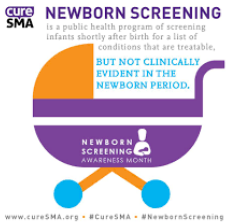


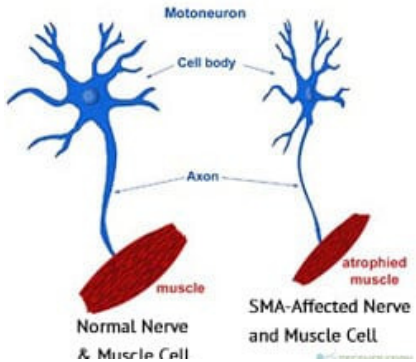
Spinal Muscular Atrophy:

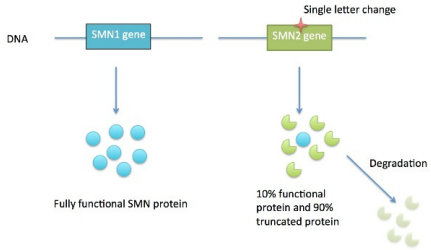
Importance of early diagnosis, management and new treatment options—and outcomes.

Dr K Selby

BC Pediatric Society

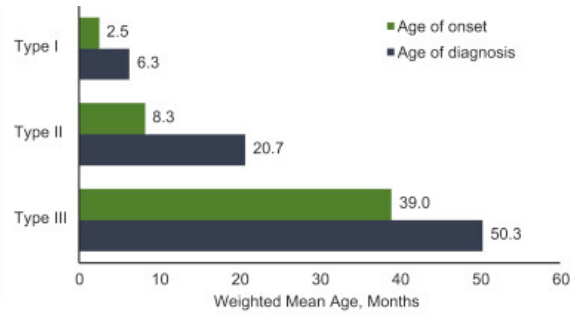
July 14 2021





Objectives

- 1. Understand SMA and the importance of early diagnosis
- 2. Understand importance of Standards of care
- 3.Discuss new treatment options, accessibility and expectations
- 4. What difference does this means to outcome



- **Disclosures**

- Clinical Trials
  - DMD: ReveraGen Pfizer, PTC, Italfarmico, Sarepta
  - SMA: Biogen/ IONIS Pharmaceuticals,
  - National Advisory Consultant Biogen and Novartis for SMA
  - Any photos not in the public domain have been consented by the family
  - Educational material for Roche, Novartis and Biogen

MUSCULAR DYSTROPHY CANADA
DYSTROPHIE MUSCULAIRE CANADA

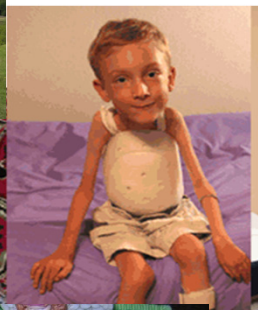
doctors of bc
Better. Together.

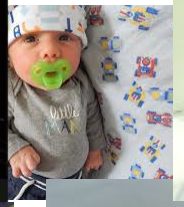
CNDR.ORG
Canadian Neuromuscular Disease Registry

cure SMA

Jesse's JOURNEY
DEFEAT DUCHENNE. CHANGE LIVES.

About SMA





Funded by:

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

MUSCULAR DYSTROPHY CANADA
DYSTROPHIE MUSCULAIRE CANADA

5q:Spinal Muscular Atrophy

- An inherited progressive neuromuscular disorder (AR)
- Caused by a defect of the SMN1 gene on Chromosome 5q
- Incidence ~1/10-11,000
- Carrier rate 1/40-60 : Leading cause of infant mortality
- Degeneration of the motor neurones in the spinal cord with progressive weakness and paralysis
- Untreated infants with type 1 SMA do not achieve motor milestones and die before the age of 2 years from respiratory failure
  - SMA type 1 **non sitters**
  - SMA type 2 **sitters**
  - SMA type 3 **walkers**
  - SMA type 4 **Adult onset**
- Potential for change of Phenotype

Genetics of SMA

- 2 main genes
  - **SMN1 gene** produces a fully functional protein
  - **Mutations SMN1 gene cause SMA**
  - **98% homozygous deletion of Exon7/8 SMN1 gene**

  - **SMN2 gene** differs from SMN1 gene by 1 nucleotide
  - **10% of SMN2 transcripts contain exon 7**
  - **Most of SMN2 lacks exon 7 and produces an inferior unstable protein which rapidly degrades**
  - Greater no. of SMN2 copies the milder the disease

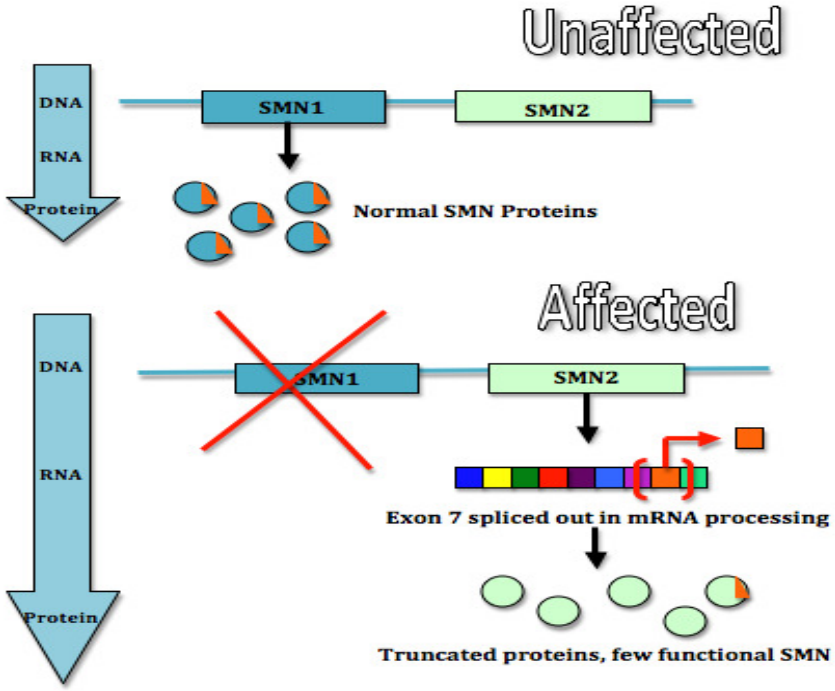


Figure 1: SMN1 and SMN2 in normal and with SMA cases

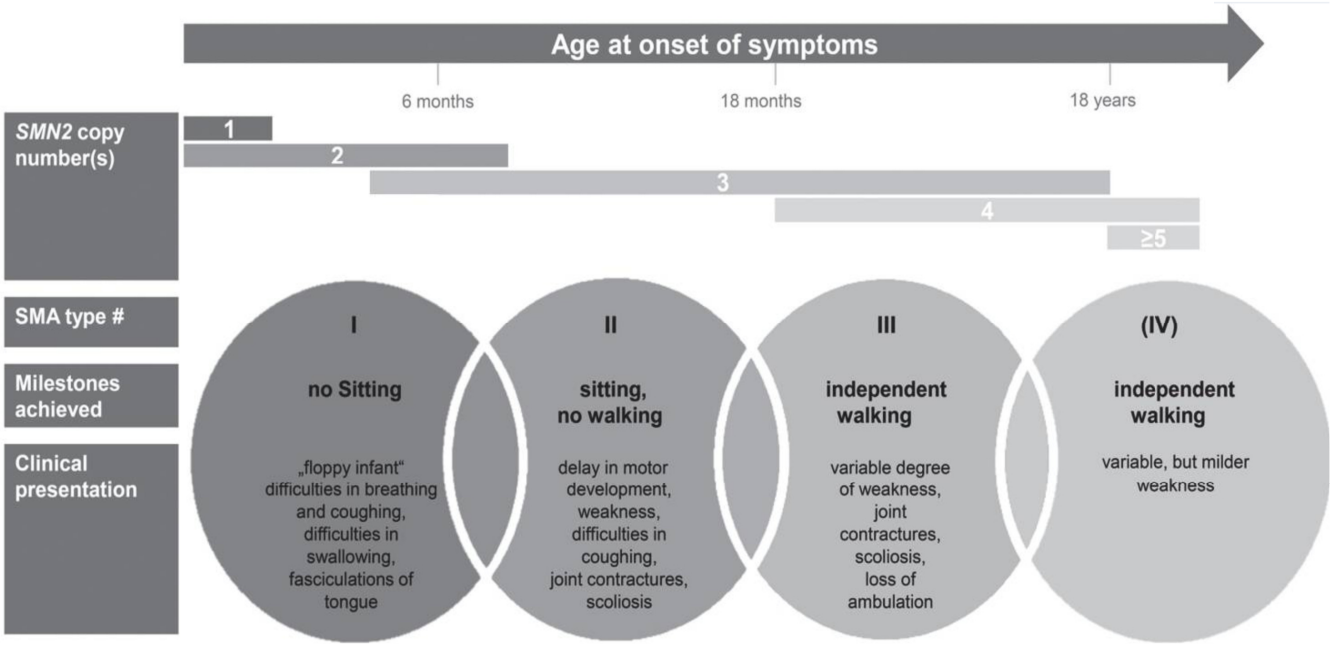
Orange= exon 7

SMA: Phenotypes

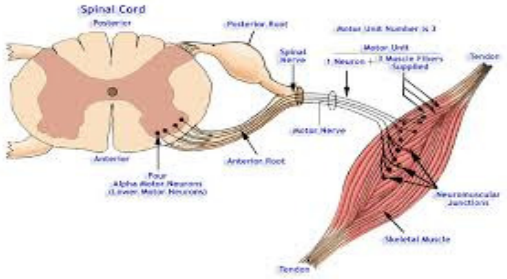
Classification

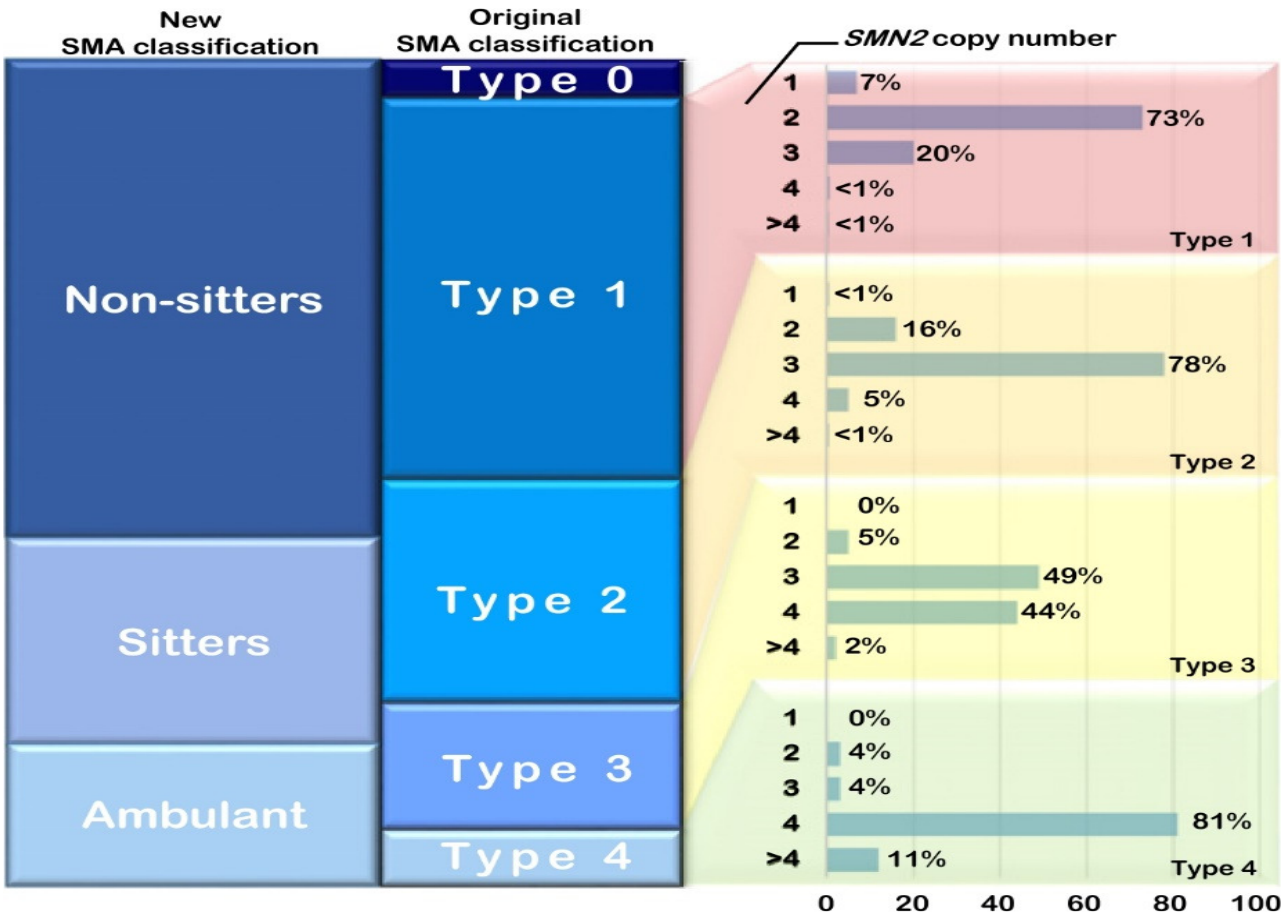
Advances in treatment of SMA–New Phenotypes, New Challenges, New Implications for Care
Schorling, D., Pechmann, A., & Kirschner, J.
Journal of neuromuscular diseases, 7(1), 1–13.

SMA 1 58%
SMA 2 29%
SMA 3 13%
SMA 4 1-2%



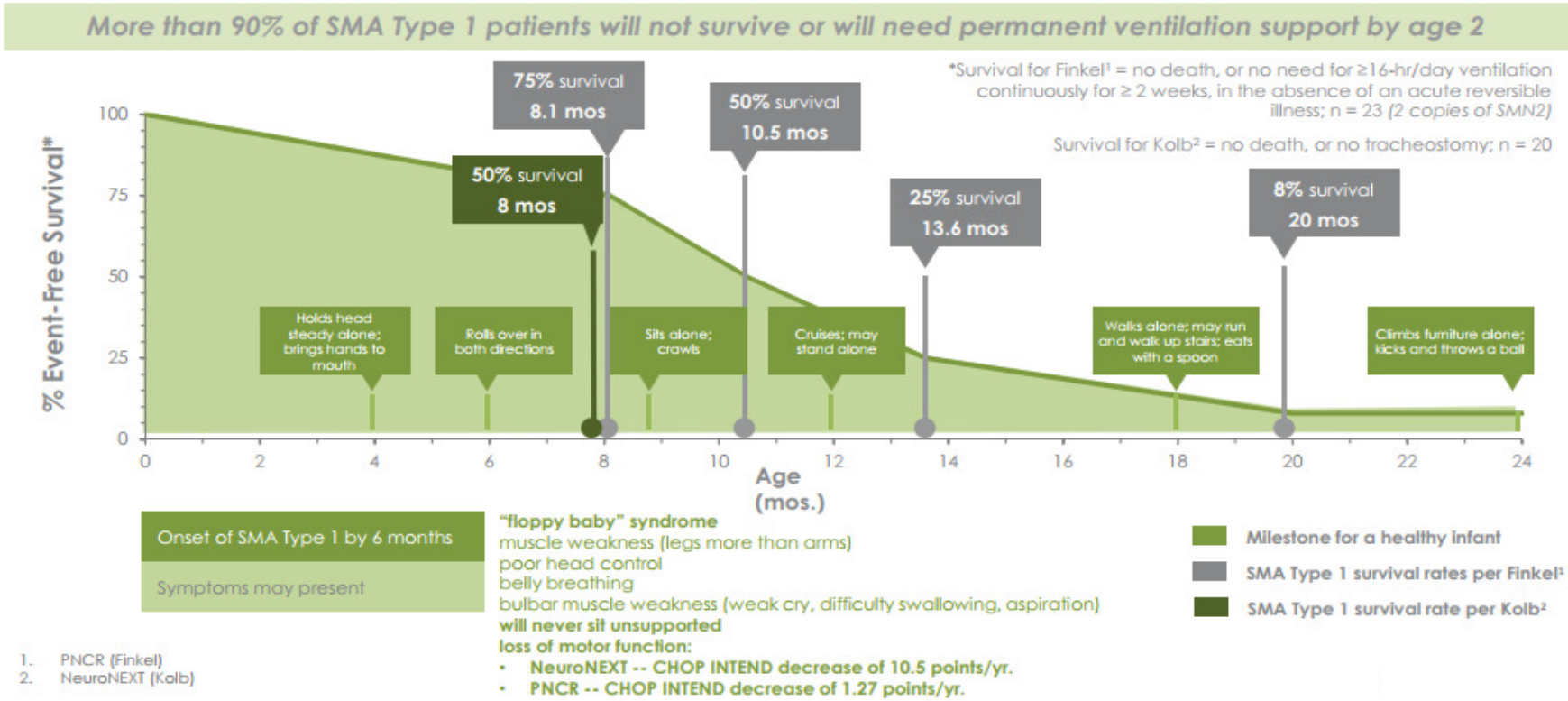
SMA classification





Natural History of SMA type 1

Observational Study of SMA type 1: Finkel et al Neurology August 26, 2014 810-817



Diagnostic journey in Spinal Muscular Atrophy: Is it still an odyssey?

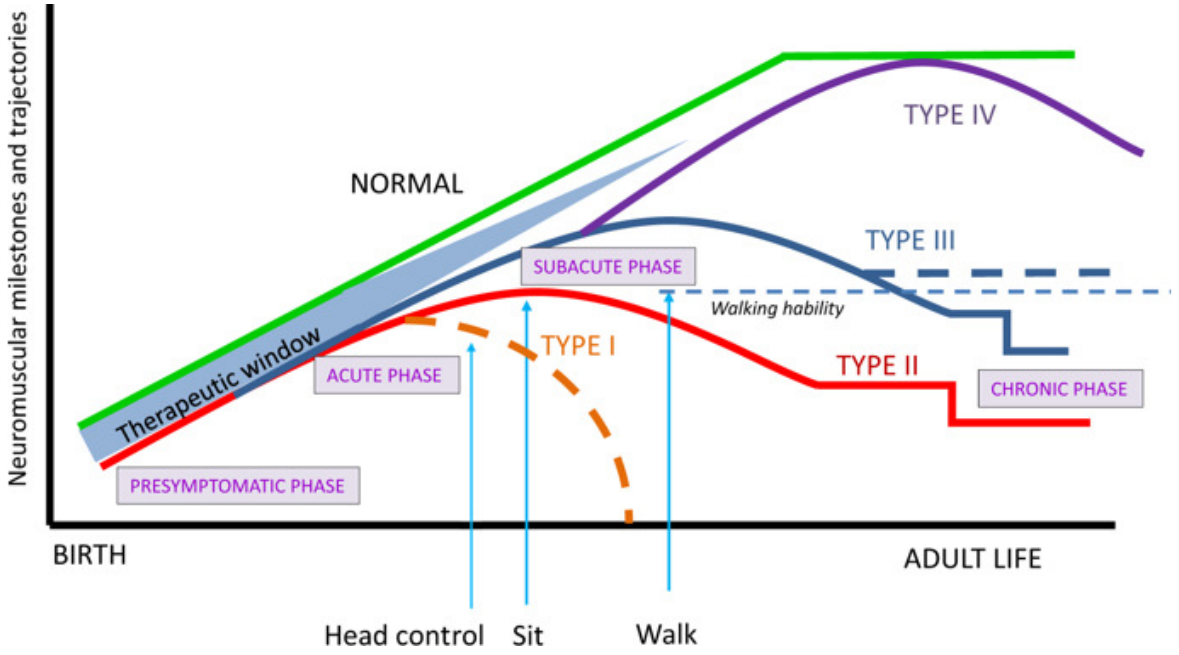
Pera MC, Coratti G, Berti B, D'Amico A, Sframeli M, Albamonte E, et al. (2020) 15(3): e0230677. https://doi.org/10.1371/journal.pone.0230677

First symptoms identified

SMA I (n:191)			SMA II (n:210)			SMA III (n:80)		
First symptoms identified	**N**	**%**	**First symptoms identified**	**N**	**%**	**First symptoms identified**	**N**	**%**
Hypotonia (general)	113	59.16%	Not acquired standing position	83	39.52%	Unsteady ambulation	23	28.75%
Developmental delay (head control)	33	17.28%	Developmental delay (sitting position)	43	20.48%	Frequent falls	18	22.50%
Absence of antigravitary movements	15	7.85%	Hypotonia (lower limbs)	38	18.10%	Difficulty in rise from the floor	10	12.50%
respiratory distress	15	7.85%	Not acquired crawling in time	4	1.90%	Difficulty in stair's climbing	9	11.25%
Developmental regression	7	3.66%	Failure to thrive	1	0.48%	Developmental delay	4	5.00%
Feeding related problems	6	3.14%	Respiratory infections	1	0.48%	Developmental regression	3	3.75%
Absence of deep tendeon reflexes	2	1.05%				Running difficulties	3	3.75%
						'Clumsy' movements	3	3.75%
						Muscle Weakness	2	2.50%
						Toe walking	2	2.50%
						Accidental finding	2	2.50%
						Tremor	1	1.25%

https://doi.org/10.1371/journal.pone.0230677.t001

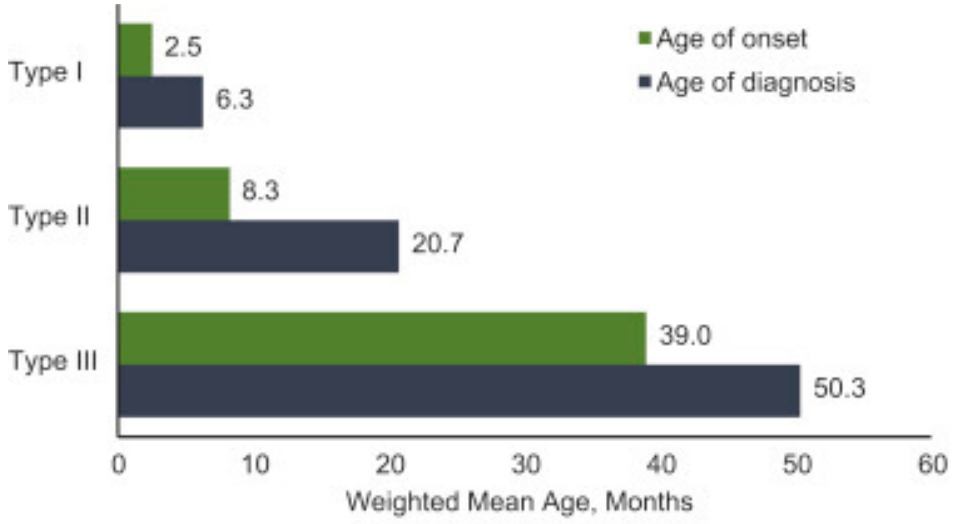
Trajectory of SMA

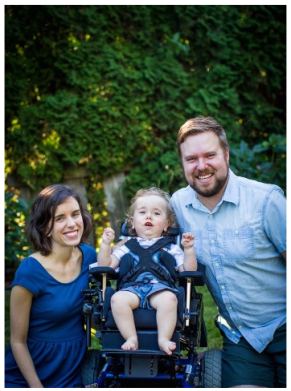


Delay in Diagnosis:

- Diagnostic delay is common in SMA
- The length of delay varied by SMA type
- New Born Screening would help to end diagnostic delay

Lin CW et al Peds Neurol 2015 Oct





Importance of standards of care and new treatment options-disease modifying therapies

- SOC guidelines
- Improved respiratory care
- Nutritional care
- Orthopedic care
- Physiotherapy
- Disease modifying therapies (DMT)
- What are the prognosticators and what has changed
- Approvals of Nusinersen, onasemnogene abeparvovec, and Risdiplam

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders ■■ (2017) ■■–■■

www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

Eugenio Mercuri [a,b,1,*], Richard S. Finkel [c,1], Francesco Muntoni [d], Brunhilde Wirth [e], Jacqueline Montes [f], Marion Main [g], Elena S. Mazzone [a,b], Michael Vitale [g], Brian Snyder [h], Susana Quijano-Roy [i,j], Enrico Bertini [k], Rebecca Hurst Davis [l], Oscar H. Meyer [m], Anita K. Simonds [n], Mary K. Schroth [o], Robert J. Graham [p], Janbernd Kirschner [q], Susan T. Iannaccone [r], Thomas O. Crawford [s], Simon Woods [t], Ying Qian [u], Thomas Sejersen [v] for the SMA Care Group

Available online at www.sciencedirect.com

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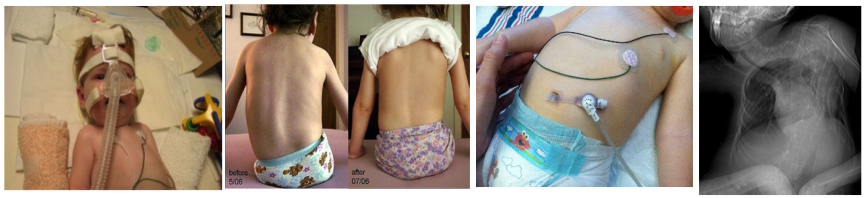
Neuromuscular Disorders ■■ (2017) ■■–■■

www.elsevier.com/locate/nmd

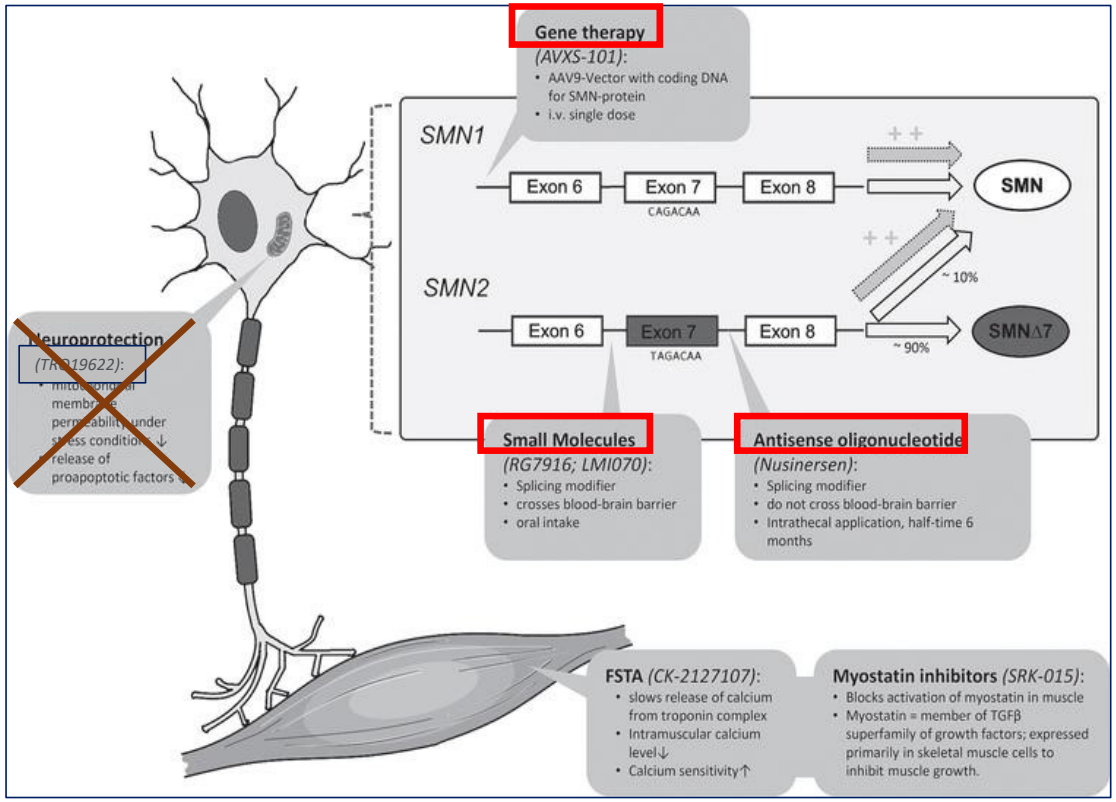
Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

Richard S. Finkel [a,1], Eugenio Mercuri [b,1,*], Oscar H. Meyer [c], Anita K. Simonds [d], Mary K. Schroth [e], Robert J. Graham [f], Janbernd Kirschner [g], Susan T. Iannaccone [h], Thomas O. Crawford [i], Simon Woods [j], Francesco Muntoni [k], Brunhilde Wirth [l], Jacqueline Montes [m], Marion Main [h], Elena S. Mazzone [b], Michael Vitale [n], Brian Snyder [o], Susana Quijano-Roy [p], Enrico Bertini [q], Rebecca Hurst Davis [r], Ying Qian [s], Thomas Sejersen [t] for the SMA Care group



Therapeutic Approaches

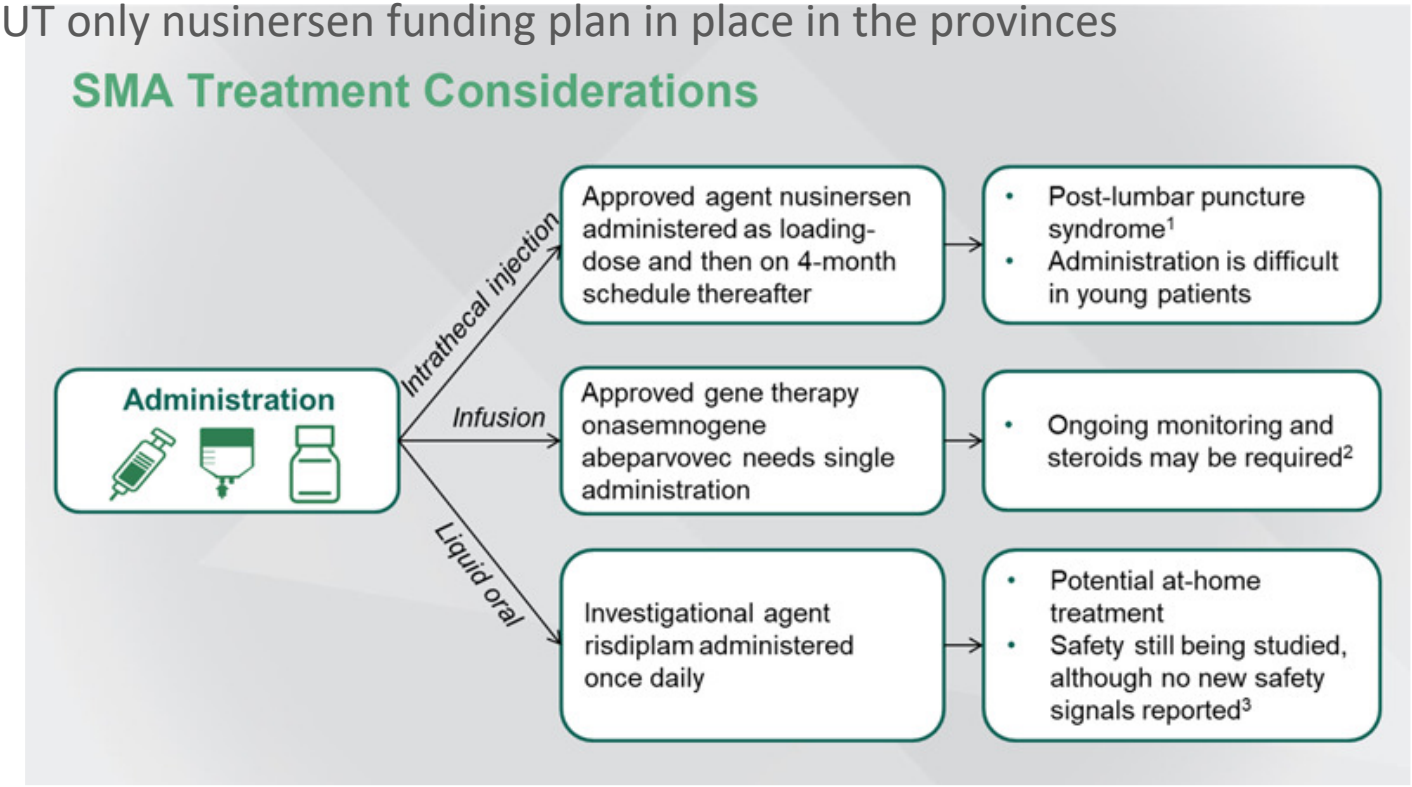
- Modify Splicing of SMN2
- Replacing the SMN1 gene
- Upregulating muscle growth



3 Possible Treatments —

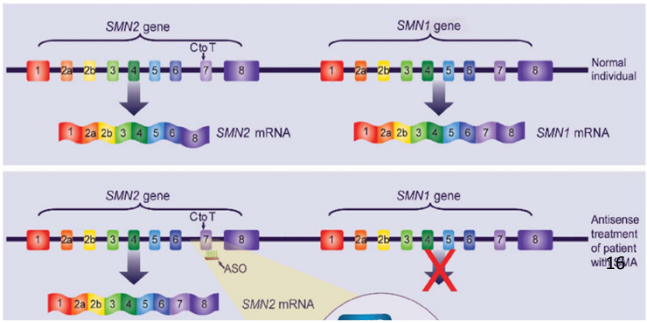
Nusinersen (IT)
Onasemnogene Abeparvovec (IV)
Risdiplam (PO)

- 3 drugs approved Health Canada
- BUT only nusinersen funding plan in place in the provinces

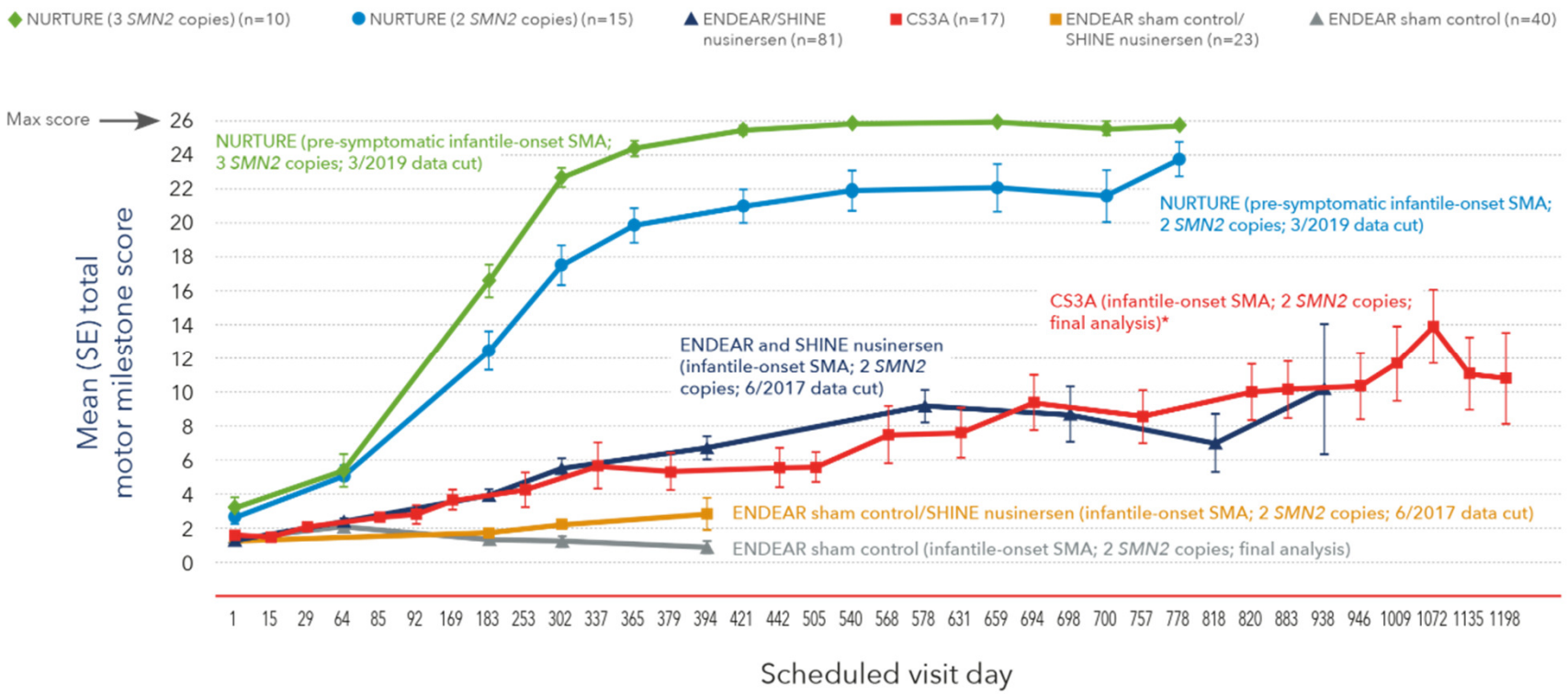


Nusinersen

- First drug approved for 5q SMA treatment in Canada during June 2017
- Antisense oligonucleotide administered IT
- Enhances the inclusion of exon 7 in mRNA transcripts of SMN2
- Results in increased production of a full length SMN protein
- After 4 initial loading doses, injected IT every 4 months



HINE Motor Milestone Scores Over Time Across Studies



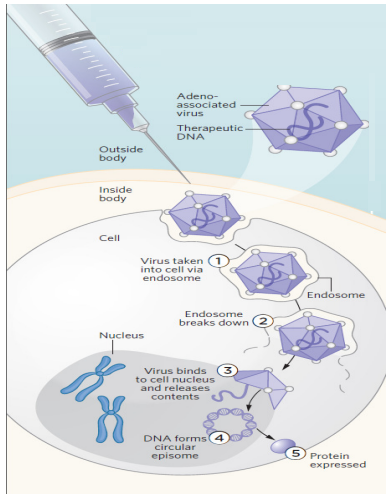
Parsons et al, CureSMA 2019, Platform Presentation

Nurture: WHO Motor Milestone Development

	Motor milestone	Expected age of achievement in healthy infants 1st-99th percentile[1]	Caregiver-reported site-confirmed achievement in NURTURE participants		Median (95% CI) age of first achievement, mo	
			3 *SMN2* copies	2 *SMN2* copies	3 *SMN2* copies	2 *SMN2* copies
	Sitting without support	3.8–9.2 months	10/10 (100%)	15/15 (100%)	6.4 (5.1–7.9)	7.9 (5.9–9.2)
	Standing with assistance	4.8–11.4 months	10/10 (100%)	15/15 (100%)	8.3 (3.5–9.5)	10.0 (5.1–13.5)
	Hands and knees crawling	5.2–13.5 months	10/10 (100%)	13/15 (87%)	8.7 (7.2–10.5)	15.5 (8.9–20.9)
	Walking with assistance	5.9–13.7 months	10/10 (100%)	13/15 (87%)	9.6 (8.0–11.8)	16.1 (11.8–18.8)
	Standing alone	6.9–16.9 months	10/10 (100%)	12/15 (80%)	11.4 (10.3–14.6)	18.6 (12.9–25.9)
	Walking alone	8.2–17.6 months	10/10 (100%)	12/15 (80%)	12.3 (11.2–14.9)	20.4 (15.5–29.7)

Parsons et al, CureSMA 2019, Platform Presentation

Gene Therapy: Onasemnogene Abeparvovec (OA)



OA is a gene therapy designed to deliver a functional copy of the *SMN1* gene to motor neuron cells in SMA patients

Single IV infusion

OA comprises the shell of a genetically engineered virus
Adeno-associated virus (AAV) 9, called a capsid,
Delivers *SMN1* transgene under continuous promotor

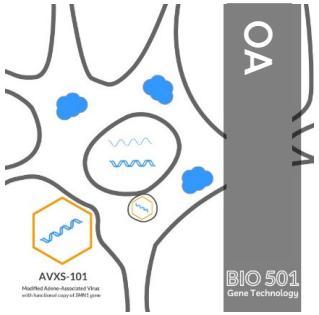
One and Done IV

Dose—according to weight

Approved in USA, Japan and Brazil for children < 2 yr

Recommendations by CADTH for use in SMA with 1-3 copies of SMN2 < 6/12

Approved in EU for SMA with up to and including 3 copies of SMN2 < 21 kg



Onasemnogene Abeparvovec

- Patients treated:

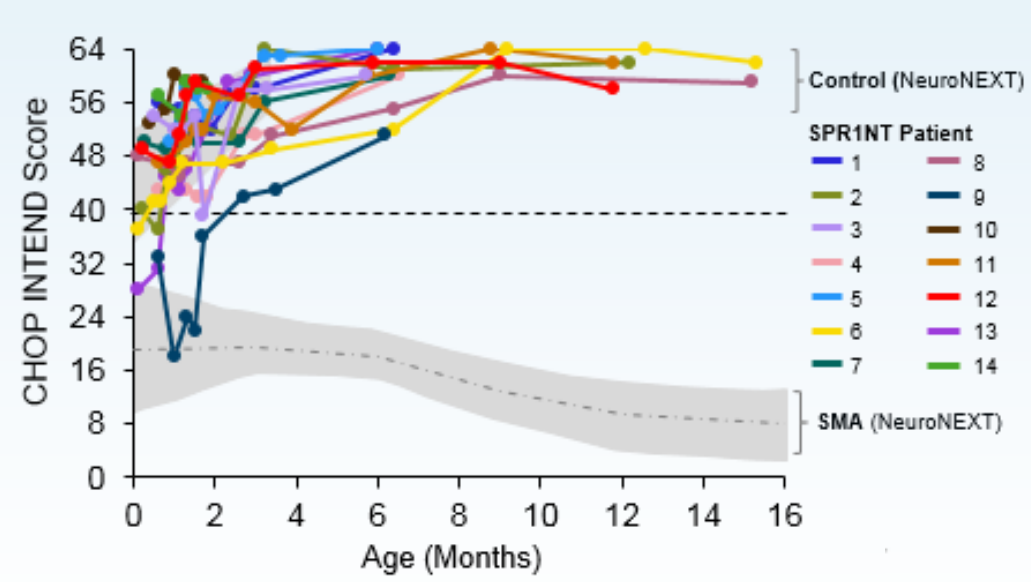
Access to dosing:	Ages:	Number treated:
START	SMA type I; < 6 months old	15
SPR1NT	SMA; pre-symptomatic 2x or 3xSMN2 copies; < 6 weeks old	30
STRIVE	SMA type I; < 6 months old	33
STRIVE-EU	SMA type I; < 6 months old	22
Managed Access Program	SMA; ≤ 2 years old	43 (*as of Dec 2019*)[1]
Commercial dosing	SMA; ≤ 2 years old	192 *(as of Dec 2019)*[1]

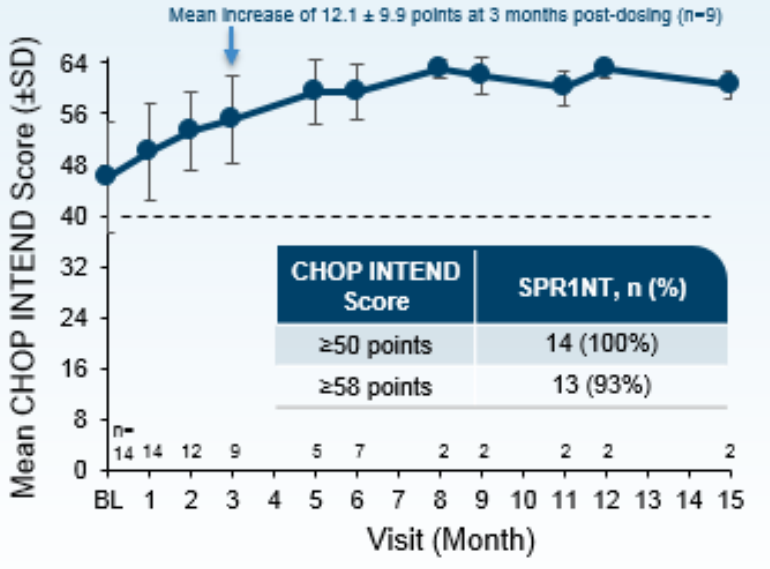
- As of June 18 2021, >1200 patients have been treated world-wide[2]

1. Chand D, et al. J Hepatol. 2020
2. Novartis Media Release – https://www.novartis.com/news/media-releases

Efficacy: SPR1NT pre-symptomatic treatment

2x*SMN2* copy patients

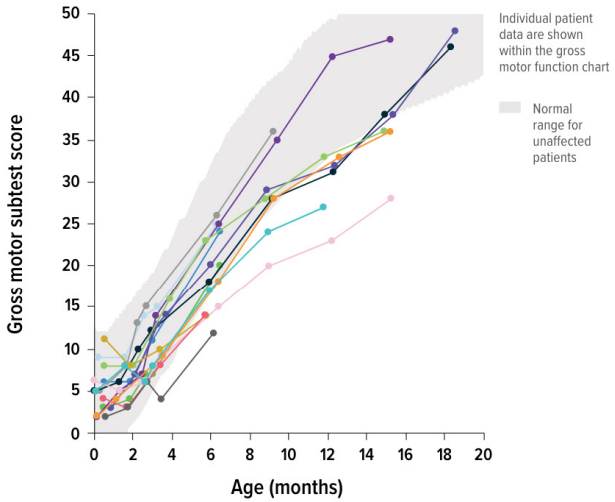




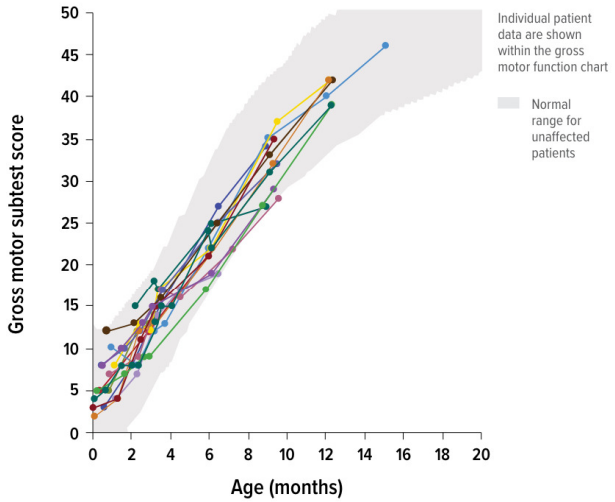
Motor Outcome in Bailey scale
Pre-symptomatic SPRINT

SPR1NT: OA enabled age-appropriate development of gross motor function

Gross motor scores of patients with 2 copies of ***SMN2*** (n=14)



Gross motor scores of patients with 3 copies of ***SMN2*** (n=15)



50% (7/14) of patients with 2 copies of *SMN2* and 100% (15/15) of patients with 3 copies of *SMN2* achieved gross motor scores similar to same-age peers without SMA, as of the Dec 2019 data cut[2,a]

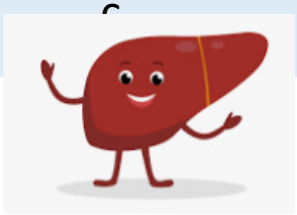
[a]Gross motor function was measured by the Bayley Scales of Infant and Toddler Development, a standardized, well-accepted tool to assess the development of children between the ages of 1 and 42 months, and compares these scores to a standardized norm.[5]

Presymptomatic treatment (June 2021)

- 100% children treated presymptomatically in the SPRINT 2 copy cohort survived without respiratory or nutritional support
- All children sat independently for > 30 seconds within the normal timeline
- Majority (11/14) went onto stand independently and 9/14 walked independently most within the normal age range
- CHOP intend >58 in 100%
- In **Symptomatic** Children with SMA type 1 82% achieved motor milestones not achieved in the natural history study and 49% sat unsupported

Management of Known Adverse Events

Hepati



Platelets

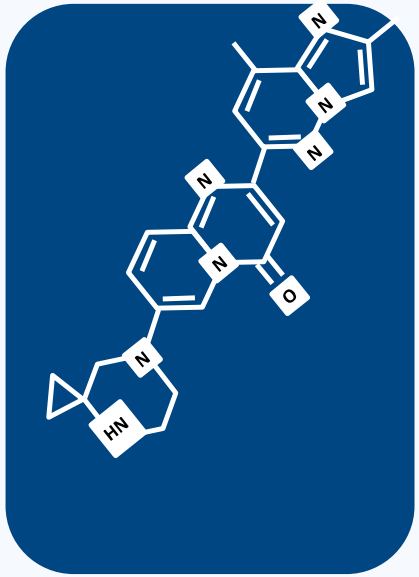
Cardiac

- Prophylactic prednisone / prednisolone:
  - Pre-treat prednisolone – 1-2 mg/kg/d – beginning *day prior* to onasemnogene abeparvovec infusion
  - Prednisolone 1-2 mg/kg/d (x30 days); wean over additional 30 days
  - Vomiting, Fever, Thrombocytopenia, Transaminitis, elevation of Troponin I
  - 3 reports of Thrombotic Microangiopathy (TMA)

Patient Selection & Preparation

- Effective disease-modifying therapy (not a “cure”)
- Motor neuron loss may begin before birth (may not fully “normalize” phenotype)
- Clinical trials focused on children < 6 months old; “real-world data” is emerging
- Less experience in older children with more severe symptoms
- Careful balance of potential benefits vs. potential side effects
- Evaluate for underlying medical conditions that might heighten risk of side effects
- Need for close & careful monitoring (months) post-dosing

Risdiplam (RG7916): An oral molecule with CNS and peripheral distribution



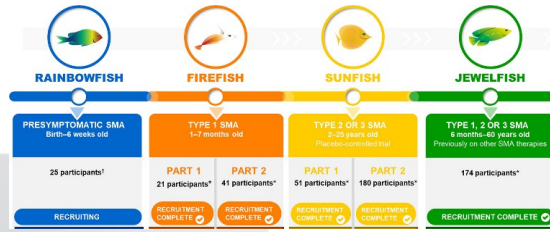
Risdiplam[1,2]

- A selective *SMN2* splicing modifier designed to bind uniquely with specificity to *SMN2* pre-mRNA
- Promotes the inclusion of exon 7 in *SMN2* mRNA and the production of full-length *SMN2* mRNA and functional SMN protein
- Orally administered with a systemic distribution
- Liquid once daily
- Penetrates the blood–brain barrier
- Developed in collaboration with SMA Foundation and PTC Therapeutics

DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Sivaramakrishnan M, et al. Nat Commun. 2017; 8:1476; 2. Cure SMA. http://www.curesma.org/news/ptc-therapeutics-update-june2018.html (Accessed Aug 2018).

PeerVoice



Managing SMA: Risdiplam Clinical Trial Programme

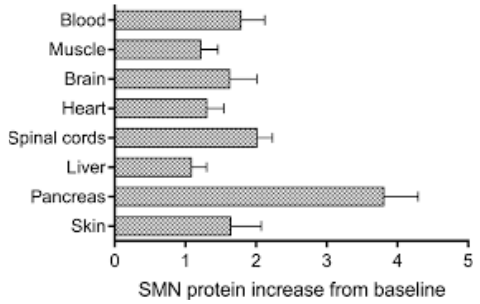
Trial (NCT)	Design	Type of SMA	Patient Age Range	Status
RAINBOWFISH (NCT03779334)[1]	Open-label, single-arm, multicentre	Presymptomatic	Infant to 6 wk	Recruiting
FIREFISH (NCT02913482) 2 Parts[2]	Open-label	Type 1	Infants	Part 2 met primary endpoint: 29% of infants (12/41) sitting without support for 5 sec by month 12[3]
SUNFISH (NCT02908685) 2 Parts[4]	Double-blind, PBO-controlled	Type 2 or 3 (nonambulatory)	2 to 25 y	Part 2 met primary endpoint: Change from baseline in the Motor Function Measure 32 scale after 1 y with risdiplam vs PBO[5] • No treatment-related safety findings leading to study withdrawal
JEWELFISH (NCT03032172) 2 Parts[6]	Open-label, exploratory	Previously treated with SMA-directed therapies	6 mo to 60 y	Recruiting

FIREFISH Study: Infants 1-7 months Type 1 SMA 2 SMN2 copies

- 41 infants
- Median age of enrollment 5.3 months
- At assessment median age of 20.7 months
- 90% showed > 4 point increase in CHOP intend
- 56% achieved a score > 40 (median increase 20 points)
- 93% were alive
- 85% did not require ventilation or any respiratory support
- 89% were able to feed orally
- 29% could sit > 5 secs at 12 months
- No treatment related safety findings led to drug withdrawal

Risdiplam in type 2 and 3 SMA (sunfish)

- Children and Adults with SMA type 2 and 3 aged 2-25 years had improved motor function and stabilization on MFM 32 score at 24 months
- Increased motor function on RULM
- No new safety concerns
- Good benefit vs risk profile
- More than 2,500 patients now treated
- Real world evidence
- S/E: RTI, pyrexia, headaches, diarrhoea, influenza and pneumonia



Treatment evolution in SMA

Primary prevention

- Reproductive carrier screening
- Reproductive options for couples at high risk

↓

Expected outcomes

- Reduction in incidence and prevalence of SMA

Secondary prevention

- Newborn screening and early treatment

↓

Expected outcomes

- Reduction in burden of SMA
- Increase in SMA prevalence
- Evolution of new phenotypes
- Personalized (precision medicine) model of care

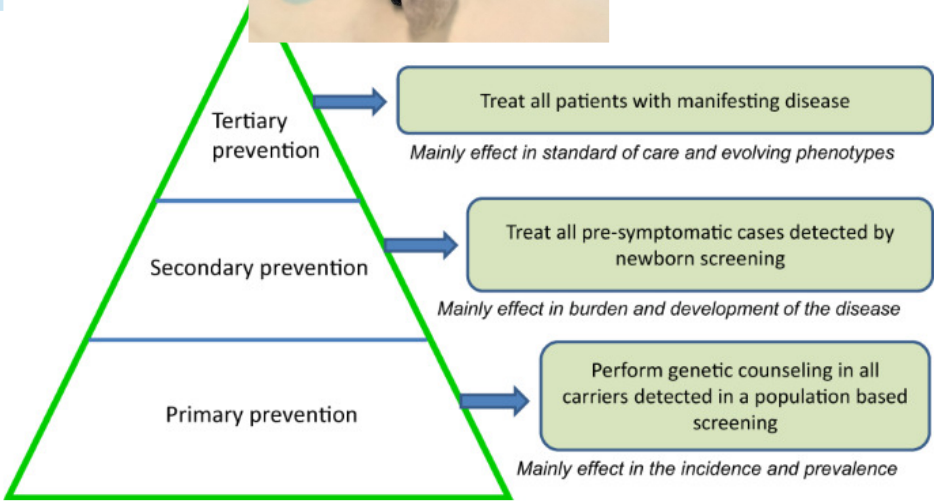
Tertiary prevention

- Treatment of symptomatic patients

↓

Expected outcomes

- Modification of natural history and disability
- Increase in SMA prevalence
- Evolution of new phenotypes
- Increase in proactive care



Now treatment choices-- 3 DMT and SOC

- What does this mean for outcomes
- What treatment should we use and when
- What are the changes in Rehabilitation
- Ensuring SOC
- What about changes in care of backs and hips and feeding and bones and equipment
- What about NB Screening
- Cost
- Combination Therapies?

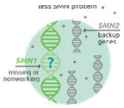
Prognostic Factors and treatment effect modifiers in SMA causing increased survival

- 1. **SMN2 Copy number**
  - Genotype/phenotype is not absolute
- 2. **SMA severity**
- **3.More aggressive SOC** –leads to increased survival---however this does not lead to acquisition of motor milestones

What are the prognosticators of **outcome** in SMA

- Introduction of Disease Modifying Treatments(DMTs) has changed the course and outcome of SMA -dramatically
- Treated patients live longer and have improved functional abilities
- Patients have improved quality of life
- Prognostic factors include
  - SMN2 copy number
  - Baseline motor, bulbar and respiratory function
  - Age of symptom onset
  - Age at treatment onset
  - Implementation of standards of care

Factors which modify outcomes of treatment



- Disease duration before initiation of DMT
- Age at treatment initiation in SMA types 1, 2 and 3
- Children with SMA 6-15 years are very susceptible to complications such as progressive contractures, scoliosis and this causes functional deterioration.
- Age of Symptom onset

- Supportive therapy
- Disease severity
- Although SMN2 copy number has a prognostic effect in untreated patients it did not lead to a better response to treatment
- Presymptomatic children with 3 copies of SMN2

Conclusions

- Disease Modifying Treatments(DMTs) in SMA are changing the disease trajectory
- Main factors in determining outcome include
  - Age at treatment initiation
  - Use of supportive therapies
  - Disease duration
  - EARLY DIAGNOSIS
  - NewBorn Screening Programs

- Need for Markers to monitor response to ongoing treatment
- Ongoing trials need to ensure adjustments for potential confounders
- Real world evidence and use of Registries-CNDR

Things We Have Learned & Things We Need To Know

- Importance of timing of treatment initiation
- Pre-symptomatic Rx shows favourable outcomes
- New Rx options are changing the natural history and phenotype of SMA
- Longer studies needed to elucidate efficacy and safety profiles and how to individualize therapy
- Do clinical trial populations reflect real world patients?
- How can we improve function with rehabilitation?
- What are the best outcome measures?
- Importance of registries

Making Standards of Care, the Standard

A Zoom meeting with SMA!