Spinal Muscular Atrophy

PANDA weekend 2023

Declarations

- Invited presentation with an honorarium from Roche – to PANDA
- FISH Risdiplam study slides supplied in part by Roche

Contents

1. Disease presentation and diagnosis (brief).
2. Standard care guidelines (brief).
3. Novel treatment options
    - Nusinersen,
    - Risdiplam
    - Onasemnogene abeparvovec (Zolgensma)

Realities and challenges

- In most RPC the prevalence of NMD is not known
  - As such the true burden is not defined
  - This challenges motivation for adequate services
- This reflects a combination of
  - Limited clinical skills
    - many patients are mislabelled with cerebral palsy
  - Lack of access to diagnostic tools
    - from CK to muscle biopsy to molecular genetics
  - Limited access to trained rehabilitation therapists and orthotic centres

MUTLTIDISCIPLINARY CARE - even in RPC

- Dedicated neuromuscular clinic
  - Trained doctor and rehabilitation therapist
- Encourage referrals of patients with known / suspected NMD
- ST, dietician, OT, tracheostomy, stoma
- Affiliated services…
  - Pulmonology, cardiology, Molecular genetics, histopathology, orthopaedics, neurodevelopment, counselling (genetic and community)
- Ideally needs to be located in tertiary setting..

Really good additions to the clinic

- Pulmonology
  - respiratory technologist part of the clinic
- NMD clinic operates parallel to cardiology clinic
  - allows for joint OPDs (better communication and compliance).
- Genetic counsellors
  - either in the clinic or available on clinic days
- Counsellor from Muscular Dystrophy Foundation
  - sits in every clinic, home visits, schools, chases up “lost patients” etc

Aims of care

Diagnosis

- NMD conditions which are important / relevant?
  - Genetic counseling e.g. SMA, Duchenne MD
  - Targeted therapies e.g. SMA, Duchenne MD

Overall management

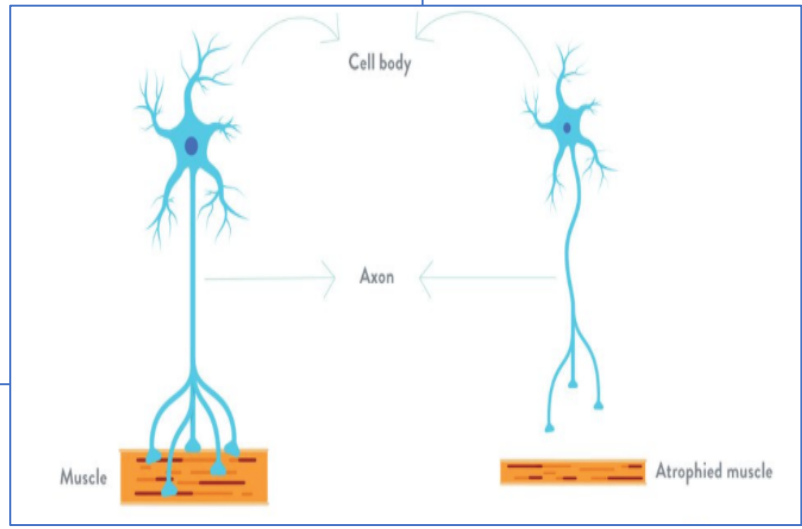
- Optimal motor capacity
- Avoidance of complications e.g. scoliosis, respiratory track infections, oromotor, nutritional challenges
- Planning optimal educational placement, orthotic devices
- i.e. “standard” not “state of the art / experimental”

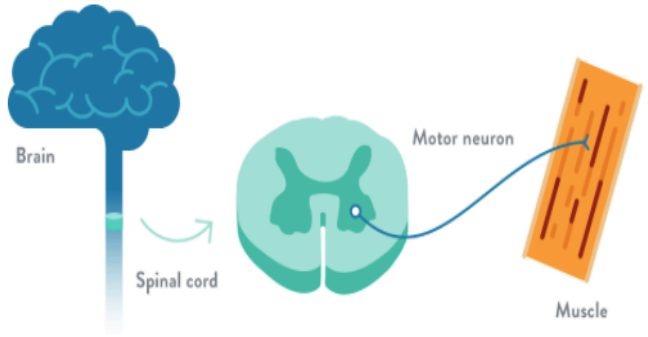
SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy

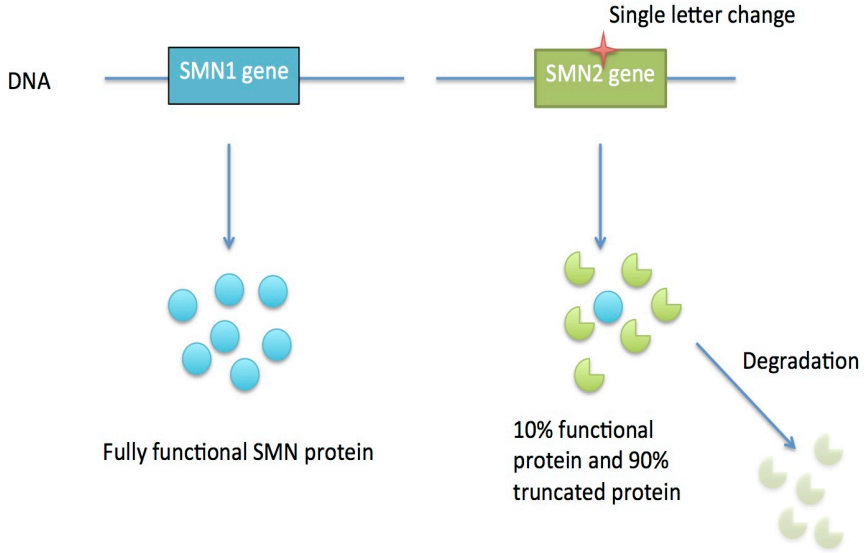
- 5q SMA commonest inherited cause of infant death
- 1 in 6000 to 1 in 10,000
  - 2nd most common autosomal recessive disease in childhood.
- In SA Genetic diagnosis available and prenatal counselling

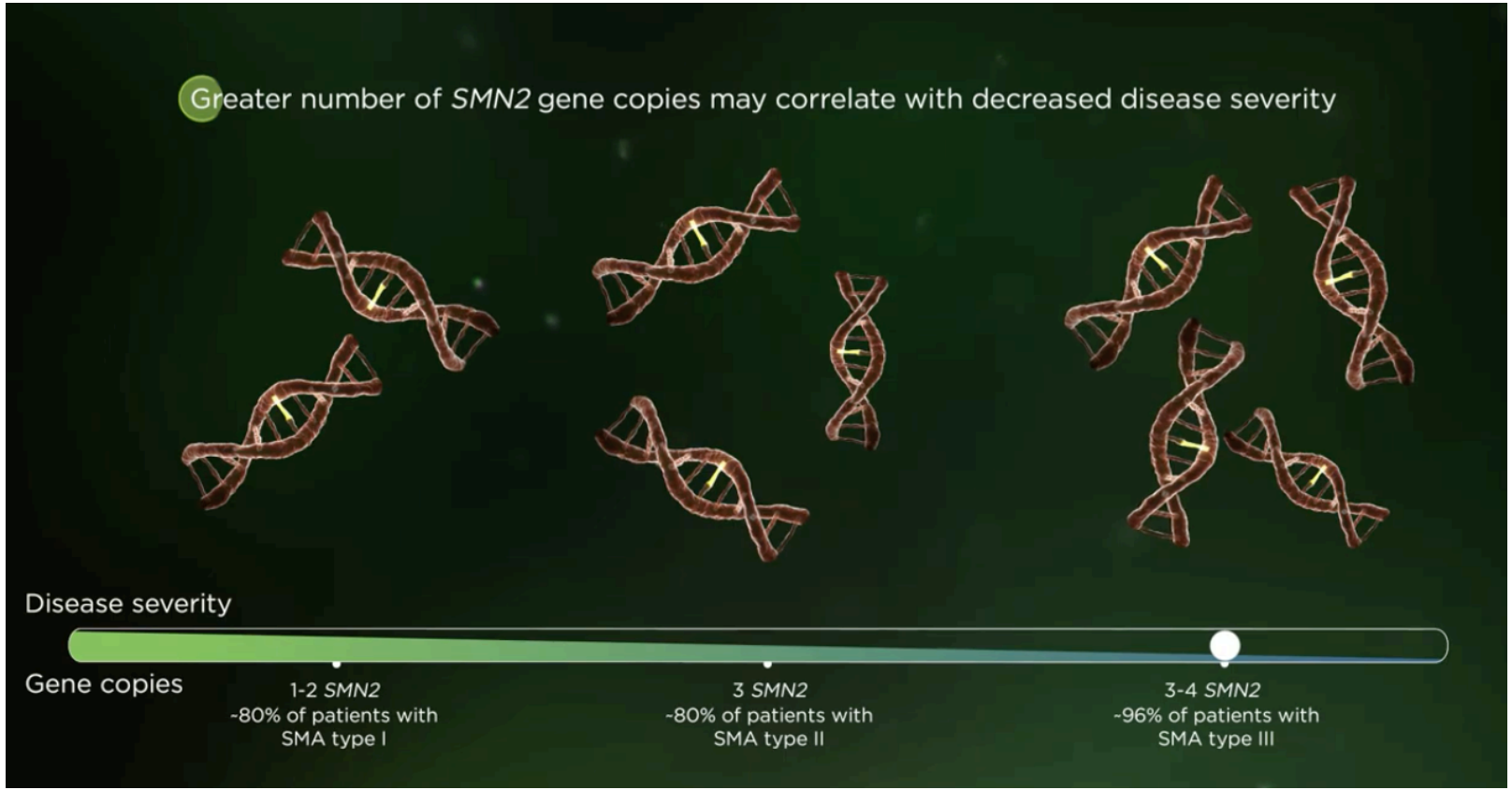
Progressive **loss or motor neurons** → Degeneration of alpha motor neuron cells in spinal cord → progressive muscle atrophy, weakness and paralysis.





The lower motor neurons, located in the spinal cord, are important cells involved in motor function in the central nervous system (CNS)[5]





SMA
– more complex!

Cellular and Molecular Life Sciences (2022) 79: 407
https://doi.org/10.1007/s00018-022-04522-9

Cellular and Molecular Life Sciences

REVIEW

The phospho-landscape of the survival of motoneuron protein (SMN) protein: relevance for spinal muscular atrophy (SMA)

Nora Tula Detering[1,3] · Tobias Schüning[1,3] · Niko Hensel[2,3] · Peter Claus[1,3]

- SMN protein is ubiquitously expressed
  - growing evidence of a multisystem phenotype in SMA
- Evidence supports potential contribution of gastrointestinal, metabolic, and endocrine defects to disease phenotype.
  - disrupted body composition, GI tract, fatty acid, glucose, amino acid, and hormonal regulation.
  - Combined have clinical impact on disease traits.
- Unclear whether these findings are secondary to widespread denervation or unique to the SMA phenotype.

International Journal of *Molecular Sciences*

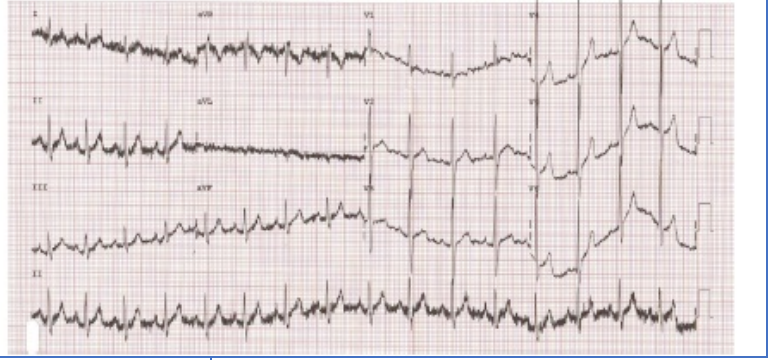
MDPI

Review

Metabolic Dysfunction in Spinal Muscular Atrophy

Marc-Olivier Deguise [1,2,3,†], Lucia Chehade [1,3,4,†] and Rashmi Kothary [1,3,4,5,6,*]

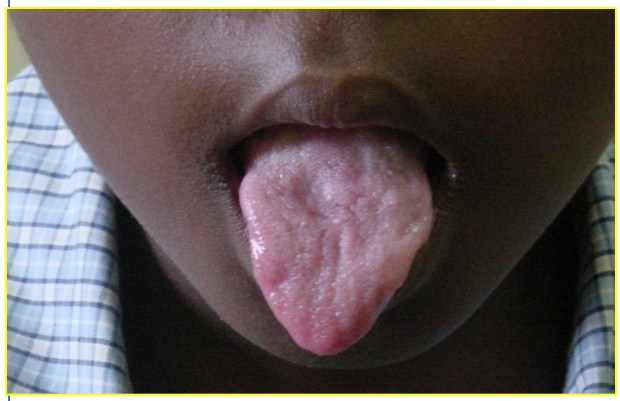
Classic phenotype

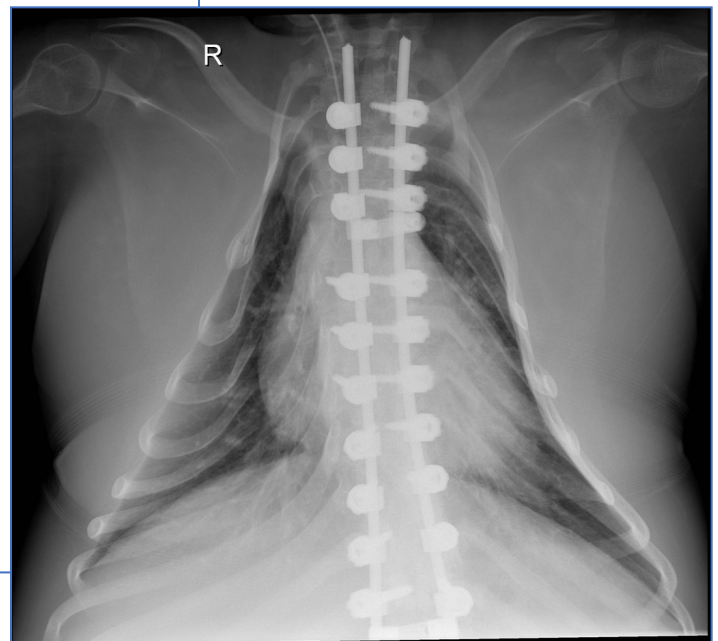


- Many centres depend on clinical and basic investigations to "confirm" the diagnosis

Key features

- Proximal weakness
- Bell shaped chest *(classic X-ray)*
- Tongue fibrillations *(fibs on ECG)*
- Distal tremor
- Normal facial expression / eye movements
- Normal intelligence





SMA Type	Age at onset	Mobility	Life expectancy	SMN2 Copies	Proportion of pt with SMA
O	Prenatal	Foetal Hypokinesia	< 6 months	1	<1
SMA Ia	<2 weeks	No head control	<2 years	2-3	50-60% (a –c)
SMA Ib	<3 months	Never roll or sit unsupported	<2 years	2-3	
SMA Ic	3-6 months	Never sit unsupported	<2 years	2-4	
SMA 2	7-18 months	Sit, but not stand unsupported	Variable	2-4	30%
SMA 3a	18months - 3 year	Walk but later loss of ambulation	Normal	3-5	10% (a and b)
SMA 3b	>3 years	Walk but later could lose ambulation	Normal	3-5	
SMA 4	Adult-2nd or 3rd decade	Stand and walk during adulthood	Normal	3-5	5%

Approach - depends on type

- Type 1 (non-sitters)
  - supportive, *not for ventilation*
- Type 2 (sitters)
  - Lots of physio,
  - monitor the back,
  - appropriate schooling ….
  - Clever children - plan for the future …..
- Type 3 (walkers)
  - diagnosis helps a lot - counselling

J Child Neurol. 2007 Aug;22(8):1027-49. Consensus statement for standard of care in spinal muscular atrophy. Wang CH, et al; Participants of the International Conference on SMA Standard of Care; Mercuri et al NMD 2018

Epidemiology

- Worldwide second most common autosomal recessive disorder in European ("white") ancestries (after cystic fibrosis)
  - Carrier frequency 1 in 40-60
  - Incidence 1 in 6000 to 1 in 11,000
- Birth incidence in Black SA pts higher estimated at 1 in 3574 (Labrum et al 2007)
- Carrier incidence estimated
  - 1 in 23 white SA
  - 1 in 50 black SA
  - NB – couldn't be reproduced in the Vorster et al paper 2020

Clin Genet 2002: 62: 165–168
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CLINICAL GENETICS
0009-9163

Short Report

Spinal muscular atrophy in black South Africans: concordance with the universal SMN1 genotype

Wilmshurst JM, Reynolds L, Van Toorn R, Leisegang F, Henderson HE. Spinal muscular atrophy in black South Africans: concordance with the universal SMN1 genotype.
Clin Genet 2002: 62: 165–168. © Blackwell Munksgaard, 2002

J M Wilmshurst[a], L Reynolds[a], R Van Toorn[a], F Leisegang[b] and H E Henderson[b]

- Western Cape patients screened for SMA over previous 20 years
  - All patients with genetic confirmation complied with the international guidelines
  - All patients with exclusion features had other conditions
- Conclusions - all patients are the same as the international form

frontiers in Genetics

ORIGINAL RESEARCH
published: 13 February 2020
doi: 10.3389/fgene.2020.00054

Spinal Muscular Atrophy in the Black South African Population: A Matter of Rearrangement?

Elana Vorster[1], Fahmida B. Essop[1], John L. Rodda[2] and Amanda Krause[1]*

[1] National Health Laboratory Service and School of Pathology, University of the Witwatersrand, Johannesburg, South Africa,
[2] Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa

(Wirth, 2000). The heterozygous deletion of *SMN1*, exon 7 rate in black SA patients with SMA who tested negative for the homozygous *SMN1*, exon 7 deletion, was previously reported to be as high at 69.5%, supporting the diagnosis of SMA in these patients and suggesting that SMA is probably due to additional unidentified mutations in this region (Labrum et al., 2007).

Epidemiology

- SMN1 – homozygous deletion exon 7 – in 94% cases worldwide
  - But reports in SA state only seen **51% of Indigenous African (black)** SMA phenotype pts.
- In pts lacking homozygous deletion exon 7 (Vorster et al 2020)
  - Didn't find pathogenic CNVs in black pts but did find **discordant copy numbers**
  - Hypothesised complex rearrangements – potentially interrupting functioning of SMN1 gene
  - The findings have huge implications for counseling, implications for newborn screening roll-out and access to pharmacogenetic interventions.

Questions

- Of the remaining black patients lacking homozygous deletion of SMN1 – how is the diagnosis of SMA made?
  - Second mutation from compound heterozygote pattern – explains 2-5% worldwide (Vorster et al)
  - Cape Town experience n=2 (SMA1 genetically confirmed in 1 and suspected other, neither were black).
- Prev study (Labrum et al 2007) on black heterozygous pts with SMA phenotype 69.5% - **but study could not confirm second mutation**.
  - Remains a clinical assumption – can't do targeted treatment with this.
- Reports allude to the influence of SMN2
  - logical based on the influence of the copy numbers for clinical expression of SMA.
  - Copy numbers are not routine for SA testing – should they be?
- We need a further multicentre study to "unpack" our SMA patients further??

Management recommendations for SMA

Briefly …….

Fig. 2. Multidisciplinary approach.

Special Issue Article

Journal of Child Neurology
Volume 22 Number 8
August 2007 1027-1049
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10.1177/0883073807305788
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Ching H. Wang, MD, PhD, Richard S. Finkel, MD, Enrico S. Bertini, MD, Mary Schroth, MD, Anita Simonds, MD, Brenda Wong, MD, Annie Aloysius, MRCSLT, HPC, Leslie Morrison, MD, Marion Main, MCSP, MA, Thomas O. Crawford, MD, Anthony Trela, BS, and Participants of the International Conference on SMA Standard of Care

5 core areas addressed

- Diagnostic / new interventions
- Pulmonology
- Gastrointestinal / nutritional
- Orthopaedics / rehabilitation
- Palliative care

Authors stated that the document should a guide rather than dictate practice. Further evidence based recommendations were needed.

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) 103–115

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,l,*], Richard S. Finkel [c,l], Francesco Muntoni [d], Brunhil
Jacqueline Montes [f], Marion Main [d], Elena S. Mazzone [a,b], Michael Vitale [g], B
Susana Quijano-Roy [i,j], Enrico Bertini [k], Rebecca Hurst Davis [l], Oscar H.
Anita K. Simonds [n], Mary K. Schroth [o], Robert J. Graham [p], Janbernd Ki
Susan T. Iannaccone [r], Thomas O. Crawford [s], Simon Woods [t], Ying Qian [u], Thon
the SMA Care Group

Fig. 2. Multidisciplinary approach.

Palliative care and Advocacy groups

- Early counseling and holistic extended family / carer support
- Early intervention PEG
- Planning for non-invasive ventilation
- Avoiding crisis management
- Multidisciplinary team approach

Patient advocacy groups / registries

- Muscular Dystrophy Foundation of South Africa. http://www.mdsa.org.za
- FightSMA (www.fightsma.org)
- Families of Spinal Muscular Atrophy (www.fsma.org)
- The Jennifer Trust (www.jtsma.org)
- https://treat-nmd.org/treat-nmd-diseases/spinal-muscular-atrophy/

Newer therapies

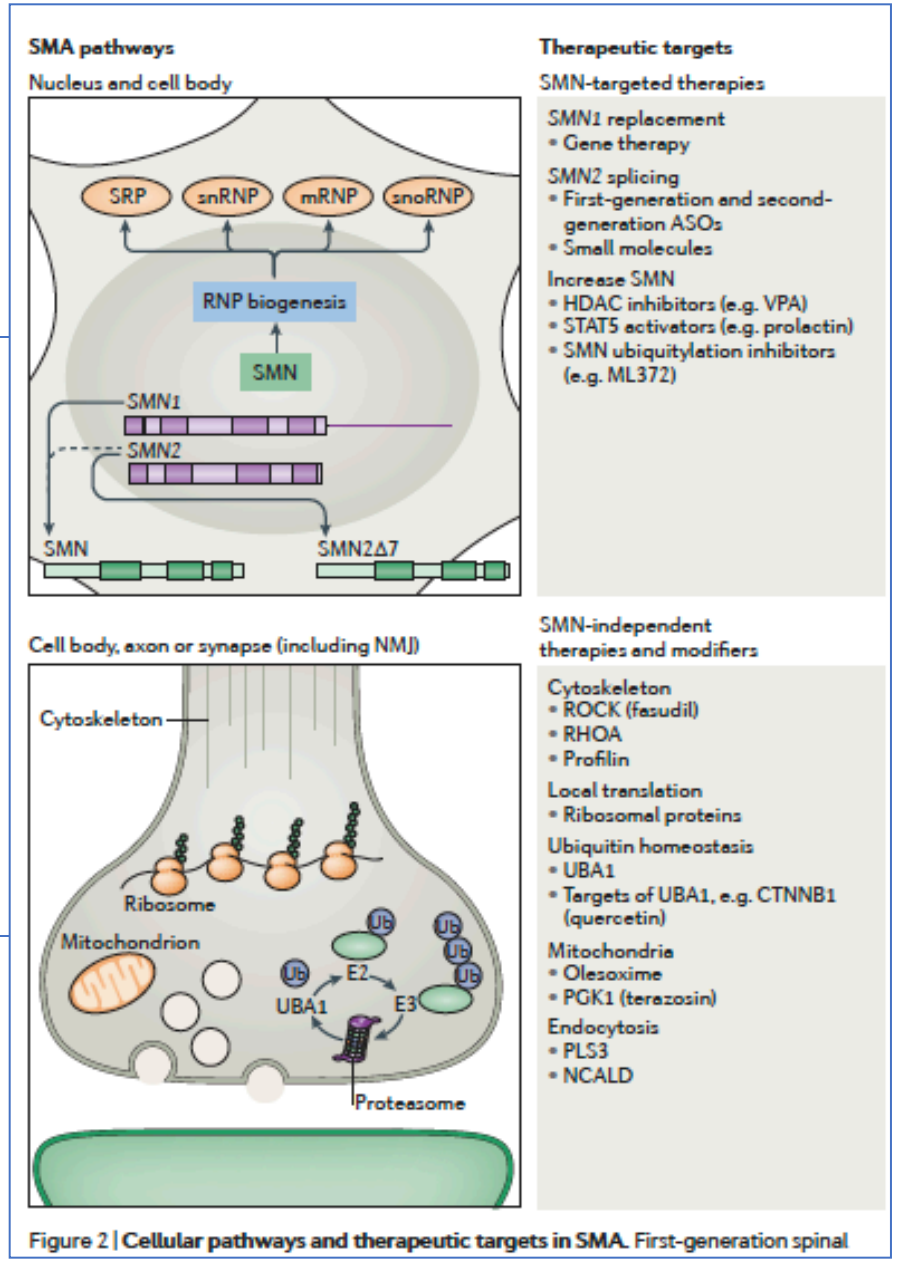


Figure 2 | **Cellular pathways and therapeutic targets in SMA.** First-generation spinal

Groen et al Nature Reviews Neurol 2018

Newer Therapies

- SMN1 gene replacement
- SMN2 splicing modifier
- Neuro protectant
- Muscle activator

European Journal of Paediatric Neurology 28 (2020) 38–43

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy

Janbernd Kirschner [a, *], Nina Butoianu [b], Nathalie Goemans [c], Jana Haberlova [d], Anna Kostera-Pruszczyk [e], Eugenio Mercuri [g, h], W. Ludo van der Pol [k], Susana Quijano-Roy [i], Thomas Sejersen [j], Eduardo F. Tizzano [f], Andreas Ziegler [l], Laurent Servais [m, n, 1], Francesco Muntoni [o, 1]

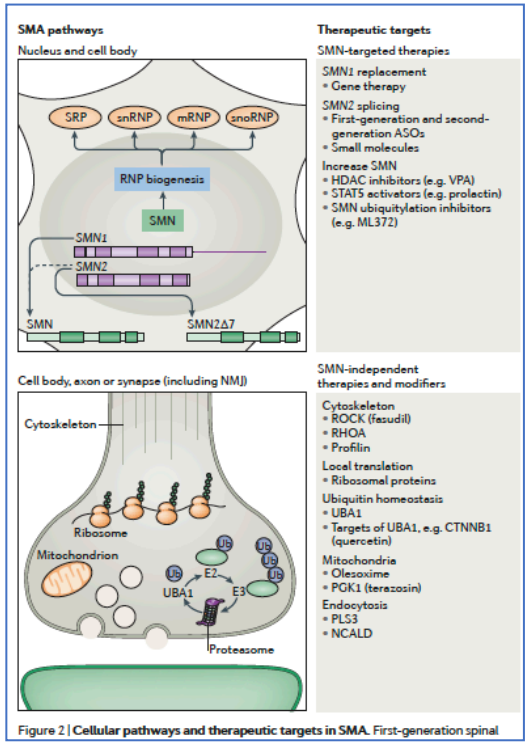
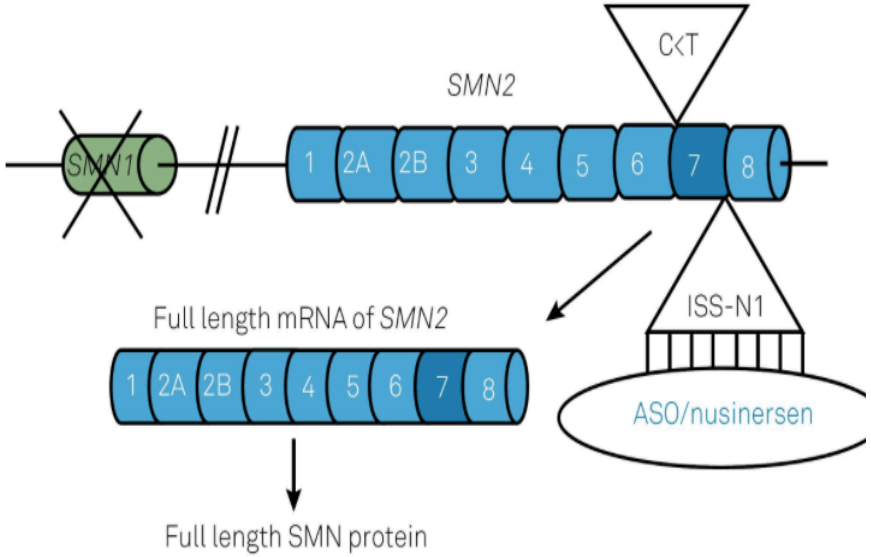


Figure 2 | **Cellular pathways and therapeutic targets in SMA.** First-generation spinal

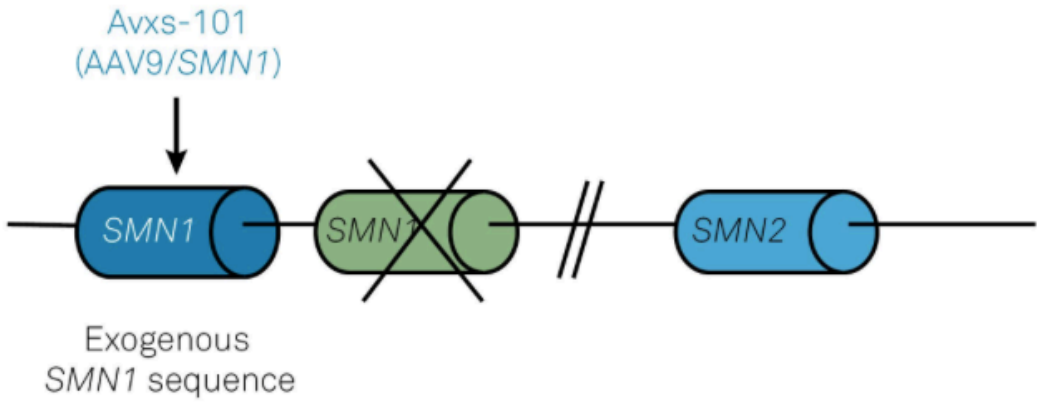
Ewout et al Nature Reviews Neurol 2018

Therapeutic Strategies



ASO binds to the Intronic Splicing site silencer (ISS-N1) down stream from exon 7….increasing exon 7 inclusion in SMN2 mRNA

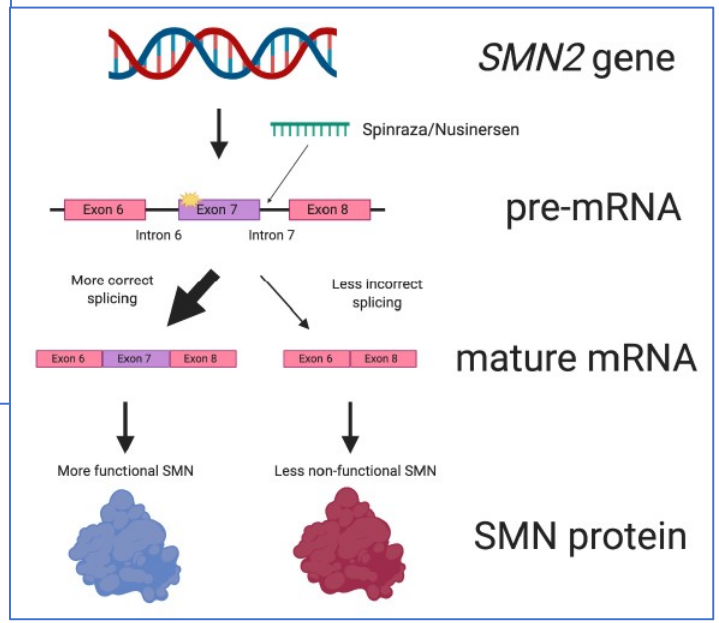
Exogenous SMN1 is inserted using AAV9



Gene therapy

FDA Approval of Nusinersen for Spinal Muscular Atrophy Makes 2016 the Year of Splice Modulating Oligonucleotides.

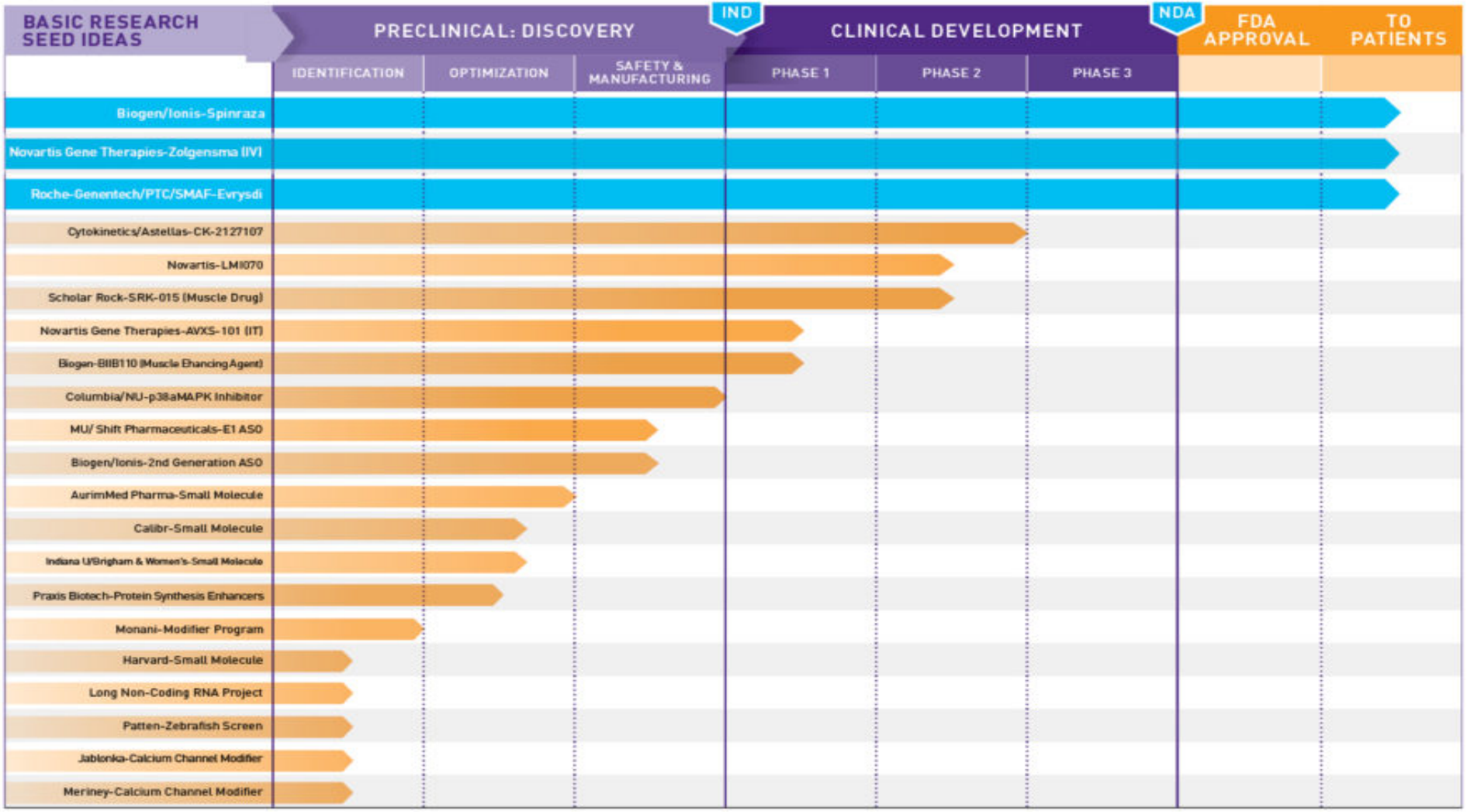
Nucleic Acid Ther. 2017 Apr;27(2):67-69 Aartsma-Rus A1.



As of 2021……

SMA DRUG PIPELINE

We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue to change the course of SMA for everyone affected, and eventually lead to a cure.



IND = Investigational New Drug **NDA** = New Drug Application Last updated: September 2020

37:100878 © 2021

Seminars in PEDIATRIC NEUROLOGY

Spinal Muscular Atrophy

Stefan Nicolau, MD,* Megan A. Waldrop, MD,*,† Anne M. Connolly, MD,*,† and Jerry R. Mendell, MD*,†

Table 1 Directed Therapy for Spinal Muscular Atrophy

	Nusinersen	Risdiplam	Onasemnogene Abeparvovec-xioi
Class	Antisense oligonucleotide	Small molecule	AAV-delivered gene therapy
Mechanism of action	Enhances splicing of *SMN2* to full-length SMN protein	Enhances splicing of *SMN2* to full-length SMN protein	Delivers a functional *SMN* transgene
Route of administration	Intrathecal	Oral	Intravenous
Frequency	4 loading doses in the first 2 months, then every 4 months	Daily	Single dose
FDA-approved age ranges	All	>2 months	<2 years
Limitations to treatment	Inability to undergo lumbar puncture	Drug interactions	Presence of AAV9 antibodies at baseline
Baseline evaluation	Platelet count, coagulation studies, urinalysis		Liver function tests, platelet count, troponin-I, AAV9 antibody titer, prednisolone treatment for 30 days
Adverse events	Thrombocytopenia, proteinuria, lumbar puncture complications	Fever, diarrhea, rash	Acute liver injury, transaminitis, thrombocytopenia, troponemia
Monitoring	Platelet count, coagulation studies, urinalysis		Liver function tests, platelet count, troponin-I

AAV, Adeno-associated virus; FDA, United States Food and Drug Administration; SMN, survival motor neuron.

NUSINERSEN/SPINRAZA

- Intrathecal injections…..
- Loading phase
  - Intensive Phase- 0, 14, 28, 63
- Maintenance phase
  - Phase- Repeat every 4 monthly
- Requires multidisciplinary team approach

was **88,600 Euros per vial…….**
(R1,7million)

Very important that LOADING doses given on the scheduled days

Side effects

- Back pain and post lumbar puncture headache
- Elevated transaminases
- Thrombocytopenia
- Proteinuria

Nusinersen impact

- Infantile SMA
  - reduced by half risk of permanent mechanical ventilation
  - Mortality reduced by 63%
  - 41% treated arm had motor function improvement compared to controls

  (Finkel et al NEJM 2017, Finkel et al Lancet 2017)
- Greatest benefit in the presymptomatic group or within 3 months of disease onset.

  (Finkel et al NEJM 2017, De Vivo et al NMD 2019)
- Older children with SMA onset after 6months treated between 2 and 12-15years of age
  - 57% had improvement in motor function, compared to 26% of the controls

  (Mercuri et al NEJM 2018, Montes et al Muscle & Nerve 2019, Darras et al Neurol 2019)

The First Orally Deliverable Small Molecule for the Treatment of Spinal Muscular Atrophy

Ravindra N Singh, Eric W Ottesen and Natalia N Singh

Department of Biomedical Sciences, Iowa State University, Ames, IA, USA.

Neuroscience Insights
Volume 15: 1–11

DOI: 10.1177/2633105520973985
SAGE

RISDIPLAM/EVRYSDI

FDA Approved 7/08/20

Evrysdi's registered SEP is **R136,846.66** per vial.
The maximum number of vials for an adult patient is 32 per year.
This caps the price at R5.2 million.

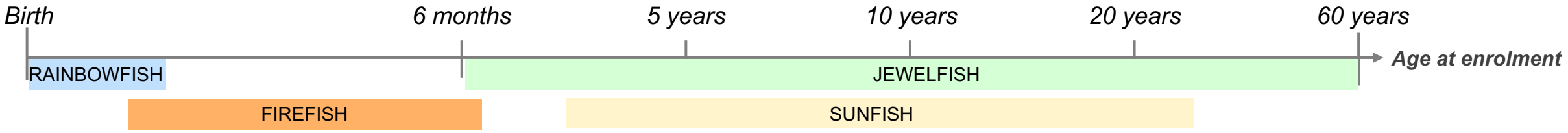
Risdiplan (Evrysadi)

- Small molecule aimed at modulating SMN2 splicing in a similar manner to the IT injections of Nusinersen
- BUT via oral route
- Ridisplam – tripled SMN protein animal models, with good safety outcomes

  (Ratni et al J Med Chem 2018)
- clinical trials completed
- Improved motor function in later-onset SMA
- Jewelfish study (Chiriboga et al 2023) – safety and pharmodynamics consistent across previously treated pts and treatment-naïve pts.

Risdiplam is being investigated in the broad range of individuals with SMA representative of the real-world spectrum of the SMA phenotype[1–5]

The FISH clinical programme has enrolled individuals with SMA across a broad spectrum of disease severity (Type 1–3), from newborns to 60-year-old adults, from pre-symptomatic to very weak individuals, both treatment-naïve and previously treated, accounting for the varied needs of the SMA population[1–4]



RAINBOWFISH[1]
- Pre-symptomatic SMA
- Birth–6 weeks old
- Efficacy and safety (N=25*)

FIREFISH[2]
- Type 1 SMA
- 1–7 months old
- Dose finding (N=21)[5]
- Efficacy and safety (N=41†)[5]

SUNFISH[3]
- Type 2 or 3 SMA
- 2–25 years old
- Dose finding (N=51)[6]
- Efficacy and safety (N=180†)[6]

JEWELFISH[4]
- Type 1, 2 or 3 SMA
- 6 months–60 years old
- Previous SMA treatment
- PK/PD and safety (N=174†)

*Target enrolment, currently recruiting; †Actual subject number enrolled.

1. ClinicalTrials.gov NCT03779334, accessed May 2020; 2. ClinicalTrials.gov NCT02913482, accessed May 2020; 3. ClinicalTrials.gov NCT02908685, accessed May 2020; 4. ClinicalTrials.gov NCT03032172, accessed May 2020; 5. Baranello G et al. 2019. Presented at the Cure SMA Annual Conference 2019, California, USA. Motor function; 6. Mercuri E et al. Presented at the Cure SMA Annual Conference, 28 June–1 July 2019, Anaheim, CA, USA.

FIREFISH Part 1: 12-month results summary*[1]

Risdiplam treatment led to a rapid and sustained dose-dependent increase in SMN protein

100% (19/19)

of infants continued treatment on risdiplam (no drug-related safety findings leading to withdrawal to date)

94% (16/17)

of infants were alive and event free†

95% (18/19)

of infants retained the ability to swallow‡

100% (21/21)

of infants were independent of permanent ventilation‡

41% (7/17)

of infants were able to sit without support for at least 5 seconds (as assessed by BSID-III)

6% (1/17)

of infants were able to stand supporting their weight (as assessed by HINE-2)

53% (9/17)

of infants were able to maintain upright head control (as assessed by HINE-2)

59% (10/17)

of infants had a CHOP-INTEND score ≥40

Infants survive, retain critical functions and achieve additional motor milestones with continued risdiplam treatment (beyond 1 year)[3]

1. Baranello G et al. Presented at the Cure SMA Annual Conference, 28 June–1 July 2019, Anaheim, CA, USA. Motor function; 2. Baranello G et al. Presented at the Cure SMA Annual Conference, 28 June–1 July 2019, Anaheim, CA, USA. Survival, ventilation and swallowing ability; 3. Baranello G et al. Presented at the International Annual Congress of the World Muscle Society, 1–5 October 2019, Copenhagen, Denmark.

FIREFISH Part 2: results

FIREFISH Part 2: 12-month results summary

The primary endpoint was met (p<0.0001)*

29% (12/41)

of infants were sitting without support for 5 seconds at Month 12, as measured by item 22 of the BSID-III Gross Motor Scale

Risdiplam treatment led to a significant improvement in motor function† (p<0.0001)‡

Infants achieved motor milestones, such as sitting and standing§, which would never be seen in untreated infants

93%
(38/41) of infants were alive at Month 12

85%
(35/41) **of infants were event free¶ at Month 12**

95%
(36/38)

of infants alive maintained the ability to swallow after 12 months of treatment

49%
(20/41)

of all infants did not require hospitalisation during the 12 months of treatment

No drug-related safety findings led to withdrawal in FIREFISH Part 2

*Performance criterion=5%, exact binomial test; †As measured by CHOP-INTEND; ‡Performance criterion=12%, exact binomial test; §As measured by the HINE-2;
¶Event free in FIREFISH is defined as alive with no permanent ventilation (i.e. no tracheostomy or BiPAP ≥16 hours per day continuously for >3 weeks or continuous intubation >3 weeks, in the absence of, or following the resolution of, an acute reversible event).
BiPAP, bilevel positive airway pressure; BSID-III, Bayley Scales of Infant and Toddler Development, Third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Section 2.
Servais L et al. Presented at a virtual meeting. 28 April 2020.

ORIGINAL ARTICLE

Risdiplam in Type 1 Spinal Muscular Atrophy

Giovanni Baranello, M.D., Ph.D., Basil T. Darras, M.D., John W. Day, M.D., Ph.D., Nicolas Deconinck, M.D., Ph.D., Andrea Klein, M.D., Riccardo Masson, M.D., Eugenio Mercuri, M.D., Ph.D., Kristy Rose, Ph.D., Muna El-Khairi, Ph.D., Marianne Gerber, Ph.D., Ksenija Gorni, M.D., Ph.D., Omar Khwaja, M.D., Ph.D., et al., for the FIREFISH Working Group*

March 11, 2021
N Engl J Med 2021; 384:915-923
DOI: 10.1056/NEJMoa2009965

- Phase 2–3, open-label study of risdiplam in SMA1 infants 1 - 7 mths
- 21 infants enrolled.
  - 4 low dose and 17 high dose for 12 months
- **Demonstrated increase in SMN protein concentrations**.
- Adverse events: pneumonia, respiratory tract infection, and acute respiratory failure.
  - At publication, 4 infants had died of respiratory complications.
- 7 infants (high-dose) and no infants (low-dose) could sit without support > 5 seconds.
- **CONCLUDED** SMA1 infants treated with oral risdiplam had increased expression of functional SMN protein in the blood.
- Higher dose risdiplam (0.2 mg/kg/day) ongoing part 2 study.

*Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, **NCT02913482.***

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls

B.T. Darras, R. Masson, M. Mazurkiewicz-Bełdzińska, K. Rose, H. Xiong, E. Zanoteli, G. Baranello, C. Bruno, D. Vlodavets, Y. Wang, M. El-Khairi, M. Gerber, K. Gorni, O. Khwaja, H. Kletzl, R.S. Scalco, P. Fontoura, and L. Servais, for the FIREFISH Working Group*

N Engl J Med 2021;385:427-35.
DOI: 10.1056/NEJMoa2102047

41 SMA1 infants
12/41 – 29% able to sit for 5 seconds

Journal of Neurology
https://doi.org/10.1007/s00415-023-11560-1

ORIGINAL COMMUNICATION

Two-year efficacy and safety of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA)

Maryam Oskoui[1] · John W. Day[2] · Nicolas Deconinck[3,4] · Elena S. Mazzone[5] · Andres Nascimento[6] · Kayoko Saito[7] · Carole Vuillerot[8,9] · Giovanni Baranello[10,11] · Nathalie Goemans[12] · Janbernd Kirschner[13] · Anna Kostera-Pruszczyk[14] · Laurent Servais[15,16,17] · Gergely Papp[18] · Ksenija Gorni[19] · Heidemarie Kletzl[20] · Carmen Martin[21] · Tammy McIver[21] · Renata S. Scalco[22] · Hannah Staunton[21] · Wai Yin Yeung[21] · Paulo Fontoura[19] · Eugenio Mercuri[5] · on behalf of The SUNFISH Working Group

- 32% pts improved from baseline motor scores
- Appeared to be maintained across 12-24 mths
- Better motor capacity compared to placebo group

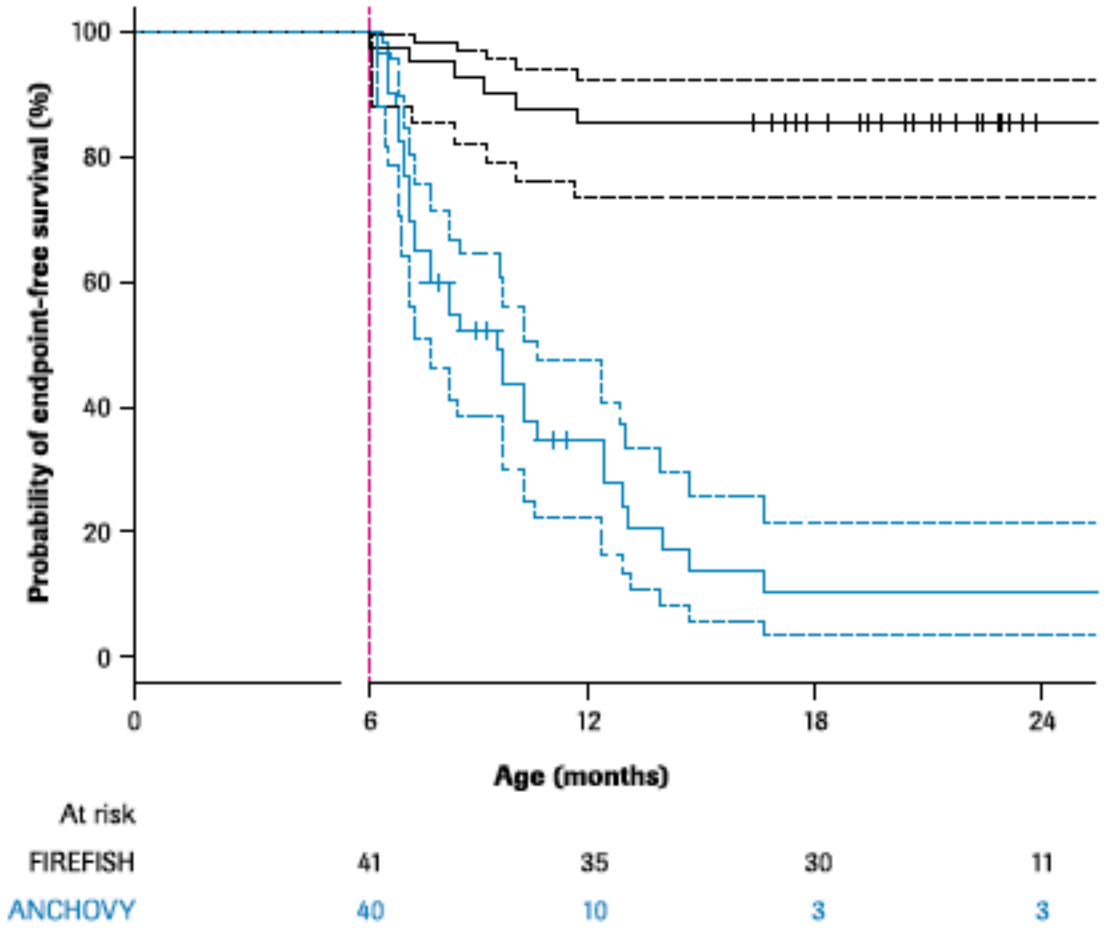
Cances et al.
Orphanet Journal of Rare Diseases (2022) 17:300
https://doi.org/10.1186/s13023-022-02455-x

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Natural history of Type 1 spinal muscular atrophy: a retrospective, global, multicenter study

Claude Cances[1,2*], Dmitry Vlodavets[3], Giacomo Pietro Comi[4,5], Riccardo Masson[6], Maria Mazurkiewicz-Beldzińska[7], Kayoko Saito[8], Edmar Zanoteli[9], Angela Dodman[10], Muna El-Khairi[11], Kseniia Gorni[12], Isaac Gravestock[13], Janine Hoffart[12], Renata S. Scalco[10] and Basil T. Darras[14] on behalf of the ANCHOVY Working Group



- ANCHOVY study…
- Showed natural Hx data
  - 60 pts from 9 countries – Asia, Europe, North and South America
- Compared to FIREFISH data
- ANCHOVY natural history for SMA differed from the FIREFISH risdiplam treated pts

ZOLGENSMA

2.1 Million USD = R38 Million

Gene Therapy – onasemnogene abeparvovec-xioi (commercial version AVXS-101, Zolgensma)

- One-time treatment for SMA
  - Delivery of recombinant gene via adeno-associated virus (AAV9)
- AVXS-101 evaluated in 15 infants (1-8mths old)
  - All had 2 copies of SMN2 – predicting SMA1 phenotype
- All had post treatment extended ventilator-free survival beyond 20mths (versus 8% controls)
- 11/12 in the higher-dose could sit independently and 2 could walk

(Mendell et al NEJM 2017)

- Data limited to under 2 years of age, but supports the benefit of the intervention.

  (Waldrop et al Pediatr 2020)

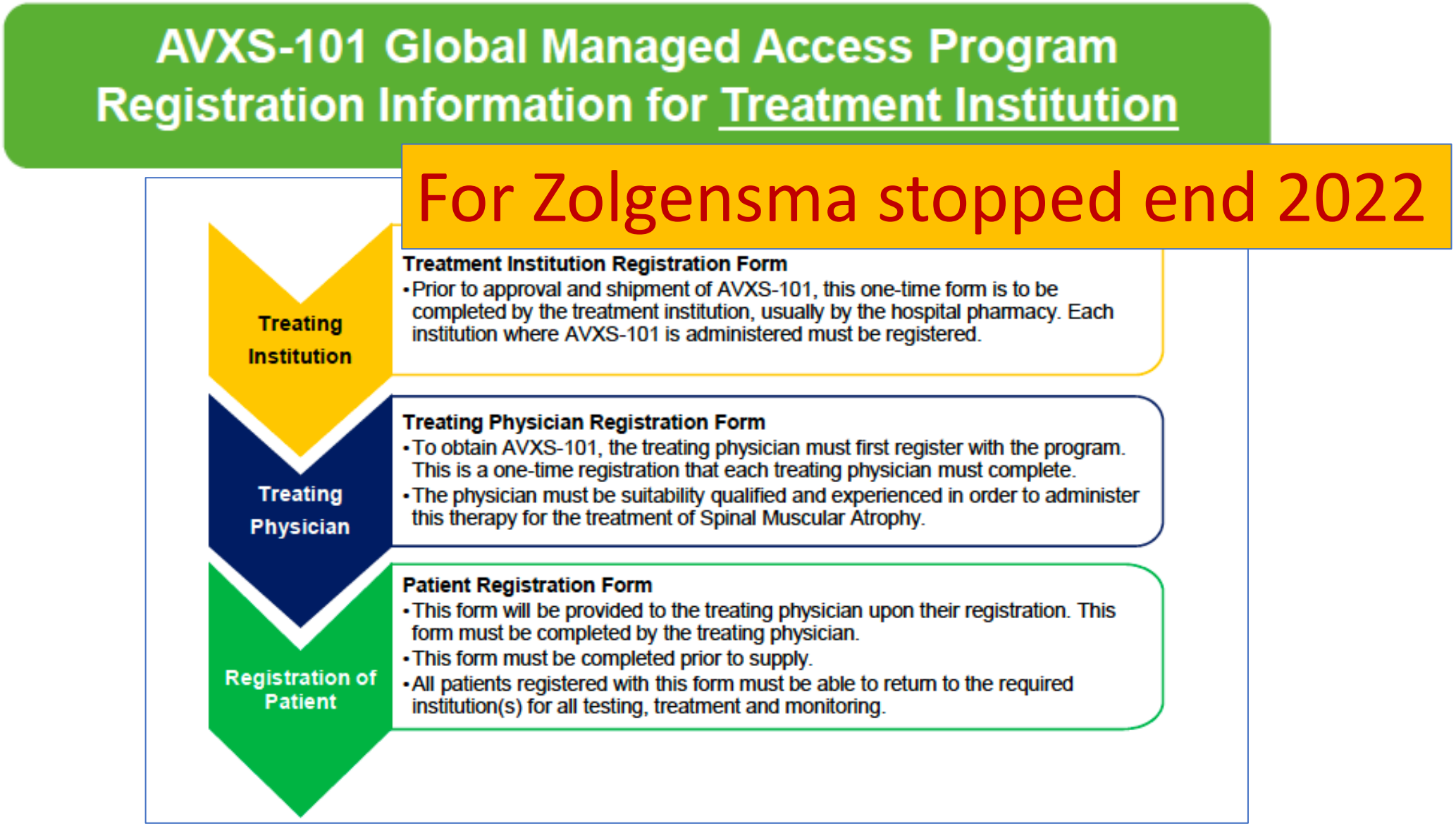
Zolgensma - safety data *(Shirley et al Mol Ther 2020, Hinderer et al Hum Gene Ther 2018, Wilson et al Hum Gene Ther 2020)*

- Concern of immunogenicity of the viral vectors
- Hepatotoxicity related to clearing of AAV by the liver
- Asymptomatic thrombocytopenia
- Serum transaminase elevations
  (Mendell et al NEJM 2017 , Waldrop et al Pediatr 2020)
- Pts with antibodies to AAV9 are excluded
- Covered with prednisone pre and during the intervention

- Optimal pt selection, administration and long-term effects are still under evaluation.
  - Clinical trial (NCT03381729) evaluation of IT route
  - In primates found toxicity of dorsal root ganglia, similar to IV complication– trial put on hold.

  (Hinderer et al Hum Gene Ther 2018)

Compassionate Access Drugs



Intrathecal Zolgensma for SMA2 study COAV101B12301 study

- Sponsored multi-country study (2022-2023/4)
- Competitive worldwide recruitment in age brackets
- Very rigid inclusion / exclusion criteria
- Detailed follow-up protocols – multiple teams involved
- 2:1 blinded sham.
  - Switch over end of the year.
  - Assuming AAV9 Ab ratio still low
- To date recruited 1 (almost 2), screened 10 – study failures mostly AAV9 ab titres raised
- Need to ensure all viable children given opportunity
- 5-13 age group quota almost reached …..

Combination therapy

- To date no head to head trials comparing nusinersen, risdiplam and gene therapy
- Comparing existing trials challenging for variation in trial design

BUT

- Overall survival, ventilator-free survival, and achievement of motor milestones all significantly higher in the pivotal trial of AVXS-101 compared to the ENDEAR trial of nusinersen in a similar age group.
  (Dabbous et al Adv Ther 2019)

- Currently unknown if combining the two treatment methods would be effective
- As no symptomatic patient symptom free post intervention, further approaches indicated
- Few reports of gene therapy administered to children on or who received nusinersen or ridisplam– appears safe but long term benefits pending
  - *(Lee et al Neurol 2019, Harada et al Muscle & Nerve 2020)*
- Studies are underway to explore this

Other therapies

- Targeting skeletal muscle

1. myostatin inhibition via SRK-015 (monoclonal antibody directed against myostatin)

   (Pirruccello-Straub et al Proc Natl Acad Sci 2007)

- Effective in mouse models, current under clinical evaluation

2. Fast skeletal muscle tropinin activation

- Aim to improve exercise tolerance and delay muscle fatigue
- Reldesemtiv assessed in phase 2 trials SMA types 2-4.

  (Chen et al Int J Mol Sci 2020)

- Albuterol (salbutamol)
- Enhances neuromuscular transmission
- Possible benefit on motor and respiratory function in type 2 and 3 SMA

  (Pane et al NMD 2008, Kinali et al Neurol 2002, Frongia et al NMD 2019, Khirani et al Pediatr Neurol 2017, Tiziano et al J Med Genet 2019)

Available online at www.sciencedirect.com

ScienceDirect

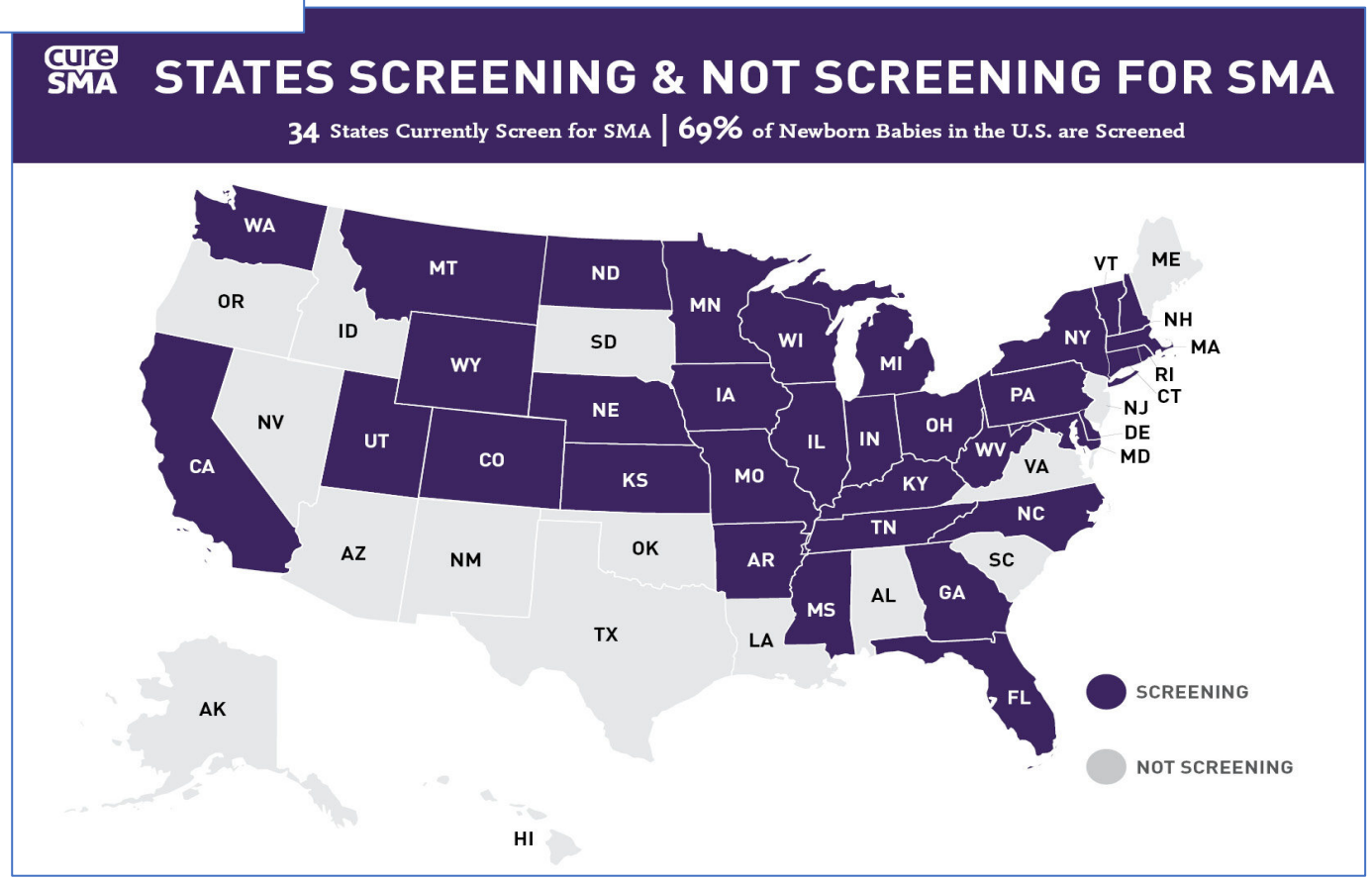
Neuromuscular Disorders 30 (2020) 93–103

www.elsevier.com/locate/nmd

244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10–12, 2019, Hoofdorp, The Netherlands

Tamara Dangouloff[a], Arthur Burghes[b], Eduardo F. Tizzano[c,*], Laurent Servais[a,d,**], on behalf of the NBS SMA Study Group[1]

Newborn screening



The ethics of access to treatments

Ethics and Disability

- Autonomy
  - Respect of patient / caregiver voice or views
- Beneficence
  - Covers concept of “care” with respect for pt autonomy avoiding paternalistic attitude
- Non-Maleficence
  - Consider the implications of intervention for physical and psychological pain
  - Balanced against “the child’s best interests”.
- Justice
  - Patient rights

Chabrol and Desguerre Arch de Pediatr 2021

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 30 (2020) 267–269

www.elsevier.com/locate/nmd

Editorial

Randomisation versus prioritisation in a managed access programme: Lessons from spinal muscular atrophy

- Explosive level of outputs related to the new interventions for SMA – in the medical literature, congresses and social media
- High level of expectation and emotive case stories released by families

JAMA Pediatrics | Special Communication

Ethical Challenges Confronted When Providing Nusinersen Treatment for Spinal Muscular Atrophy

Alyssa M. Burgart, MD, MA; David Magnus, PhD; Holly K. Tabor, PhD; Erin Daksha-Talati Paquette, MD, JD; Joel Frader, MD; Jaqueline J. Glover, PhD; Brian M. Jackson, MD, MA; Charlotte H. Harrison, PhD, JD, MPH; David K. Urion, MD; Robert J. Graham, MD; John F. Brandsema, MD; Chris Feudtner, MD, PhD, MPH

JAMA Pediatr. 2018;172(2):188-192. doi:10.1001/jamapediatrics.2017.4409
Published online December 11, 2017.

- **Cost:** (Biogen): US$750 000 6 injections per year, US$375 000 per year for each subsequent injection.
- **Limitation of evidence**: outstanding data needed on sustained benefit and safety
  - Small studies and results not all equating to clinical efficacy. Rare condition so may need years to collect enough comparable pts to draw conclusions
- **Informed consent**: Need to constantly update, decisions about when to stop, alternate therapies

JAMA Pediatrics | Special Communication

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JAMA Pediatr. 2018;172(2):188-192. doi:10.1001/jamapediatrics.2017.4409
Published online December 11, 2017.

- **Treatment Allocation**: risk of patient queues, bottle neck, delay gaining access. Lumbar Puncture maybe complex in vulnerable child.
- **Fair distribution of roles and responsibilities**: Geographic access to care – ethics of expanding treatment centres, but must be financed, how would draw on resources affect children with other disorders?
- **Transparency and Stakeholder engagement**: insight into treatment availability could affect relocation and self-referral practice.

Agosto et al. Orphanet J Rare Dis (2021) 16:78
https://doi.org/10.1186/s13023-020-01593-4

Orphanet Journal of Rare Diseases

LETTER TO THE EDITOR Open Access

Do we always need to treat patients with spinal muscular atrophy? A personal view and experience

Caterina Agosto[1*], Eleonora Salamon[1], Antuan Divisic[1], Francesca Benedetti[2], Luca Giacomelli[3], Aashni Shah[3], Giorgio Perilongo[4] and Franca Benini[1]

- N=17 infants SMA type 1 – early nusinersen intervention
  - 6 stopped RX nusinersen (AE or lack efficacy)
  - 11 responded RX, but continue to need MDT
- N=18 children SMA type 2
  - 5 stopped RX
  - 13 continued RX with good response in 6
- Authors noted that use of the intervention needed to be balanced against the discomfort and not automatically assumed to have response in all

Archives de Pédiatrie 27 (2020) 7S50–7S53

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Review article

Ethical aspects in the care of a child with infantile spinal muscular atrophy (SMA)

B. Chabrol[a,*], I. Desguerre[b]

[a]*Centre de référence des maladies neuromusculaires de l'Enfant, Neuromuscular Commission of French Society of Pediatric Neurology, Filière FINELMUS, Hôpital d'Enfants, CHU Timone, 13385 Marseille cedex 5*
[b]*Centre de référence des maladies neuromusculaires de l'Enfant, Neuromuscular Commission of French Society of Pediatric Neurology, Filière FINELMUS, Hôpital Necker, rue de Sèvres, 75015 Paris*

- Noted the need for ethical conduct in the care of children with SMA.
- Standardise interventions regardless of whether receive antisense oligonucleotide treatment
- Concerned bias in care occurring
- Promoted ongoing role for palliative care support regardless of treatment direction

Received: 15 October 2018 | Revised: 12 September 2019 | Accepted: 27 September 2019

DOI: 10.1111/bioe.12695

ORIGINAL ARTICLE

bioethics WILEY

Drugs, genes and screens: The ethics of preventing and treating spinal muscular atrophy

Christopher Gyngell[1,2] | Zornitza Stark[1,2] | Julian Savulescu[2,3]

- Promoted the need to continue “ex-ante” interventions e.g.
  - carrier screening,
  - prenatal testing,
  - preimplantation genetic diagnosis,
  - gene editing
- Aim to reduce the incidence of SMA.

Kiefer et al. Orphanet Journal of Rare Diseases (2020) 15:194
https://doi.org/10.1186/s13023-020-01477-7

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Experiences of caregivers of children with spinal muscular atrophy participating in the expanded access program for nusinersen: a longitudinal qualitative study

Petra Kiefer[1], Janbernd Kirschner[1,2], Astrid Pechmann[1] and Thorsten Langer[1*]

(2020) 15:194

- Caregivers of infants with SMA type 1
  - Part of the extended access program nusinersen
- Intervention changed caregiver perspectives
  - Severely limited life expectancy / palliative approach to more optimistic view – hopes for longer life and positive development
- Anxiety of “unknown” intervention
  - Caregivers felt ”there was no alternative”
- Study raised issue that families need to be empowered in decision taking.

frontiers in Medicine

PERSPECTIVE
published: 23 December 2020
doi: 10.3389/fmed.2020.608249

Development and Use of Gene Therapy Orphan Drugs—Ethical Needs for a Broader Cooperation Between the Pharmaceutical Industry and Society

Sandor Kerpel-Fronius[1†], Varvara Baroutsou[2†], Sander Becker[3†], Roberto Carlesi[4†], Luis Collia[5†], Brigitte Franke-Bray[6†], Peter Kleist[7†], Chieko Kurihara[8†], Luis Filipe Laranjeira[9†], Kotone Matsuyama[10†], Shehla Naseem[11†], Johanna Schenk[12†] and Honorio Silva[13†]*

OPEN ACCESS

Edited by:
Mette Due Theilade Thomsen,

- Noted with the roll-out of gene therapy raised new types of challenges across
  - Scientific
  - Financial
  - Social
  - Ethical
- For the Pharmaceutical industry, regulators and society

Development and Use of Gene Therapy … Kerpel-Frontius et al Front Med 2020: Recommendations 1

- Close cooperation between pharmaceutical industry and society to develop orphan gene therapy

1. Fully transparent health technology negotiations in a close and long-lasting, contractually fixed cooperation between manufacturers and local health-care stakeholders for sharing medical and scientific benefits, the financial risks as well as the burdens of post-authorisation clinical and regulatory development

Development and Use of Gene Therapy … Kerpel-Frontius et al Front Med 2020: Recommendations 2

2. Parties should agree on fair, locally affordable drug price without the usually very high premium calculated to compensate for the low number of patients,

- 15-20 yrs long payment by installment with risk-sharing especially considering the late outcome of treatment is unknown.
- Society support patient registry, specialised hospitals, adequate long-term follow-up and coordinated management of financial transactions

Development and Use of Gene Therapy … Kerpel-Frontius et al Front Med 2020: Recommendations 3

3. Post authorisation treatment and prolonged observation of additional new cases coordinated by society should provide real world data needed for modern complex registry evaluation of gene therapy products by the competent authorities.

Development and Use of Gene Therapy … Kerpel-Frontius et al Front Med 2020: Recommendations 4

4. Aim that fair sharing of benefits and risks as well-organised cooperation of society with industry in collection of real work evidence will result in better drug evaluation and improved accessibility due to lower prices.

Childhood spinal muscular atrophy: controversies and challenges

Eugenio Mercuri, Enrico Bertini, Susan T Iannaccone

Lancet Neurol 2012; 11: 443–52

- Effective standards of care = patients able to benefit from effective interventions
  - E.g. antisense oligonucleotides
- To prepare for clinical trials –need cooperation on an international scale between
  - clinicians,
  - scientists,
  - industry,
  - government
  - volunteer organisations
  - caregivers / patients

Thank you

Any questions?