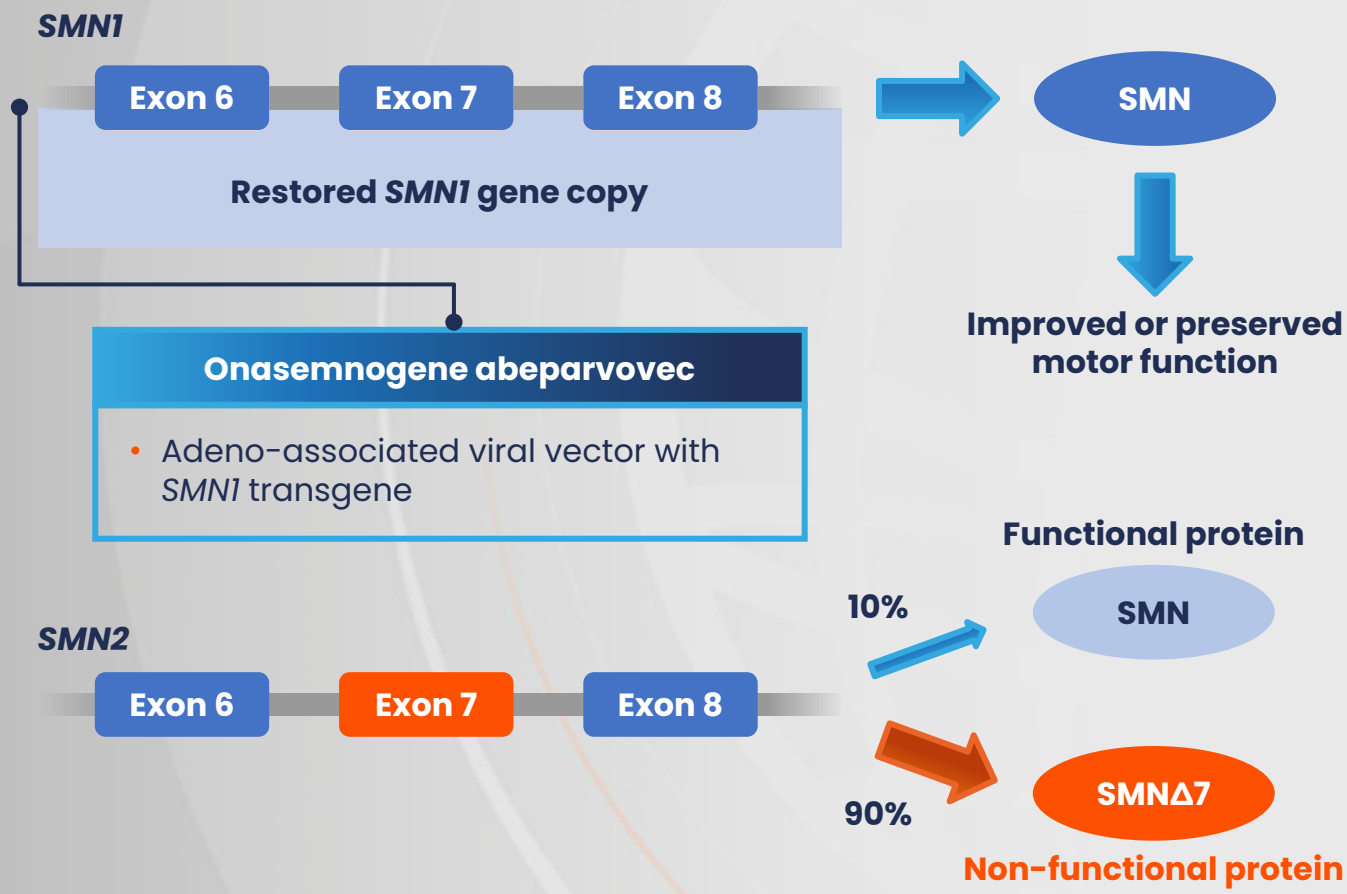

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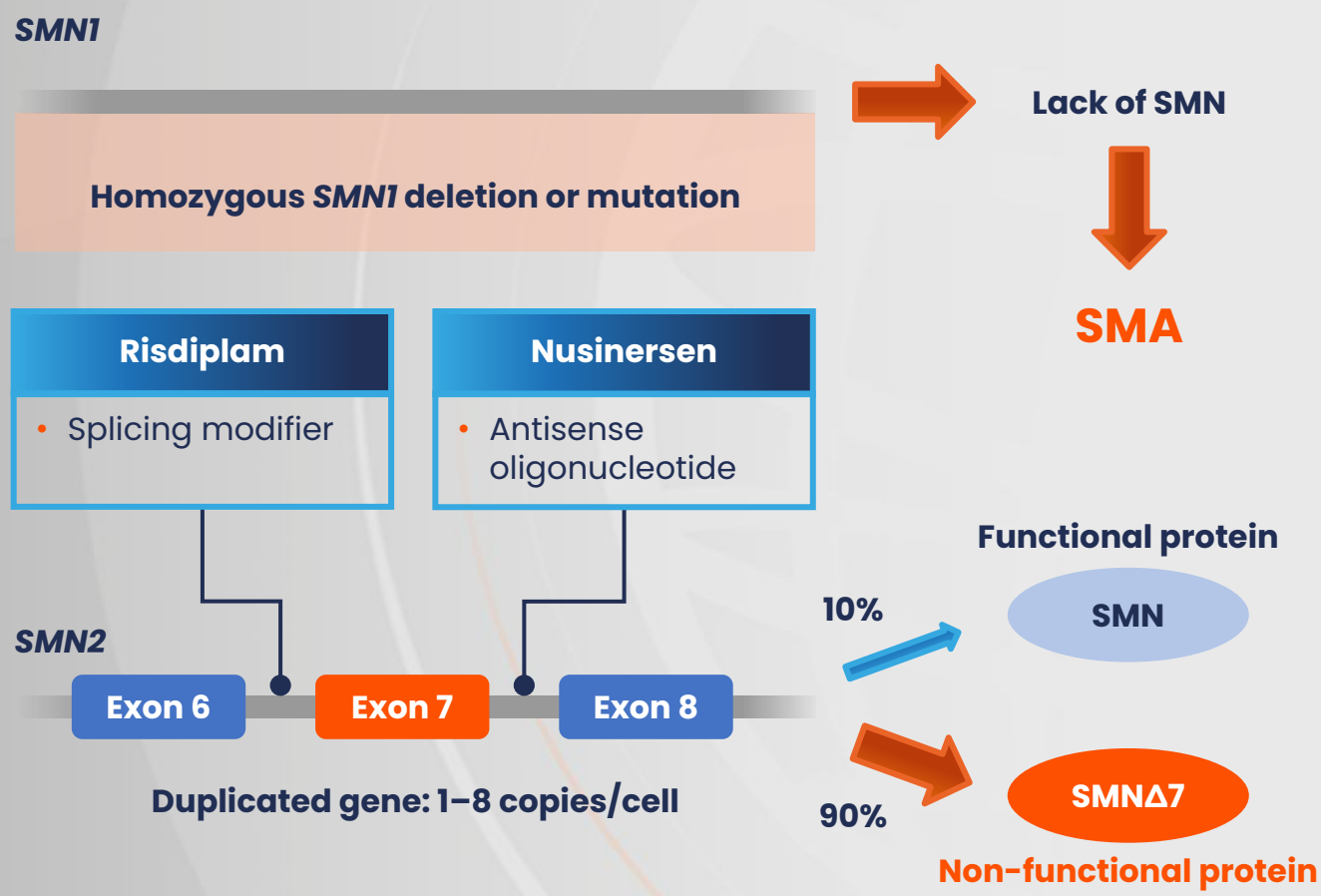
Approved therapies for SMA: Mechanism of action

Nusinersen and risdiplam target *SMN2*



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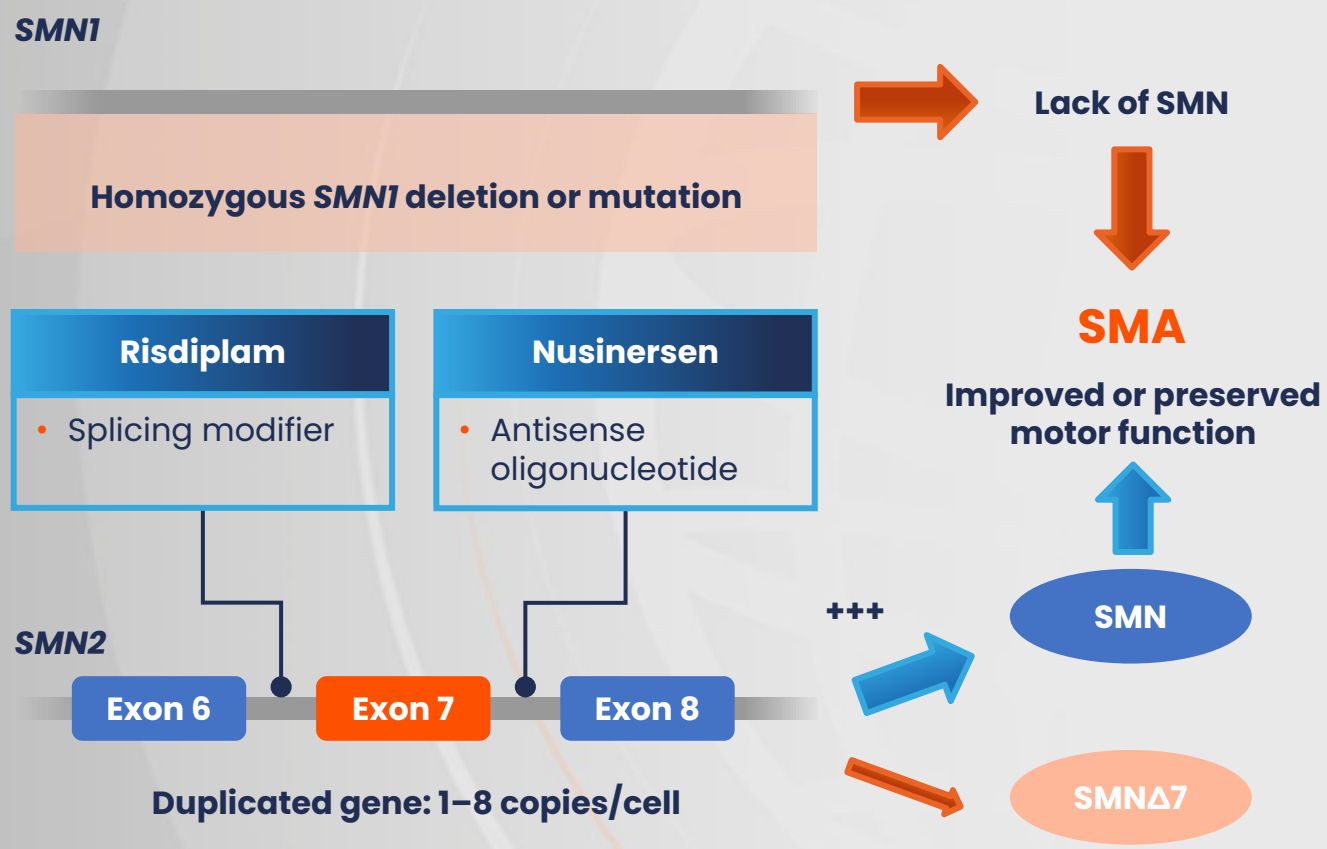

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Schorling DC, et al. *J Neuromuscul Dis*. 2020;7:1–13.

FDA-approved therapies for SMA

Route of administration and approval for different patient populations

Nusinersen[1]

- For paediatric and adult patients
- Intrathecal injection every 4 months

Onasemnogene abeparvovec[2]

- For paediatric patients <2 years of age
- Single IV dose

Risdiplam[3]

- For patients ≥2 months of age
- Oral once daily

FDA, US Food and Drug Administration; IV, intravenous; SMA, spinal muscular atrophy.

1. FDA. Nusinersen. Prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf (accessed February 14, 2022);
2. FDA. Onasemnogene abeparvovec. Prescribing information. Available at: https://www.fda.gov/media/126109/download (accessed February 14, 2022);
3. FDA. Risdiplam. Prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf (accessed February 14, 2022).

FDA-approved therapies: SMA type 1

Onasemnogene abeparvovec

- STR1VE[1]
- **Outcome shown**: Independent sitting for 30 seconds at 18 months

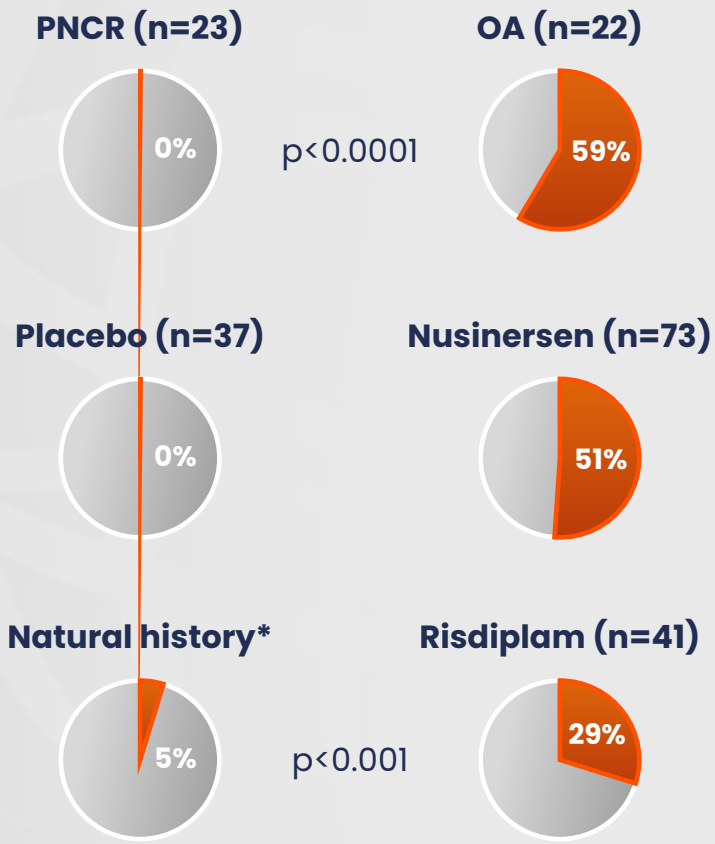
Nusinersen

- ENDEAR[2]
- **Outcome shown**: Motor milestone response at 13 months

Risdiplam

- FIREFISH[3]
- **Outcome shown**: Independent sitting for 5 seconds at 12 months

Percentage of patients achieving outcome



*An arbitrary conservative value of 5% was used.

FDA, US Food and Drug Administration; OA, onasemnogene abeparvovec; PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy.

1. Day JW, et al. *Lancet Neurol.* 2021;20:284–93; 2. Finkel RS, et al. *N Engl J Med.* 2017;377:1723–32; 3. Darras BT, et al. *N Engl J Med.* 2021;385:427-35.

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Onasemnogene abeparvovec: Infants with SMA type 1 and type 2

Observational study

Onasemnogene abeparvovec – Observational study[1]

- N=76
- SMA type 1 or type 2
- Mean weight 9.1 kg (range: 4.0–15.0 kg)*
- 58 (76%) were pre-treated with nusinersen

6 months after gene replacement therapy

- **82%** of patients had an **improvement in motor function** (CHOP-INTEND and HFMSE score)
- **Children pre-treated with nusinersen** showed a **significant increase in motor function** (CHOP-INTEND; p=0.0003)

*The mean age was 16.8 months (range 4.0–59.0 months); onasemnogene abeparvovec is approved in the EU for weights up to 21 kg.[2]

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EMA, European Medicines Agency; HFMSE, Hammersmith Functional Motor Scale—Expanded; SMA, spinal muscular atrophy.

1. Weiss C, et al. *Lancet Child Adolesc Health*. 2022;6:17–27; 2. EMA. Onasemnogene abeparvovec. Summary of product characteristics. Available at: https://www.ema.europa.eu/en/medicines (accessed February 14, 2022).

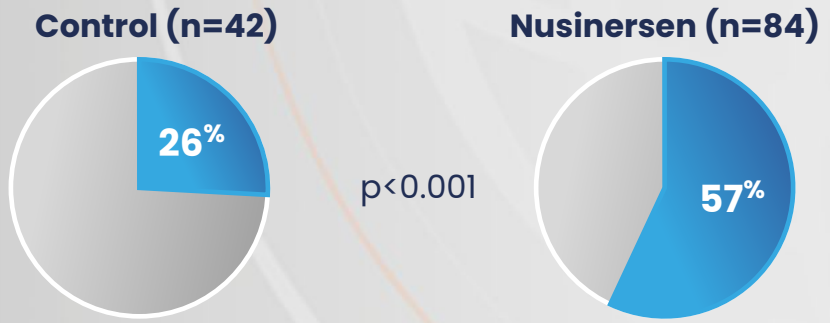
Nusinersen: Children with SMA type 2 and type 3

Clinical trial

Nusinersen – CHERISH

- N=126
- Symptom onset at >6 months of age
- Aged 2–12 years at enrolment
- Ability to sit independently
- No history of ability to walk independently
- 88% with two *SMN2* gene copies
- **Outcome shown:**
  HFMSE score increase of ≥3 points at 15 months

Percentage of patients achieving outcome



HFMSE, Hammersmith Functional Motor Scale—Expanded; SMA, spinal muscular atrophy; SMN, survival motor neuron.
Mercuri E, et al. *N Engl J Med*. 2018;378:625–35.

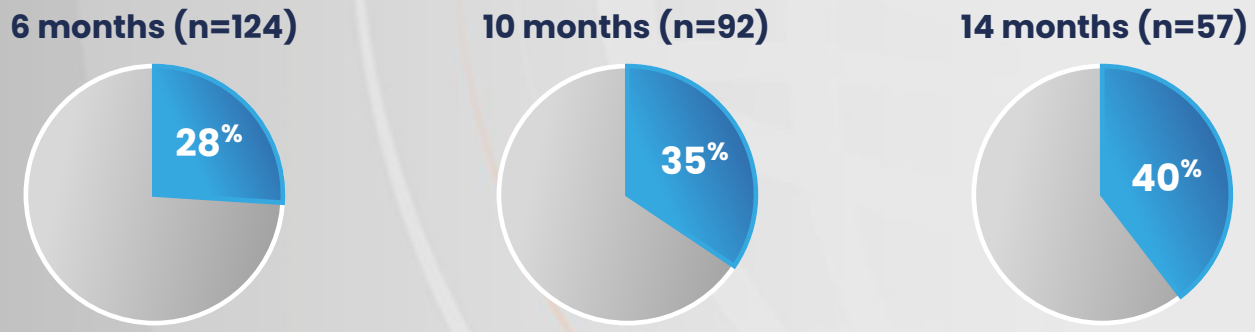
Nusinersen: Adults with SMA type 2 and type 3

Observational study

Nusinersen – Observational study

- N=139
- Aged 16–65 years
- **Outcome shown:**
  Clinically meaningful improvement in motor function (≥3 points in HFMSE) at 6, 10 and 14 months

Percentage of patients achieving outcome



Motor function scores were significantly increased at all time points compared with baseline (p<0.0001)

HFMSE, Hammersmith Functional Motor Scale—Expanded; SMA, spinal muscular atrophy.
Hagenacker T, et al. *Lancet Neurol*. 2020;19:317–25.

Risdiplam: Children and adults with SMA type 2 and type 3

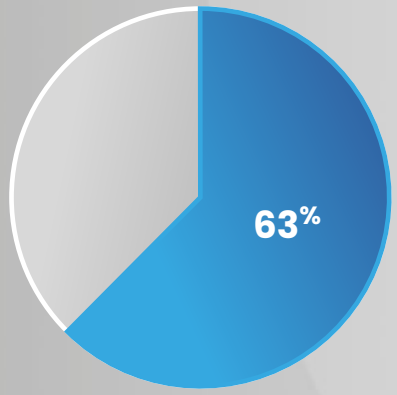
Clinical trial

Risdiplam – SUNFISH part 1

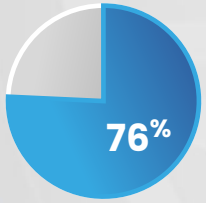
- SMA type 2 or type 3
- Aged 2–24 years
- **Outcome shown:**
  Clinically meaningful improvement in motor function (≥3 points in MFM) at 12 months

Percentage of patients achieving outcome

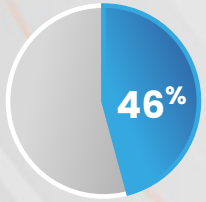
All patients (n=30)



2–11 years (n=17)



12–24 years (n=13)



Risdiplam treatment leads to stabilization or improvements in motor function in patients with SMA type 2 or 3

MFM, motor function measure; SMA, spinal muscular atrophy.

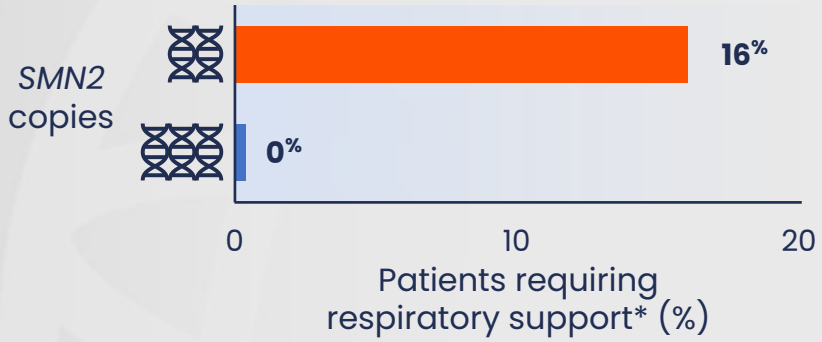
Mercuri EM, et al. Presented at: 23rd International Annual Congress of the World Muscle Society, Mendoza, Argentina. October 2–6, 2018.

Impact of *SMN2* copy number on treatment outcome

Treatment outcome in pre-symptomatic infants depending on *SMN2* copy number

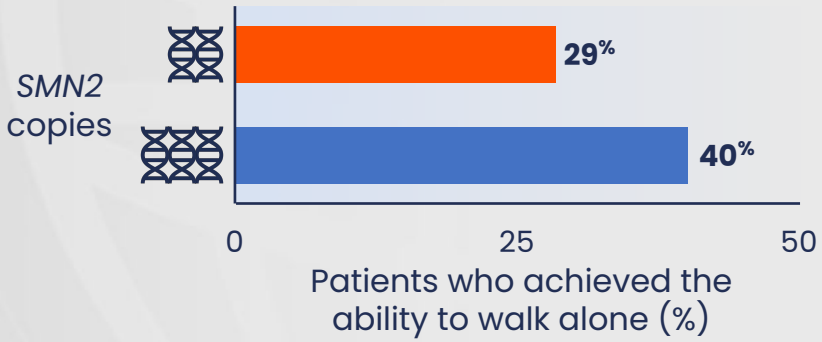
Nusinersen – NURTURE[1]

Median age at last visit: 34.8 months



OA – SPR1NT[2]

Median age at last visit: 15.6 months for 2x *SMN2* and 15.2 months for 3x *SMN2*



More favourable treatment outcome is observed in patients with three compared with two *SMN2* gene copies

* ≥6 hours per day for 7 consecutive days.

OA, onasemnogene abeparvovec; SMN, survival of motor neuron.

1. De vivo DC, et al. *Neuromuscul Disord*. 2019;29:842–56;
2. EMA. Onasemnogene abeparvovec. Summary of product characteristics. Available at: https://www.ema.europa.eu/en/medicines (accessed February 14, 2022).

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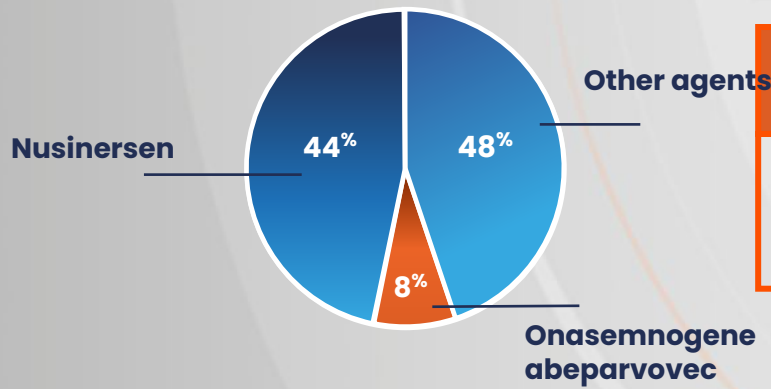
Risdiplam: Previously treated infants, children and adults

Ongoing clinical trial

Risdiplam – JEWELFISH[1]

- N=174
- Aged 6 months–60 years
- Previously treated
- **Primary endpoints:** Safety and PK/PD
- **Secondary endpoint:** SMN protein in blood

Treatment history[2]



Preliminary analyses: 18 patients completed 12 months of treatment[2]

- A median **two-fold increase in SMN protein** vs baseline was observed[2]

PD, pharmacodynamics; PK, pharmacokinetics; SMN, survival motor neuron.
1. NCT03032172. Available at: www.clinicaltrials.gov/ct2/show/NCT03032172 (accessed February 14, 2022); 2. Chiriboga CA, et al. *Neurology*. 2021;96(Suppl. 15):2316.

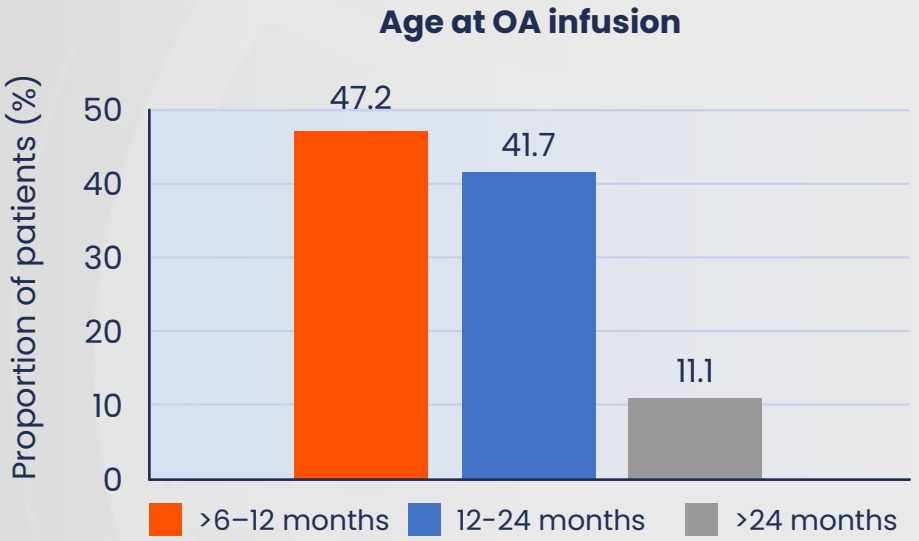
Onasemnogene abeparvovec: Infants and young children

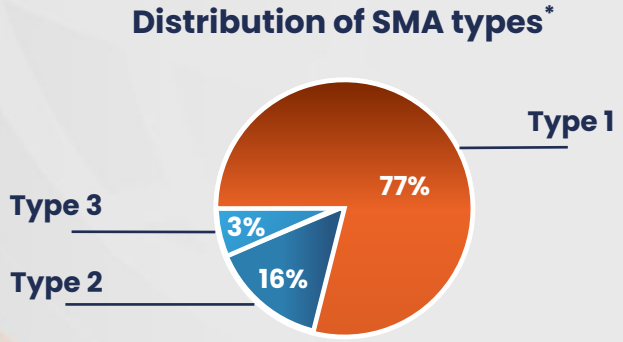
Ongoing clinical trial

OA – RESTORE

- N=36
- Infants and young children
- Age at OA infusion: >6 months
- A range of disease severities (2–4 copies of *SMN2*)

- **Goal:**
  To obtain real-world data on treatment outcomes for OA





*Type was based on observed SMN copy number.
OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy; SMN, survival motor neuron.
Servais L, et al. Presented at: MDA Clinical & Scientific Conference (virtual). March 15–18, 2021. Poster #76.

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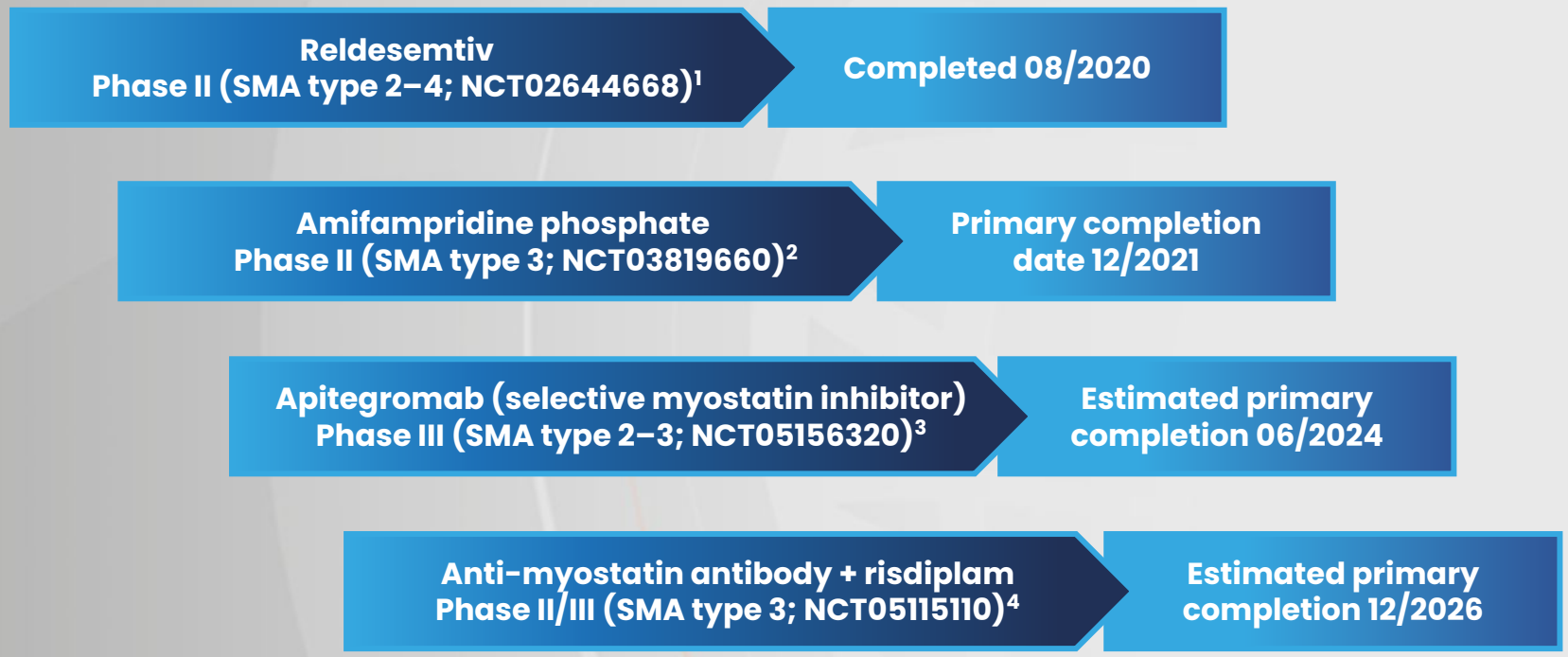
Investigational agents



SMA, spinal muscular atrophy.

1. NCT02644668. Available at: www.clinicaltrials.gov/ct2/show/NCT02644668 (accessed February 14, 2022);
2. NCT03819660. Available at: www.clinicaltrials.gov/ct2/show/NCT03819660 (accessed February 14, 2022);
3. NCT05156320. Available at: www.clinicaltrials.gov/ct2/show/NCT05156320 (accessed February 14, 2022);
4. NCT05115110. Available at: www.clinicaltrials.gov/ct2/show/NCT05115110 (accessed February 14, 2022).

Conclusions

Available data suggest approved treatments for SMA improve outcomes in all patients

The therapeutic landscape is changing for all phenotypes of SMA; available evidence suggests patients benefit from treatment irrespective of disease phenotype

Benefits from treatment are most evident when it is initiated early, before symptom onset

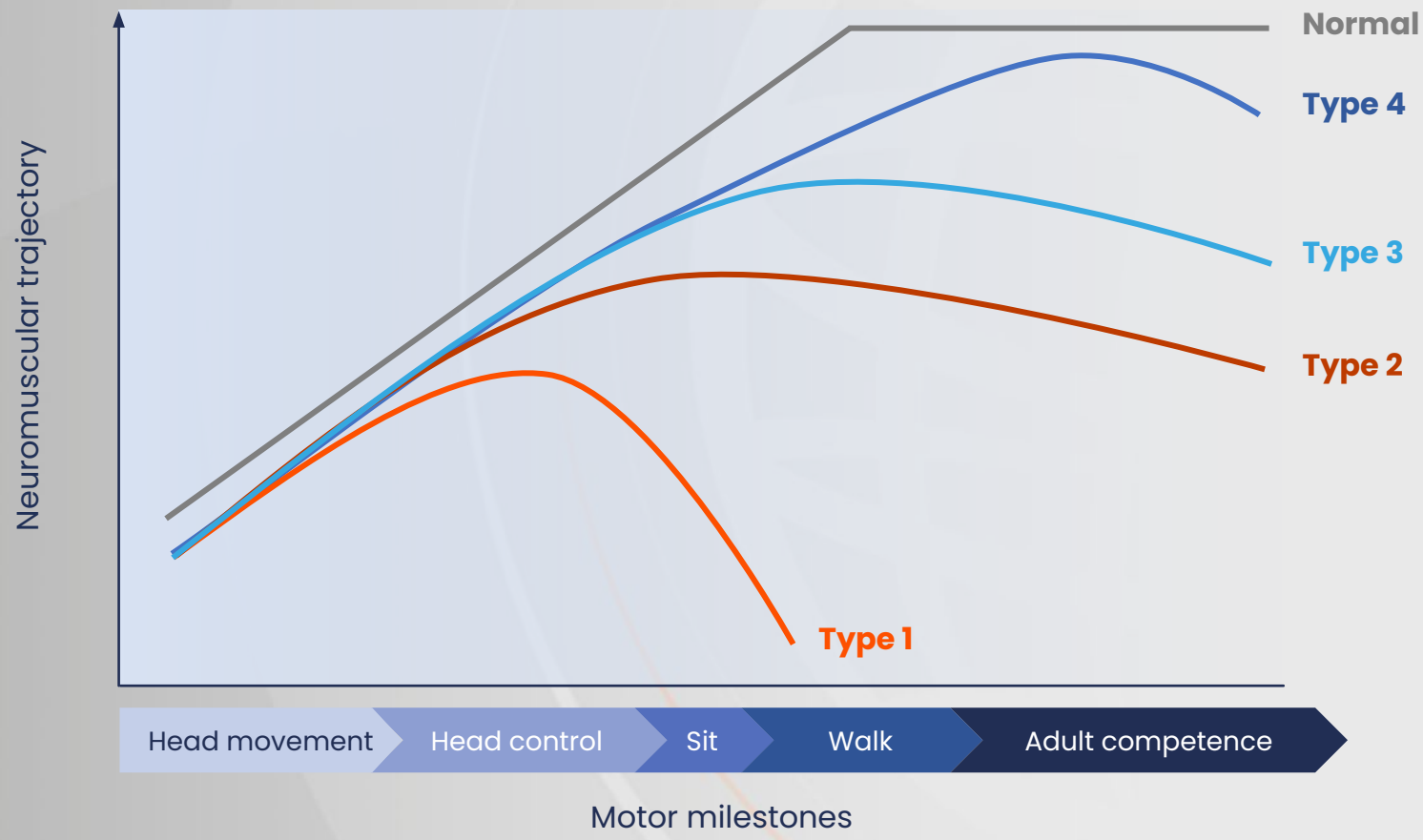
The number of *SMN2* copies affects treatment outcomes for all approved disease-modifying therapies

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

The natural history of SMA and how this is changing with DMTs

Natural history of SMA

Neuromuscular trajectories for different SMA phenotypes vs the normal trajectory



SMA, spinal muscular atrophy.
Figure adapted from Serra-Juhe C, Tizzano EF. *Eur J Hum Gen*. 2019;27:1774–82.

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Natural history of SMA

Neuromuscular trajectories for different SMA phenotypes vs the normal trajectory

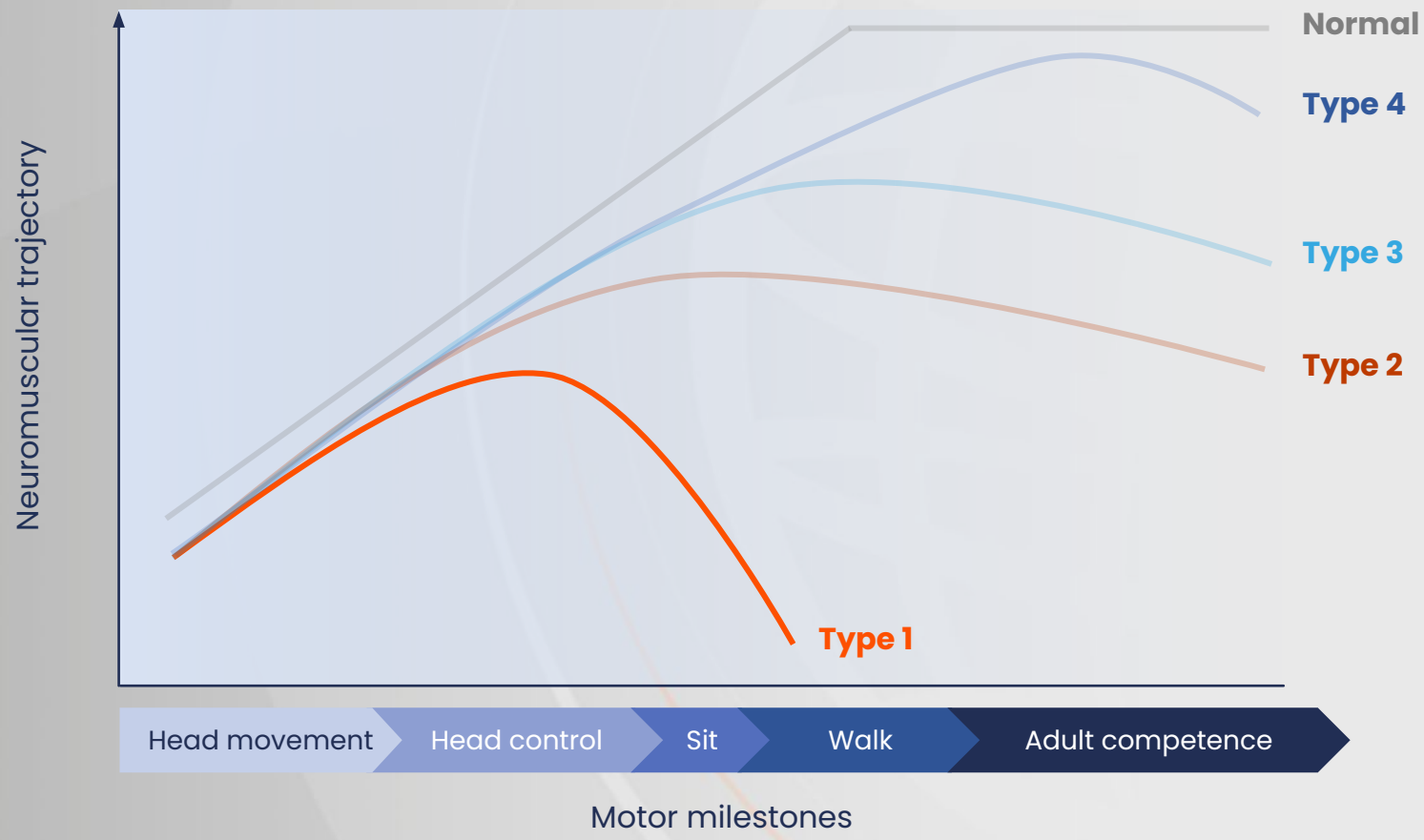

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Figure adapted from Serra-Juhe C, Tizzano EF. *Eur J Hum Gen*. 2019;27:1774–82.

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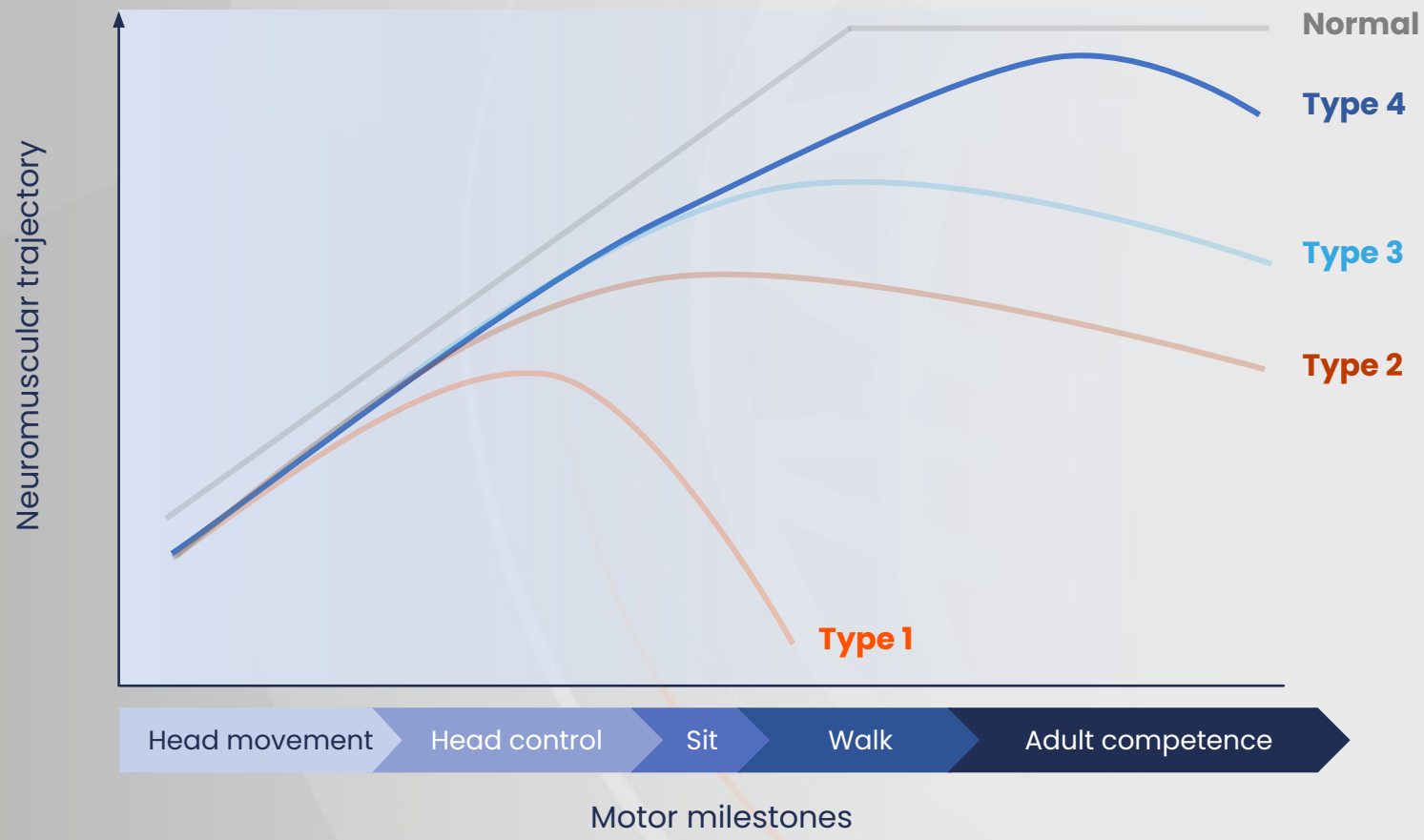

SMA, spinal muscular atrophy.
Figure adapted from Serra-Juhe C, Tizzano EF. *Eur J Hum Gen*. 2019;27:1774–82.

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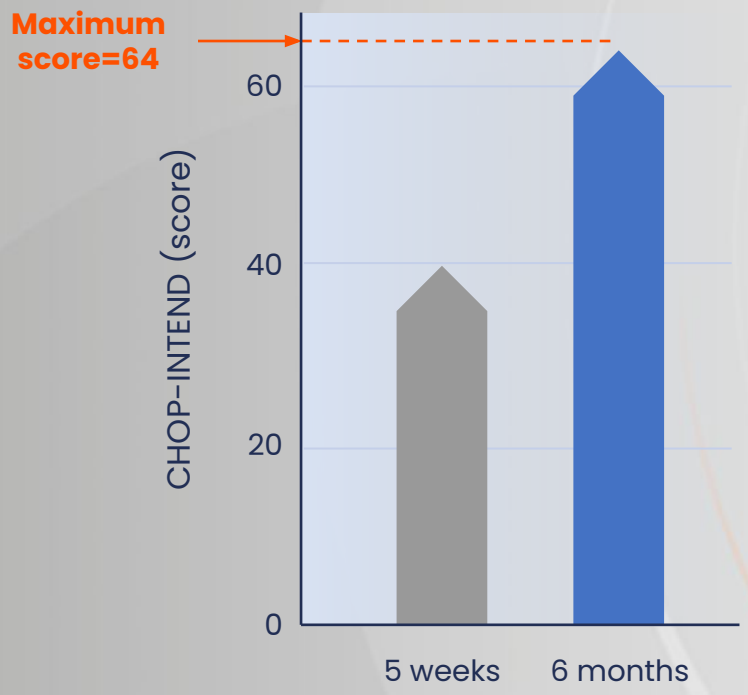
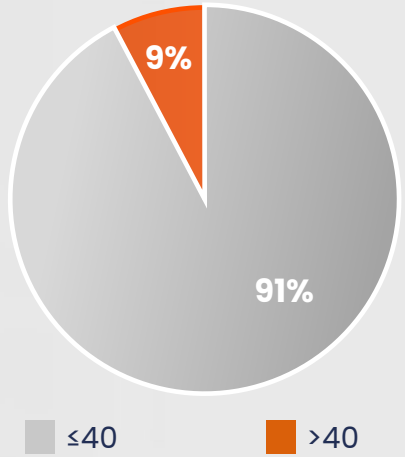
Natural history of SMA type 1

Disease progression is precipitous in infants with SMA type 1

Healthy infants
Typical CHOP-INTEND scores[1]



Infants with SMA type 1
(ENDEAR study; N=22)
Proportion of 5-month-old infants with CHOP-INTEND score >40[2,3]



Few children with SMA type 1 have a CHOP-INTEND score >40 at 6 months[3]

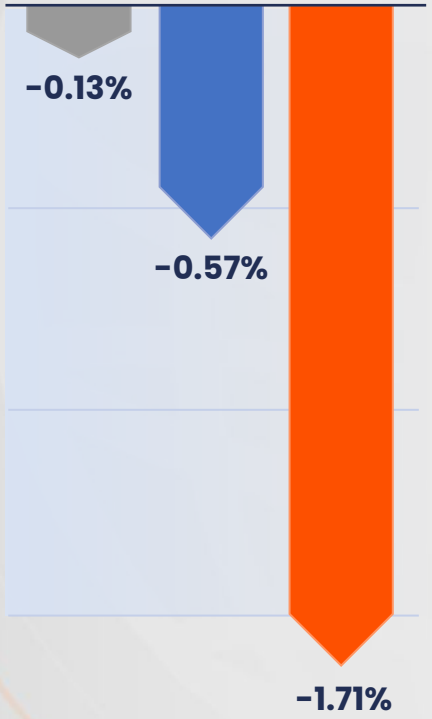
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy.

1. Kolb SJ, et al. *Ann Clin Transl Neurol*. 2016;3:132–45; 2. Finkel RS, et al. *N Engl J Med*. 2017;377:1723–32; 3. Mercuri E, et al. *Orphanet J Rare Dis*. 2020;15:84.

Natural history of SMA type 1

Rate of decline in motor function varies with disease severity

Infants with SMA type 1
Rate of decline in motor function according motor function score (CHOP-INTEND) at baseline



CHOP-INTEND scores at baseline

- Mild: 39–41
- Typical: 20–40
- Severe: <22

Motor function declines rapidly in infants with SMA type 1; the lower the motor function, the more rapid the rate of decline

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy.
De Sanctis R, et al. *Neuromusc Disord*. 2018;28:24–8.

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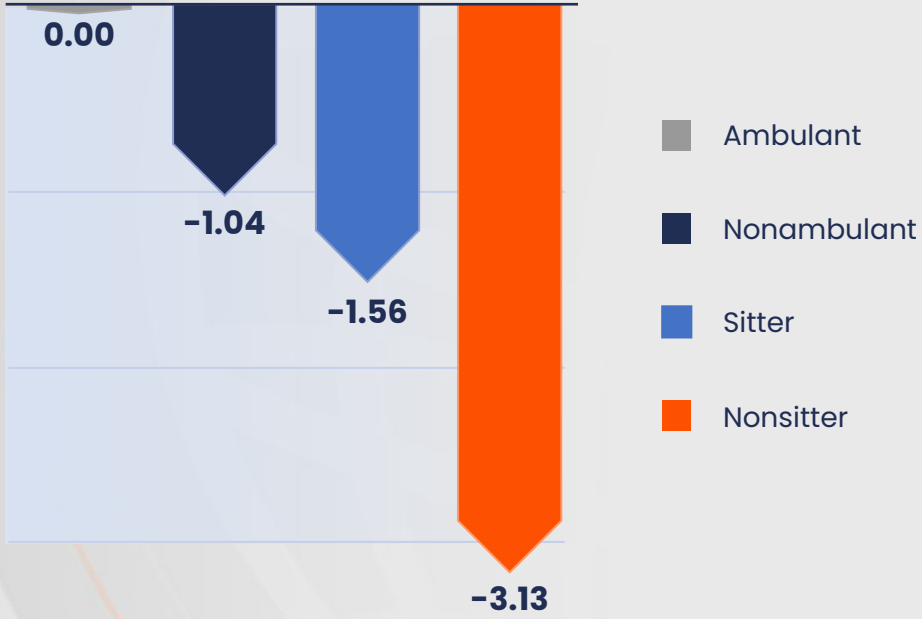
Natural history of SMA type 2 and type 3

Great variability in disease progression for SMA type 2 and type 3

Patients with SMA type 2 and type 3
Decline in motor function (MFM-32) over 24 months



MFM-32, 32-item Motor Function Measure; SMA, spinal muscular atrophy.
Annoussamy M, et al. *Ann Clin Transl Neurol*. 2021;8:359–73.

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Natural history of SMA type 2 and type 3

Great variability in disease progression for SMA type 2 and type 3

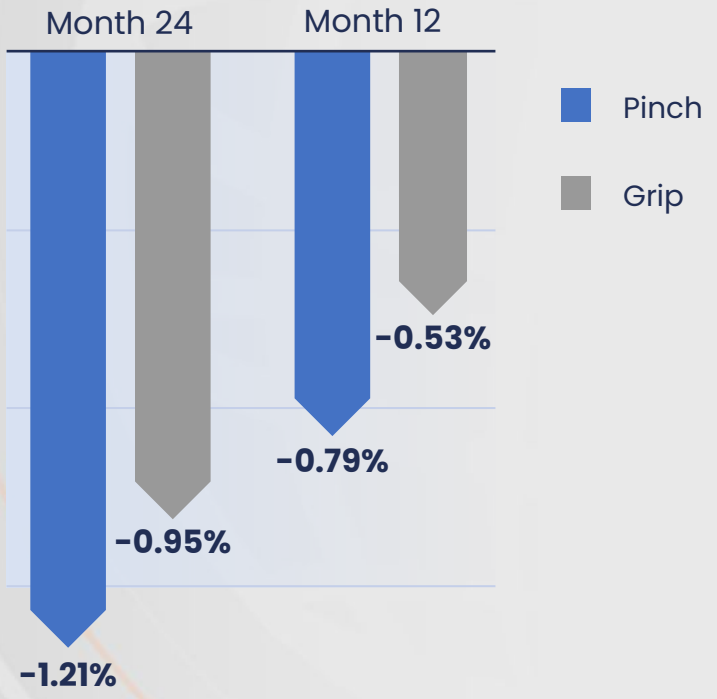
- Progressive decline of lung function in childhood in early-onset SMA, with relative stabilization during adulthood
- Normal lung function is usually observed in patients with later-onset SMA types

SMA, spinal muscular atrophy.
Wijngaarde CA, et al. *Orphanet J Rare Dis.* 2020;15:88.

Natural history of SMA type 2 and type 3

Great variability in disease progression for SMA type 2 and type 3

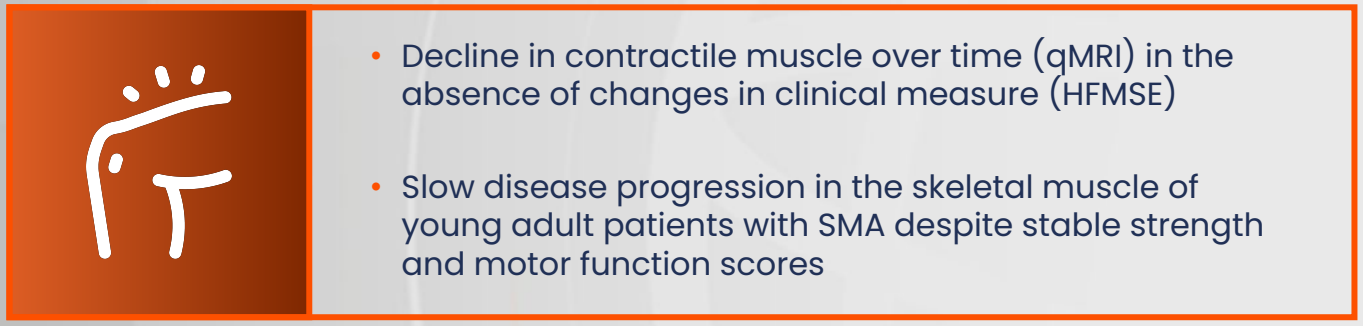
Patients with SMA type 2 and type 3
Progressive decline in upper limb strength from baseline to 24 months



SMA, spinal muscular atrophy.
Annoussamy M, et al. *Ann Clin Transl Neurol*. 2021;8:359–73.

Natural history of SMA type 2 and type 3

Standard clinical measures may not be sensitive to disease progression in milder SMA phenotypes

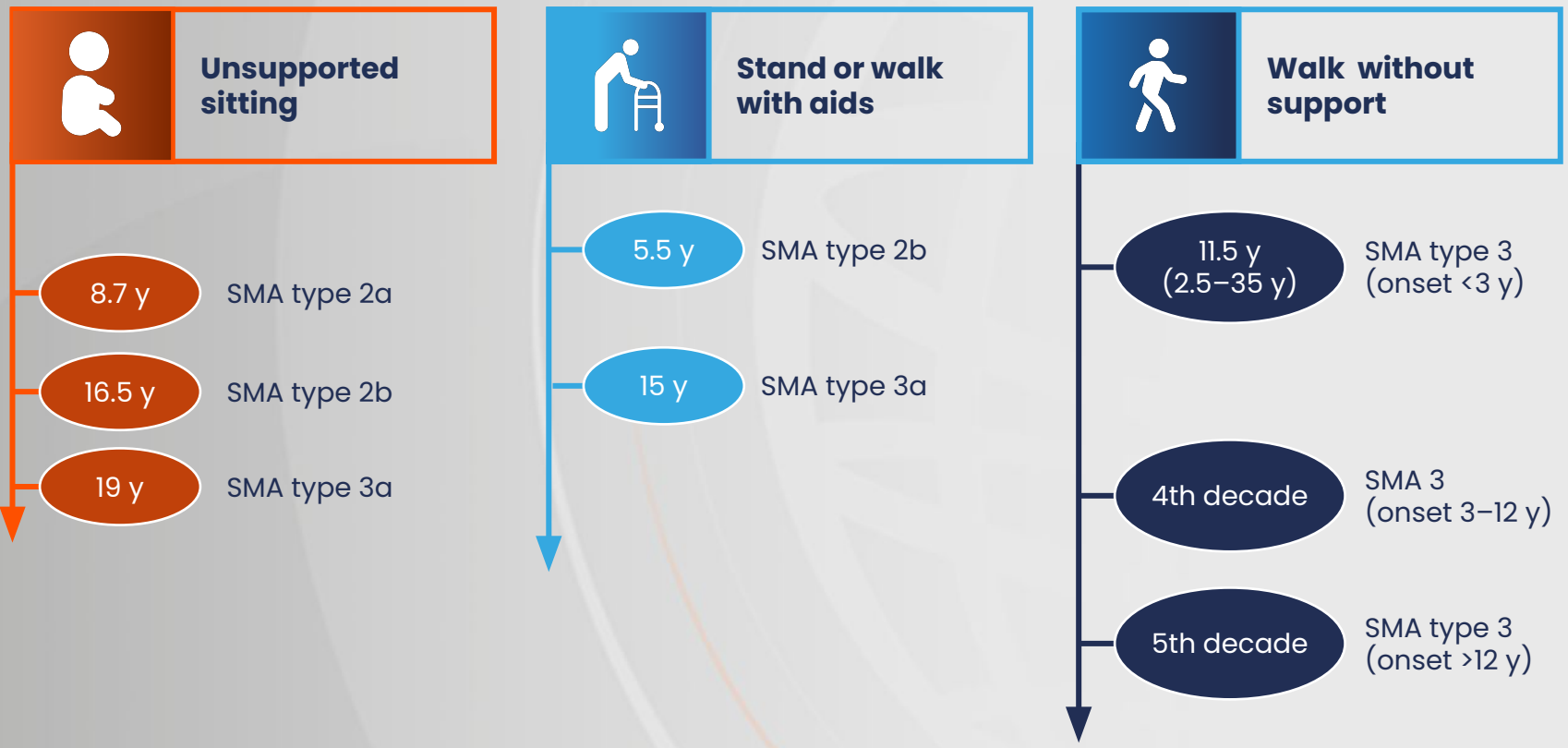


- Decline in contractile muscle over time (qMRI) in the absence of changes in clinical measure (HFMSE)
- Slow disease progression in the skeletal muscle of young adult patients with SMA despite stable strength and motor function scores

HFMSE, Hammersmith Functional Motor Scale—Expanded; qMRI, quantitative magnetic resonance imaging; SMA, spinal muscular atrophy.
Otto LAM, et al. *NMR Biomed*. 2021;34:e4473.

Natural history of SMA type 2 and type 3

Progressive muscle weakness and loss of motor function characterize all SMA types at different ages



SMA, spinal muscular atrophy; y, year.
Wadman RI, et al. *Eur J Neurol*. 2018;25:512–18.

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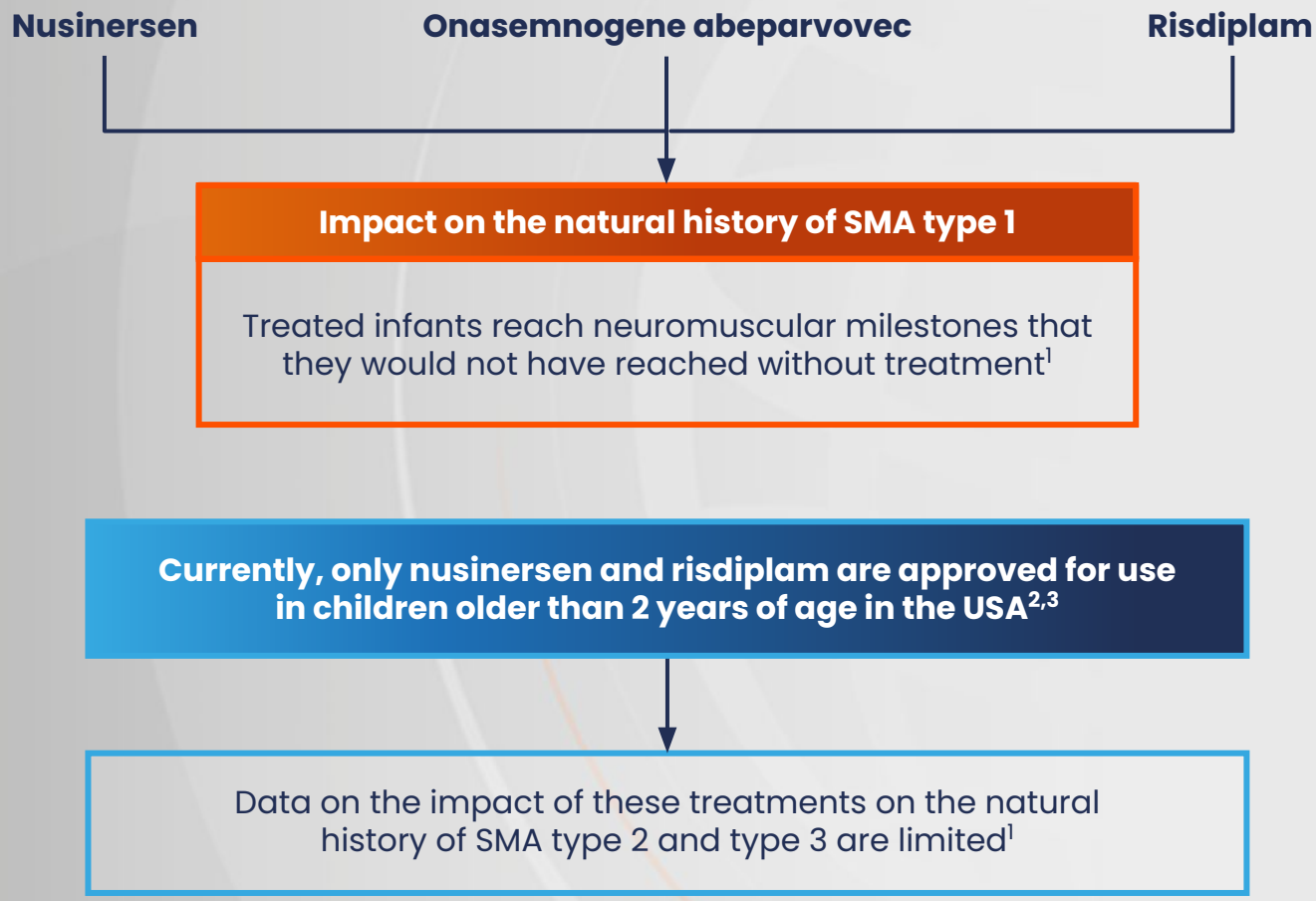
Impact of therapeutic agents on the natural history of SMA



FDA, US Food and Drug Administration; SMA, spinal muscular atrophy.

1. Mercuri E, et al. *Nat Rev Neurol.* 2020;16:706–715;
2. FDA. Nusinersen. Prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf (accessed February 14, 2022);
3. FDA. Risdiplam. Prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf (accessed February 14, 2022).

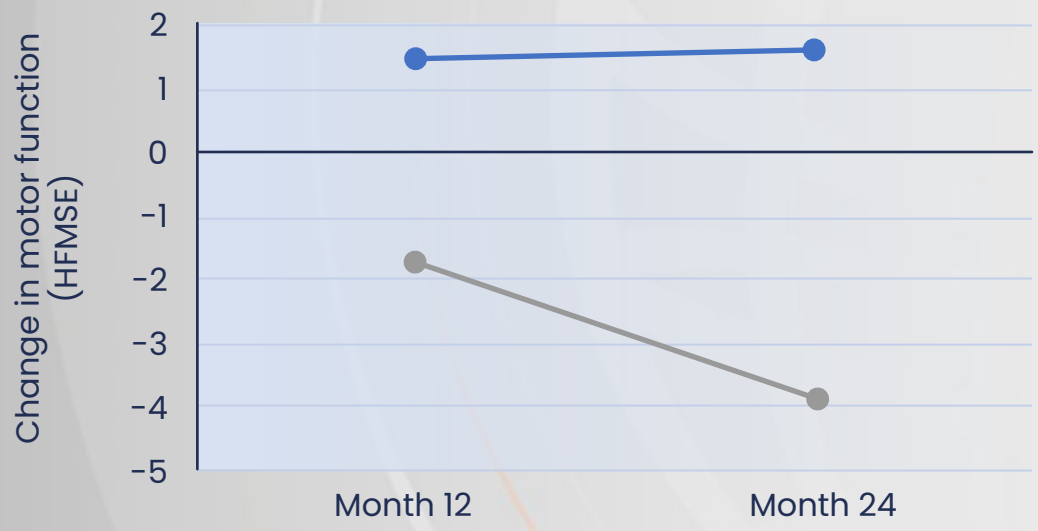
Impact of therapeutic agents on the natural history of SMA

Treatment with nusinersen: Children with SMA type 2 and type 3[1]

Primary endpoint[1,2]
Change from baseline in motor function (HFMSE)

Untreated (N=37; type 2, n=20)
mean age: 10.2 years

Treated (N=30; type 2, n=14)
mean age: 10.6 years



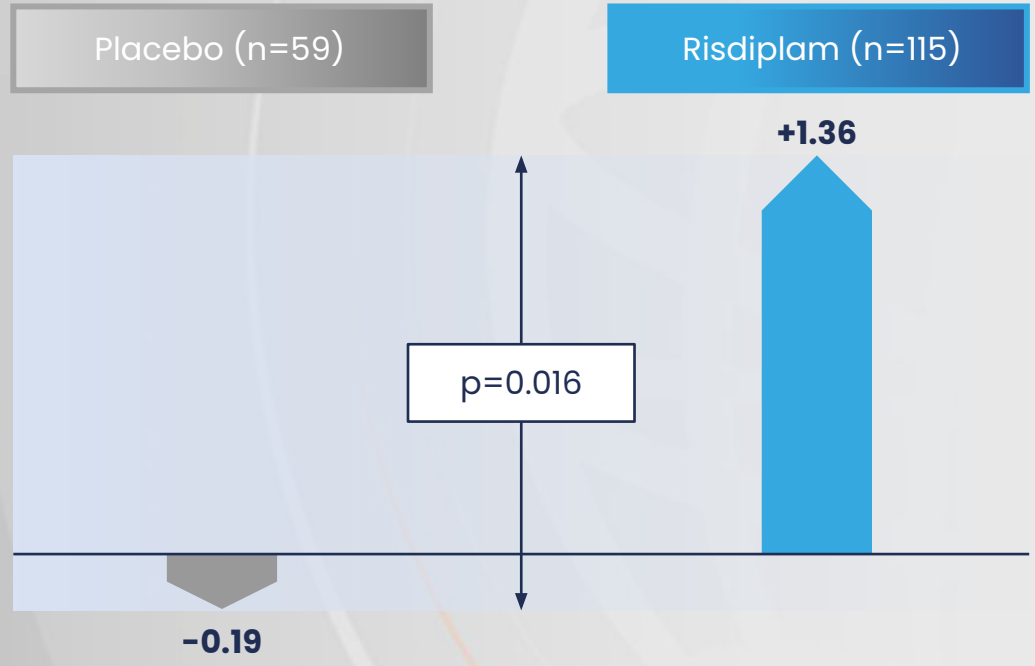
Nusinersen minimized loss of motor function in patients with SMA type 2 and type 3[2]

HFMSE, Hammersmith Functional Motor Scale—Expanded; SMA, spinal muscular atrophy.
1. Mendonça, RH, et al. J *Neuromuscul Dis*. 2021;8;101–8; 2. Coratti G, et al. J *Orphanet Rare Dis*. 2021;16:430.

Impact of therapeutic agents on the natural history of SMA

Treatment with risdiplam: Patients aged 2–25 with SMA type 2 or non-ambulant type 3[1–3]

Primary endpoint[1,2]
Change from baseline in motor function at 12 months (MFM-32)



Gains in motor function at month 12 were maintained or continued to increase to month 24 across primary and secondary endpoints[3]

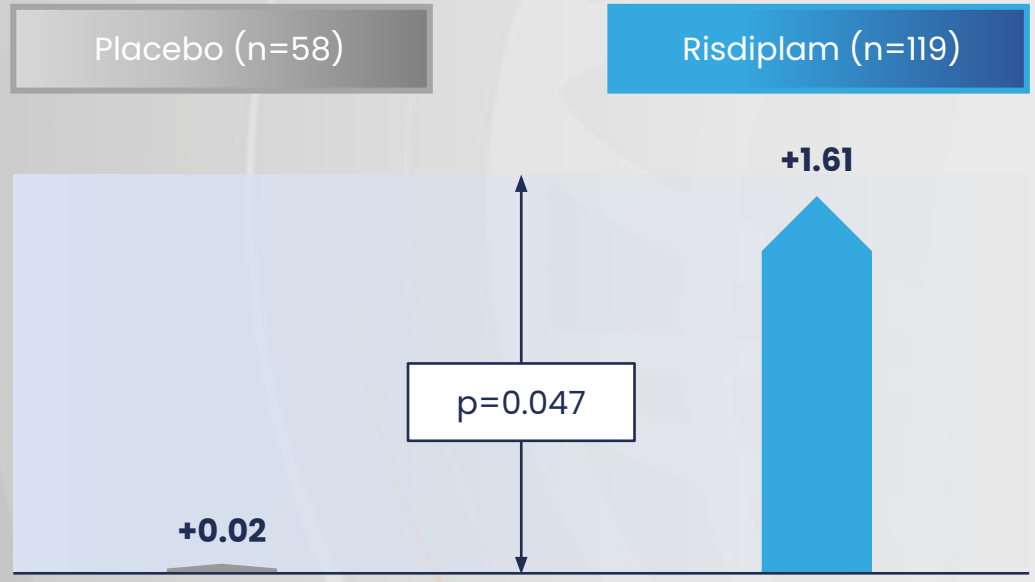
MFM-32, 32-item Motor Function Measure; SMA, spinal muscular atrophy.

1. Mercuri E, et al. *Lancet Neurol.* 2022;21:42–52; 2. NCT02908685. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02908685 (accessed February 14, 2022); 3. SMA UK. 2021. Available at: www.smauk.org.uk/blog/treatments-research/ (accessed March 29, 2022).

Impact of therapeutic agents on the natural history of SMA

Treatment with risdiplam: Patients aged 2–25 with SMA type 2 or non-ambulant type 3[1–3]

Secondary endpoint[1,2]
Change from baseline in upper limb function at 12 months (RULM)



Gains in motor function at month 12 were maintained or continued to increase to month 24 (primary and secondary endpoints)[3]

RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

1. Mercuri E, et al. Lancet Neurol. 2022;21:42–52; 2. NCT02908685. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02908685 (accessed February 14, 2022);
3. SMA UK. 2021. Available at: www.smauk.org.uk/blog/treatments-research/ (accessed March 29, 2022).

Conclusions

Available data suggests approved treatments for SMA improve outcomes in later-onset SMA phenotypes

Available treatments are not a cure; they improve the natural history

Outcomes are likely to be better, if treatment is initiated earlier; decisions about when to start treatment are challenging in adolescent and adult patients with reasonable physical function

Treatments have only been available since 2016; it is important for clinicians to provide feedback to improve understanding of the long-term efficacy and safety of approved treatments

SMA, spinal muscular atrophy.