Spinal Muscular Atrophy « SMA » : a New Therapeutic Era with Nusinersen

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Grant support to conduct clinical trials on SMA from Ionis/Biogen;
Serves as a consultant to Biogen, AveXis, Roche, Biologix, Cytokinetics
Serves as a scientific/medical advisor for non profit organizations such as SMA Europe, TREAT-NMD, FUNDAME, FAME Chile, Familias SMA Argentina and Famiglie SMA Italy.

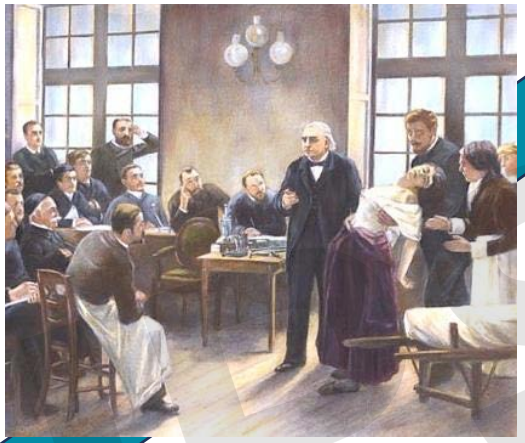
Knowledge on SMA on the last 150 years

Protocols of treatments

2017

Translational research

2000



Genetic diagnosis

1990-1999

Gene cloned in 1995 by the group of Dr. J. Melki, Paris.

Clinical diagnosis

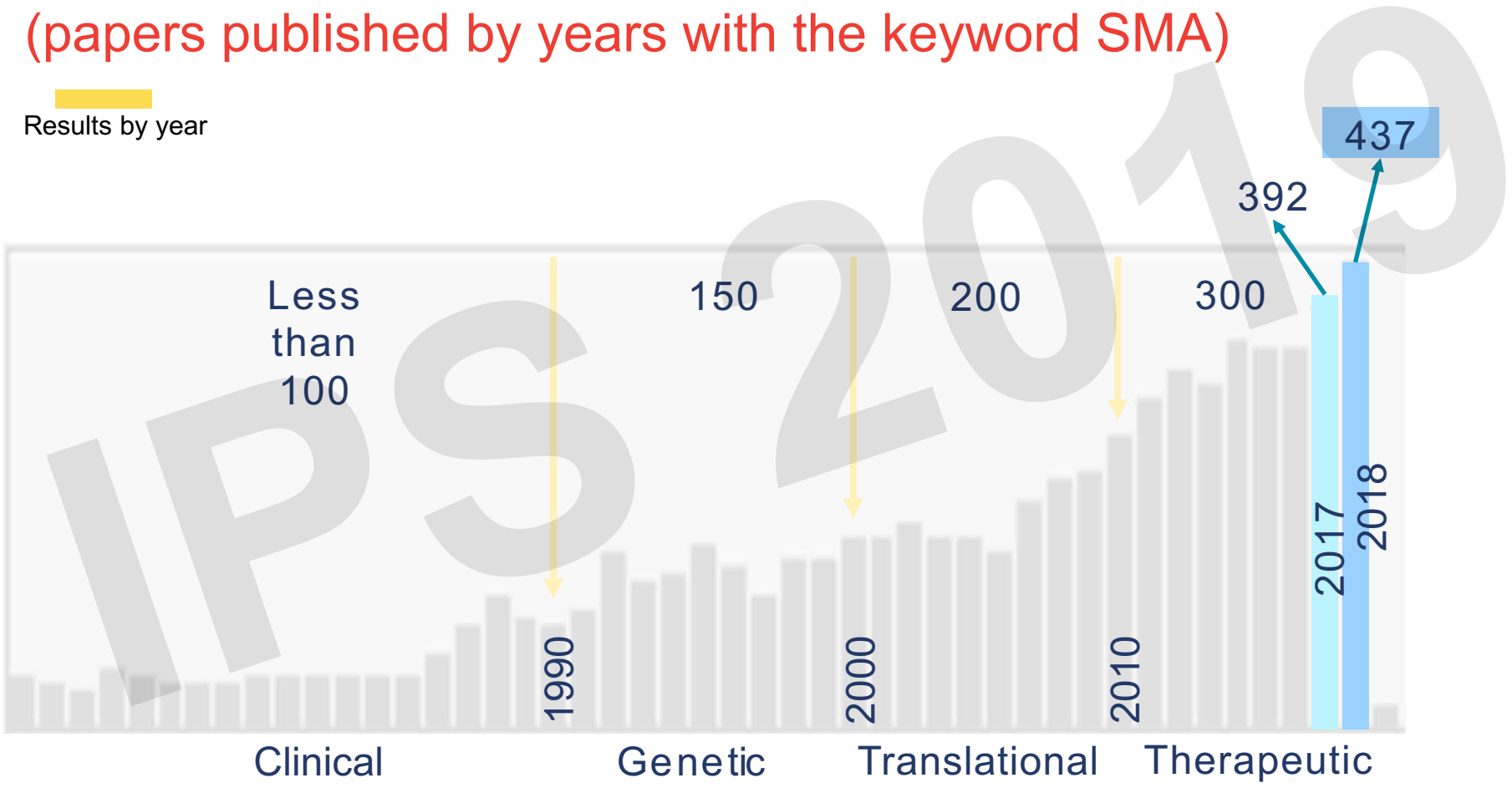
1950-80

Disease description

1850-1890

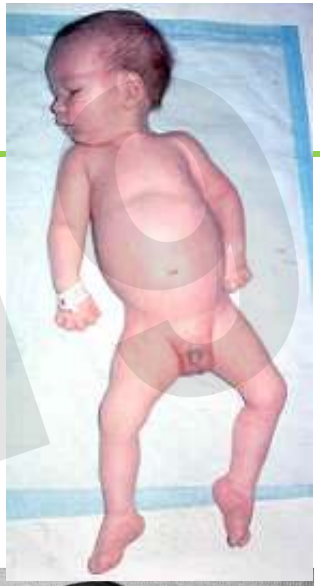
Growing interest in SMA research in the last 30 years

(papers published by years with the keyword SMA)

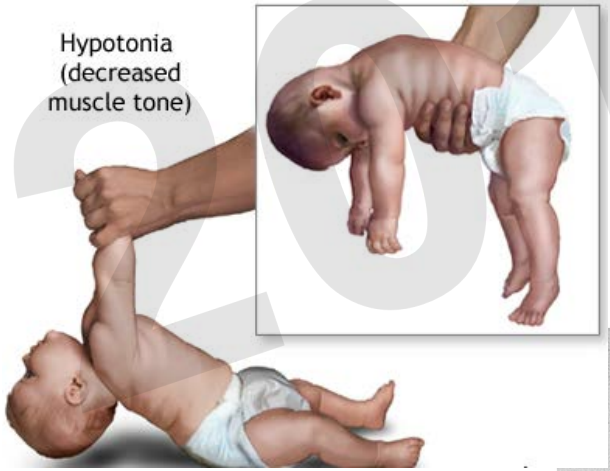


E Tizzano PubMed 2018 last entrance Dec 2018

Type I or Werdnig-Hoffman



The most severe form



Severe hypotonia (floppy baby)

May present arthrogryposis

Bell shaped thorax

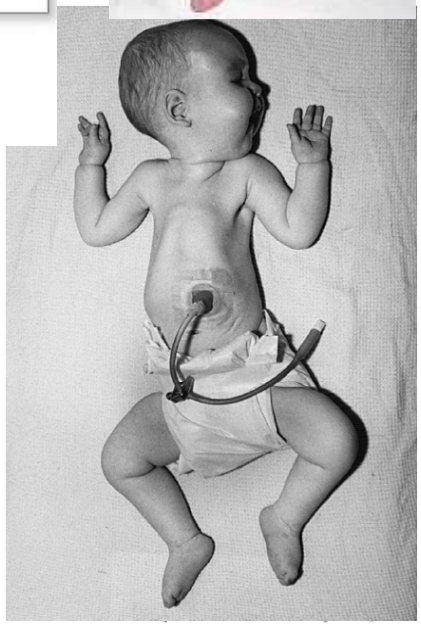
Paradoxical respiration

Lingual fasciculation

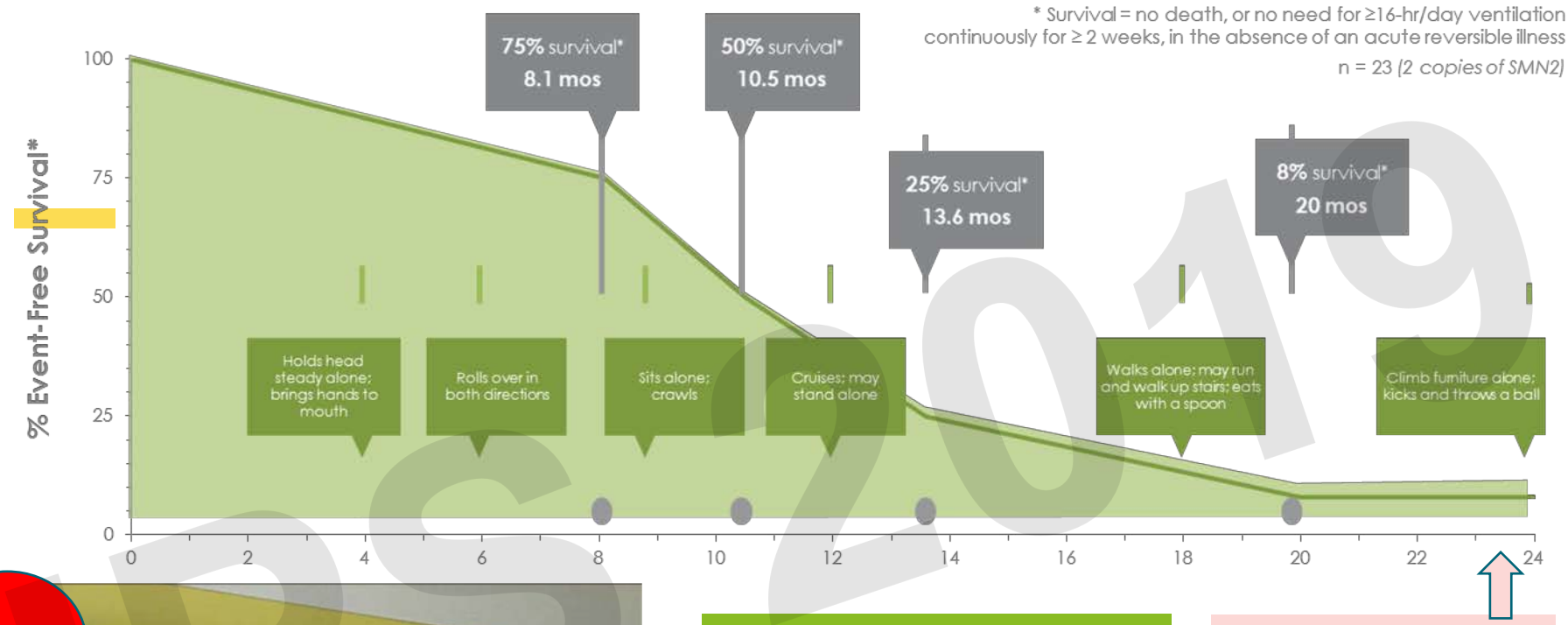
Areflexia but sphincter and sensitivity conserved

Bulbar muscle weakness (weak cry, difficulty swallowing , aspiration)

Poor or null head control



90% of SMA Type 1 patients will not survive to the age of 2



SMA Type 1

- **"Floppy baby" syndrome**
- Muscle weakness (legs more than arms)
- Poor head control
- Belly breathing
- Bulbar muscle weakness (weak cry, difficulty swallowing, aspiration)
- **Will never sit unsupported**

More than 90% of type I patients die at age of 2 years

SPINRAZA® (nusinersen) 12mg solution for injection

Finkel et al., 2014; E TIZZANO Hosp. V. Hebron Barcelona Spain with permision and authorization (D. Sproule)

Type II
Intermediate form

Usually asymptomatic until 6 months

They are sitters

Consultation for delay in standing or walk

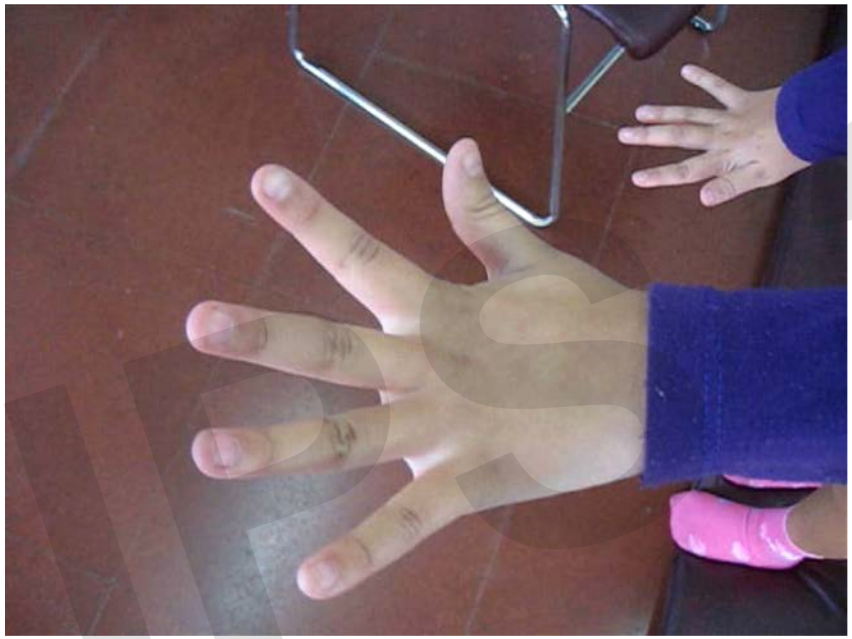
Usually hyporeflexia and tremor

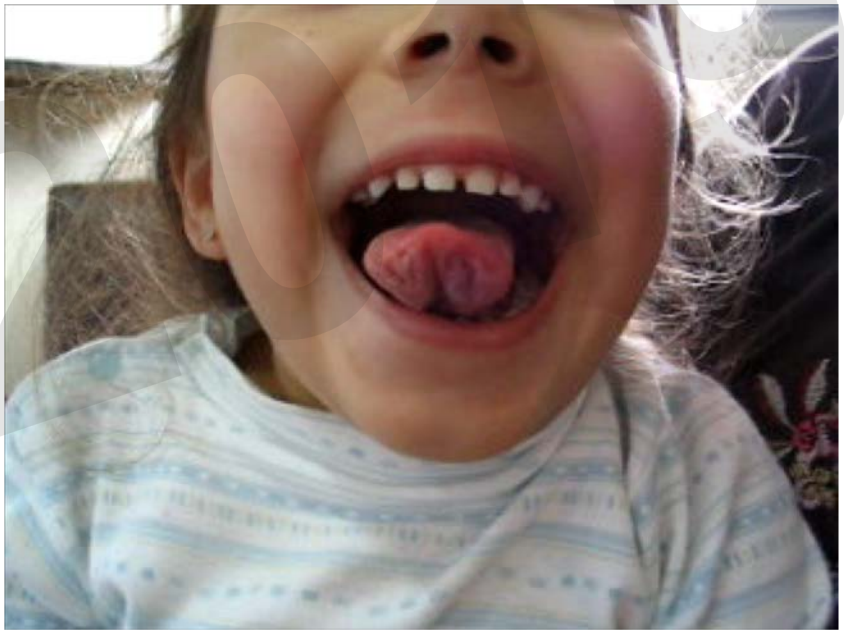
Scoliosis is developed during the first years

Prognosis according to respiratory performance

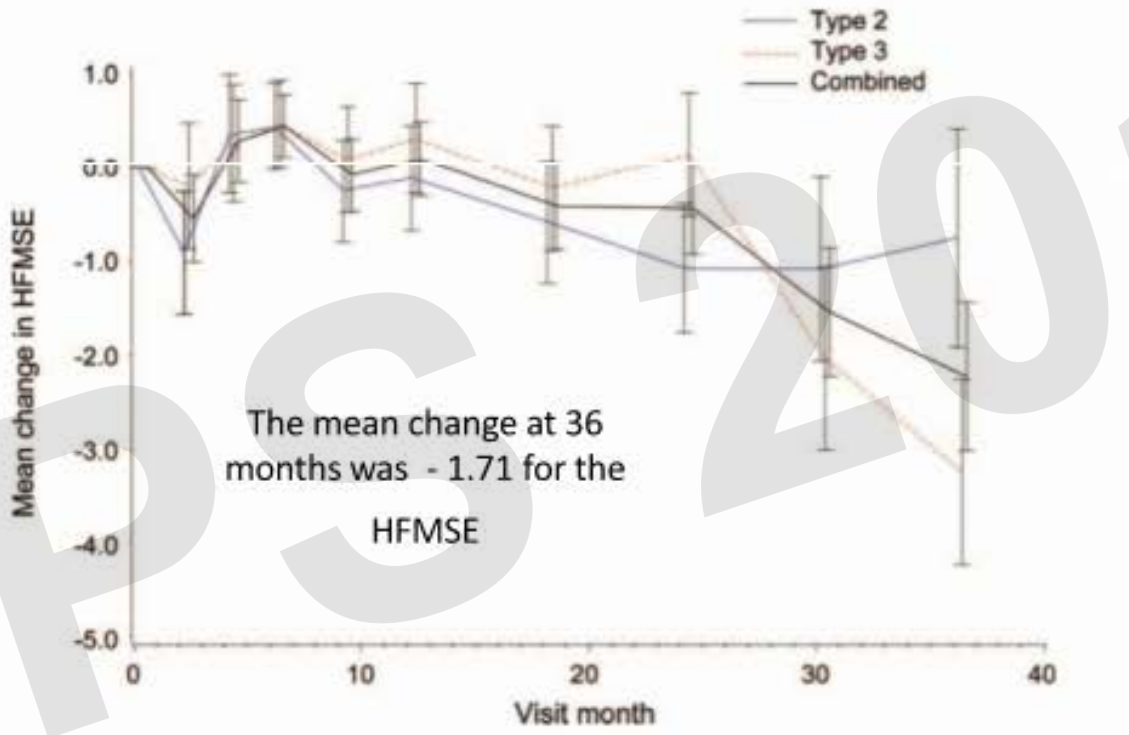
Survival from 240 type II patients (who sat but never walked) was 98.5% at 5 years and 68.5% at 25 years (Zerres et al., 1997)

Two main findings of denervation: tremor and fasciculations





Typically, type II cases present a decline in motor function with some stable periods



Motor function appeared to decline in a nonlinear fashion when evaluated beyond 12 months, a finding confirmed by each of the 3 motor function measures

Kauffmann et al., 2012

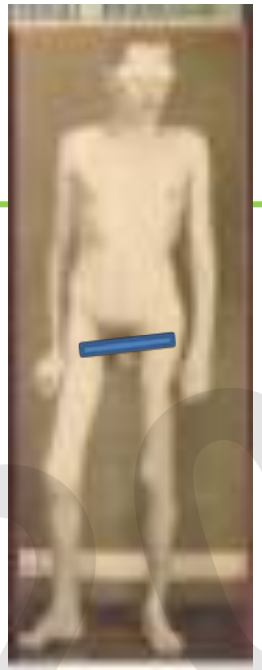
Patients with type II are those who reach sitting status.

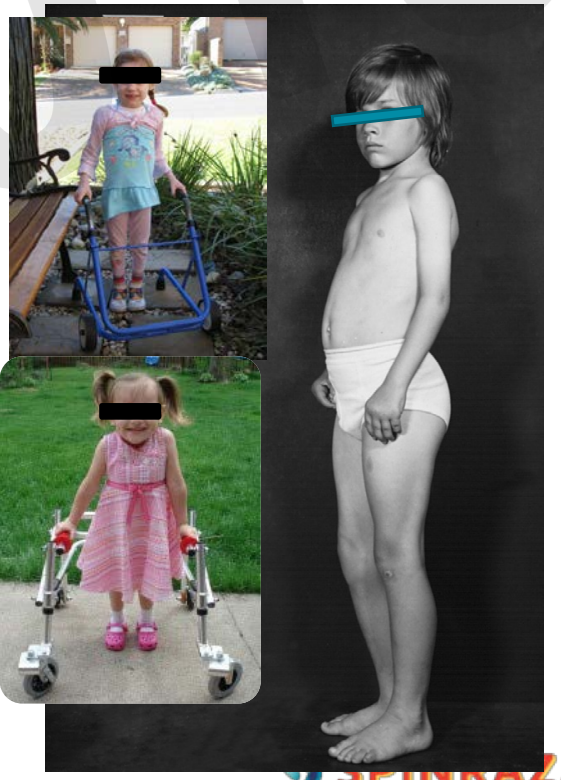
Some patients lose this capacity later (weak type II/type II a)

Others reach standing and may perform some walk with help (strong type II/type IIb)

Patients are confined to wheelchair.

Type III
or Kugelberg-Welander





The mildest form

Onset after 18 months

Able to walk independently

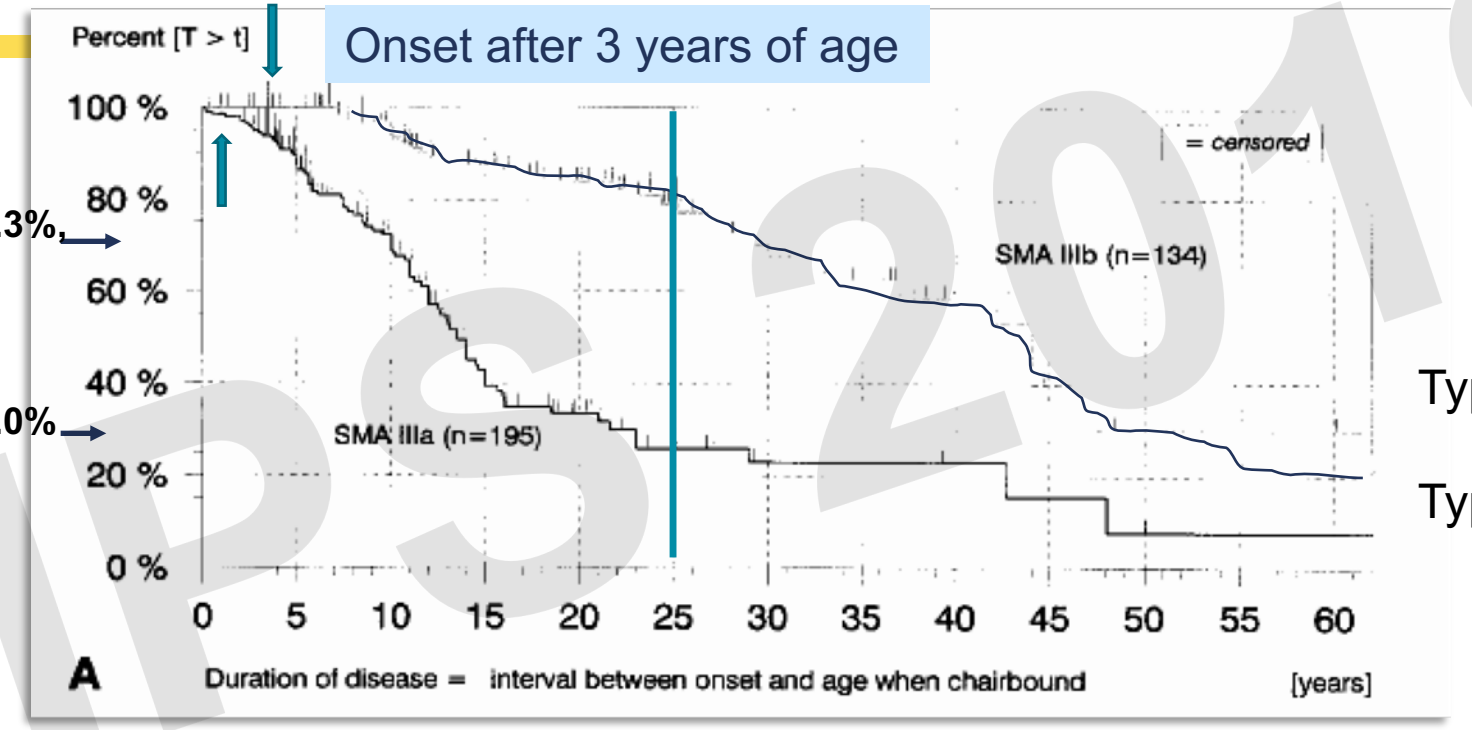
Proximal weakness with difficulties to change sitting position or walk upstairs.

Frequent falls

Scoliosis according to muscular weakness

Lumbar hyperlordosis

Natural walking history type III



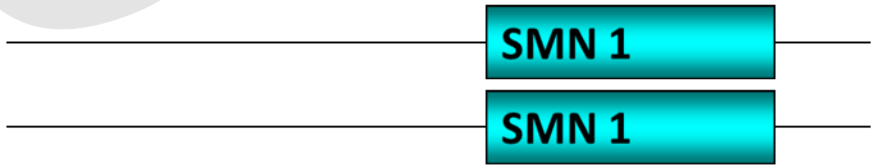
Type IIIb

Type IIIa

Zerres et al., J Neurol Sci. 1997;146: 67-72.

Determinant gene SMN1

Mutations in SMN1 (deletions, point mutations) are detected in affected patients and confirm disease

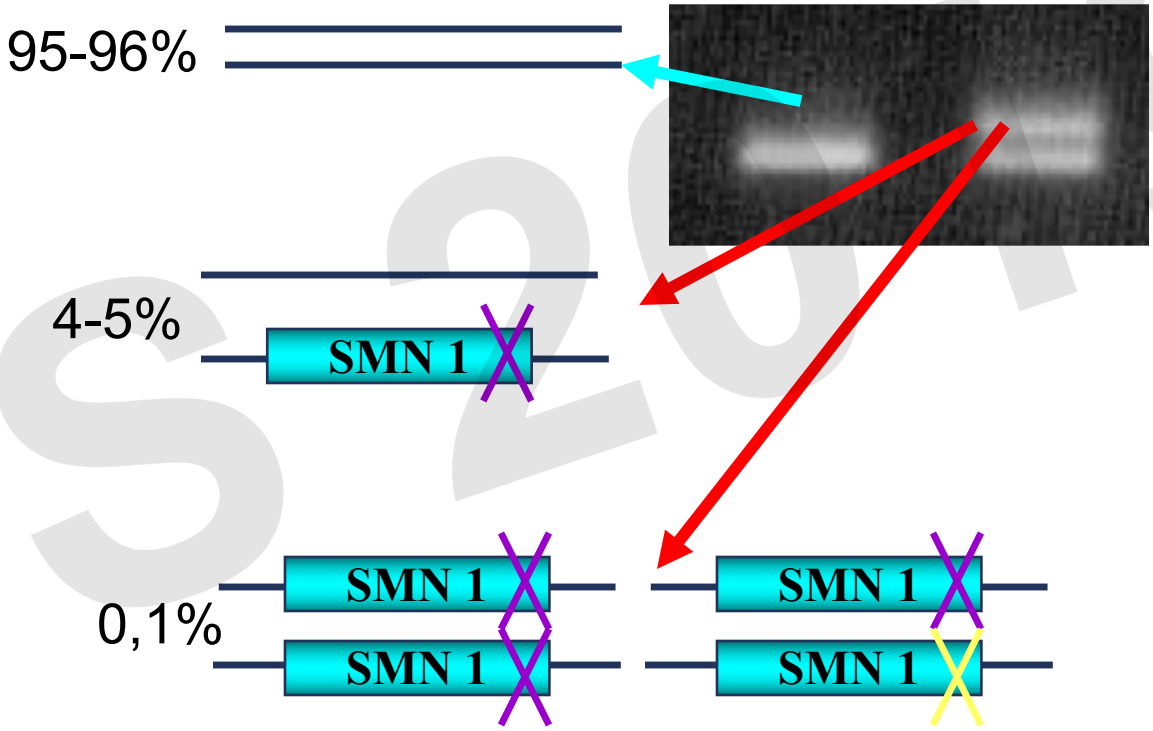


Alias et al., 2009

Genetic confirmation of 5q SMA

Qualitative

Proximal predominant weakness
Reduced or absent reflexes
Tongue fasciculations
Limb tremor



Alias et al., 2009 based in 745 genetically confirmed cases

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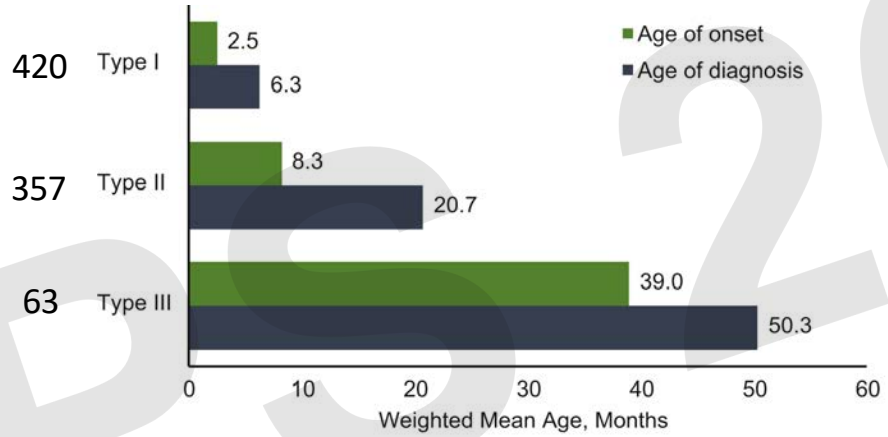
Allows only diagnosis of homozygous deletion in exon 7

CURRENT CLINICAL PARADIGM :
Despite straightforward genetic testing diagnosis is often delayed



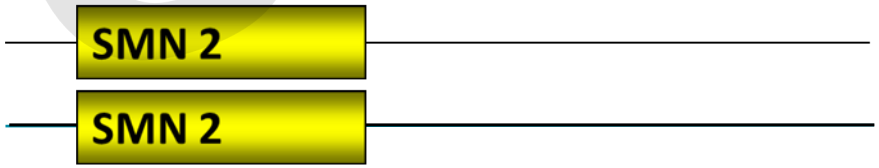
Lin et al., Ped Neurol 2015

Need for awareness to avoid patient´s odissey

- Molecular genetic testing is now the standard tool for diagnosis of SMA
- Due to the efficiency of molecular testing and high frequency of SMA in the hypotonic or “floppy” infant, independent authors, Arnold et al, recommend that it is an early consideration in any infant with weakness or hypotonia

Modifier gene SMN2

SMN2 a homologous copy of SMN1 is present in ALL SMA patients and the number of copies varies from 1 to 5

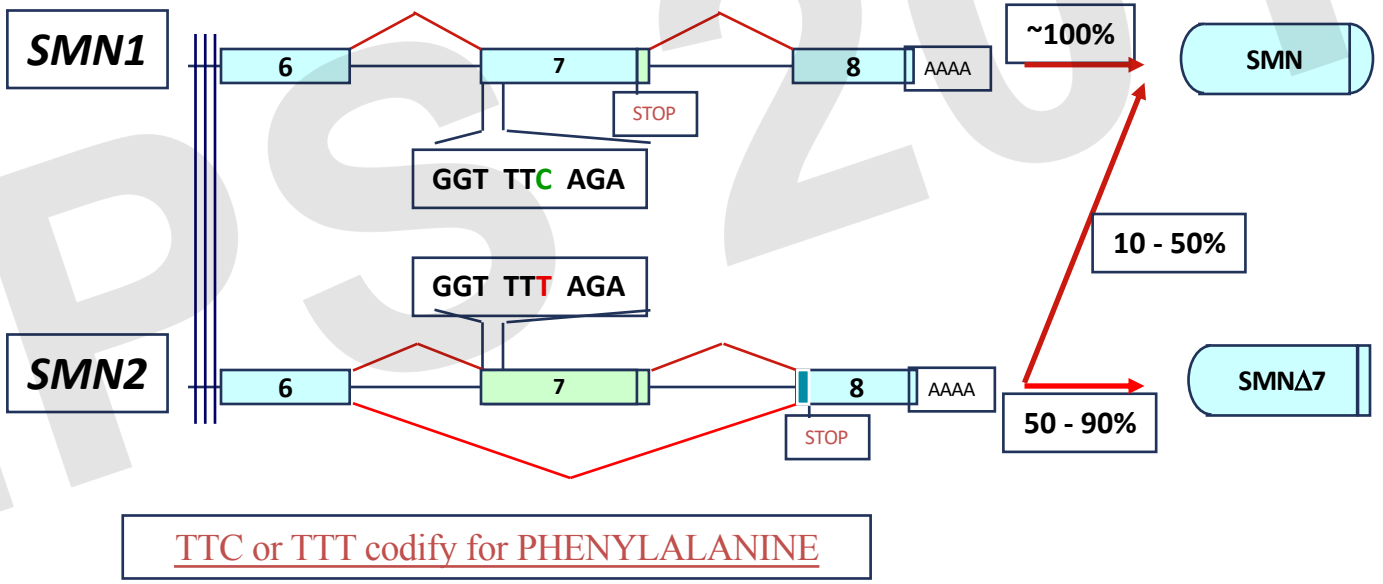


Calucho et al., 2018

C>T transition in exon 7 makes this exon more prone to be excluded in mRNA

WHY?

and NOT?

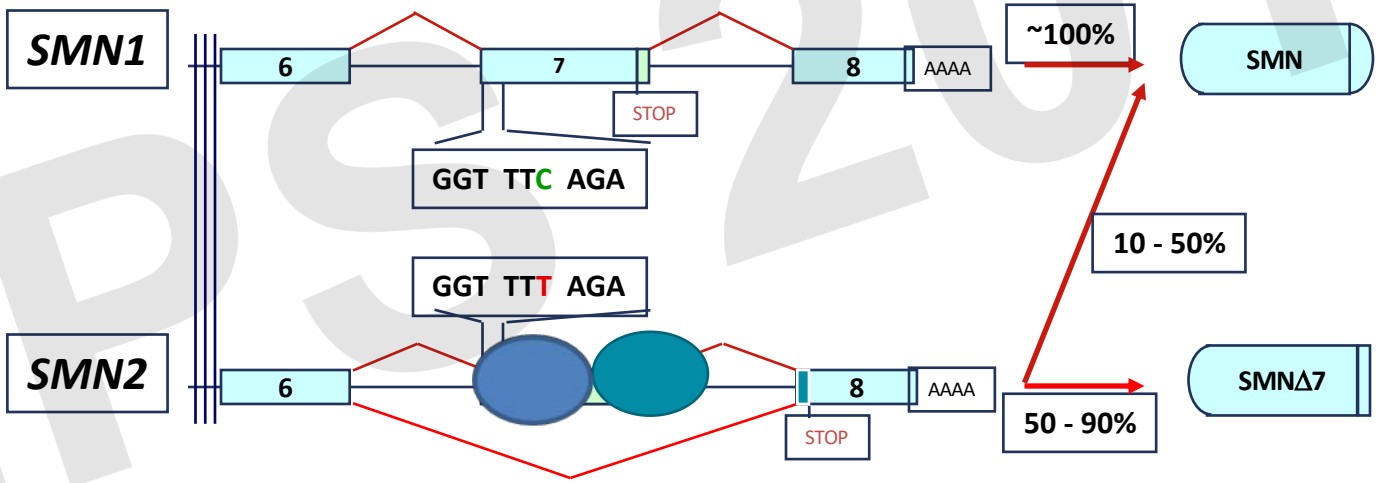


TTC or TTT codify for PHENYLALANINE

WHY?

and NOT?

C>T transition in exon 7 makes this exon more prone to be excluded in mRNA

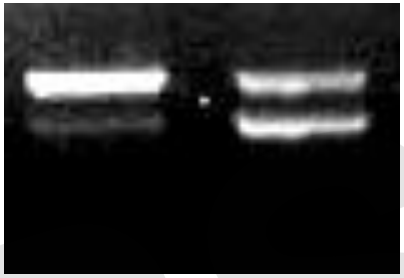


TTC or TTT codify for PHENYLALANINE

A decrease of SMN protein in spinal cord causes SMA

Control SMA

SMN1+SMN2 SMN2



SMN transcripts

Ex7

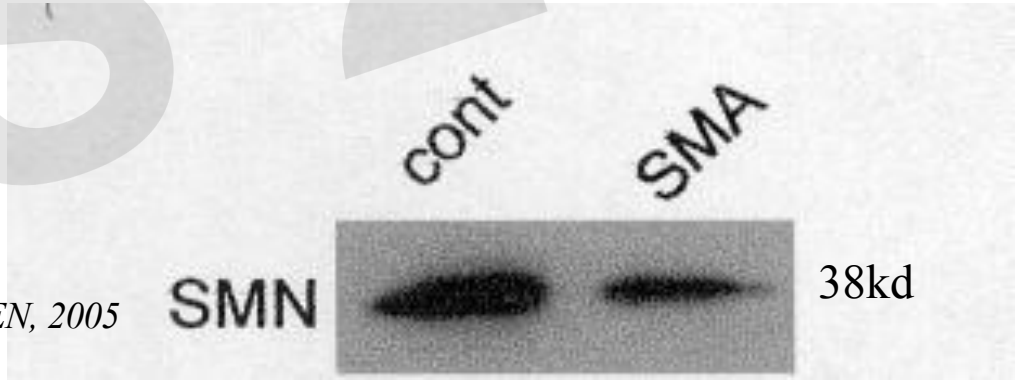
FL SMN (COMPLETE)

delta 7 SMN (INCOMPLETE)

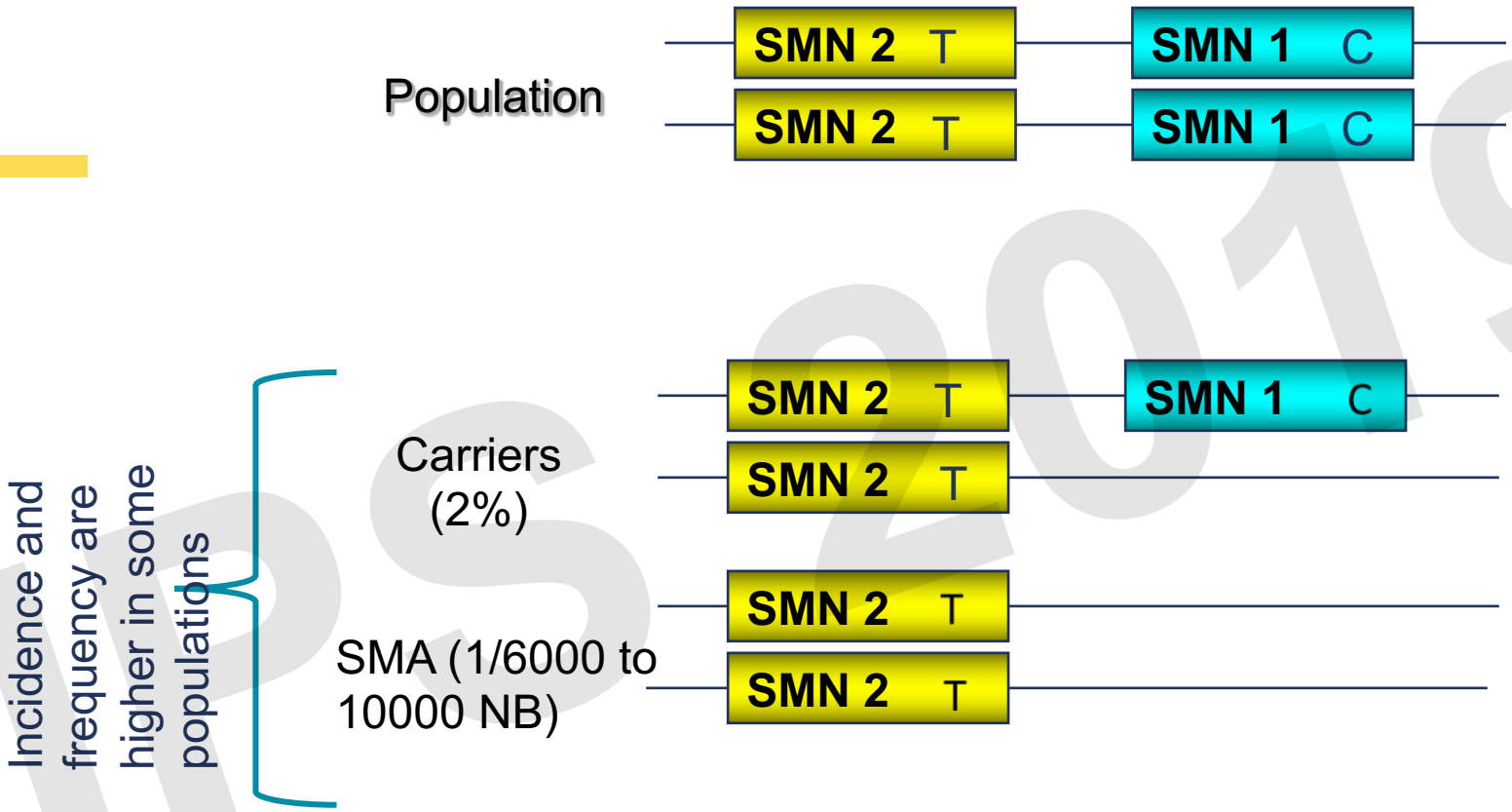
SMN mRNA and protein in fetal SPINAL CORD

(15 weeks)

Soler-Botija et al., JNEN, 2005



SMN1+SMN2 SMN2



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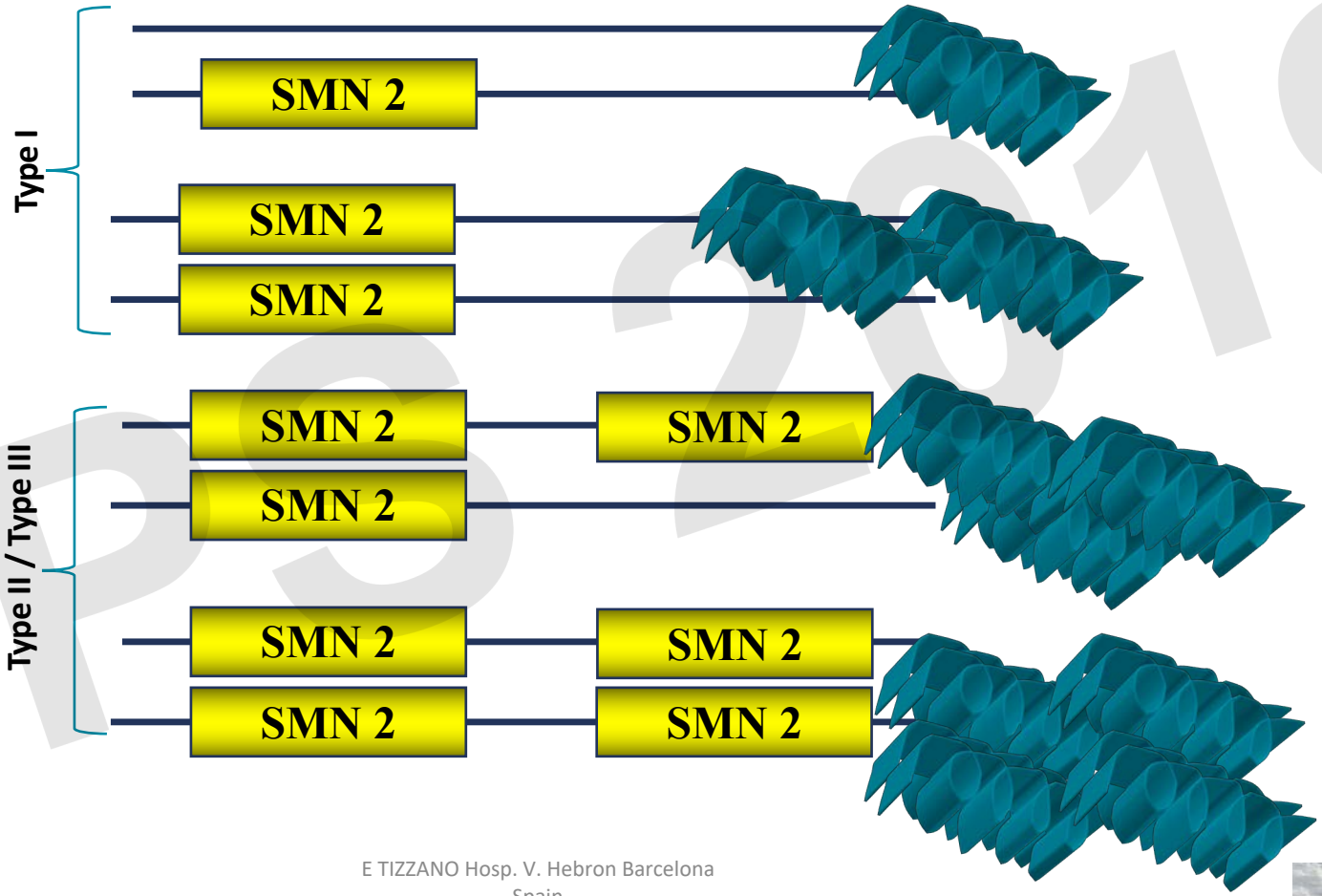
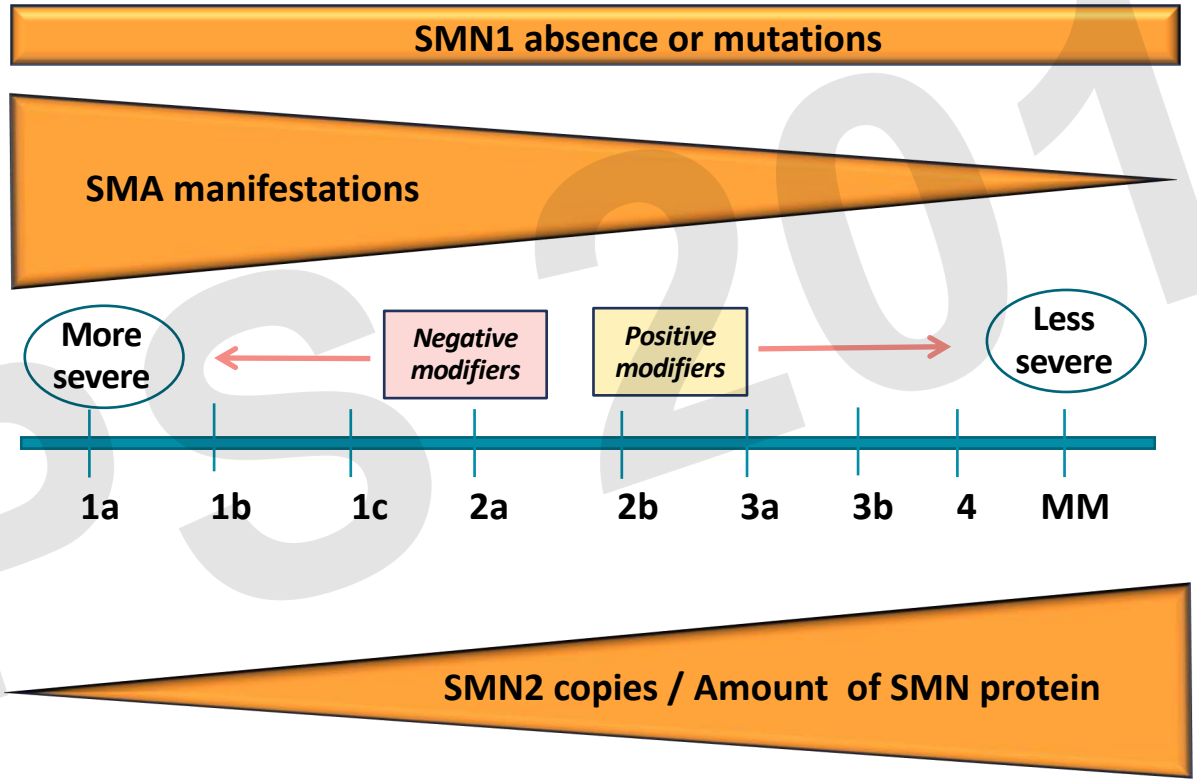
Barcelona Spain

SMN2 copies in SMA patients

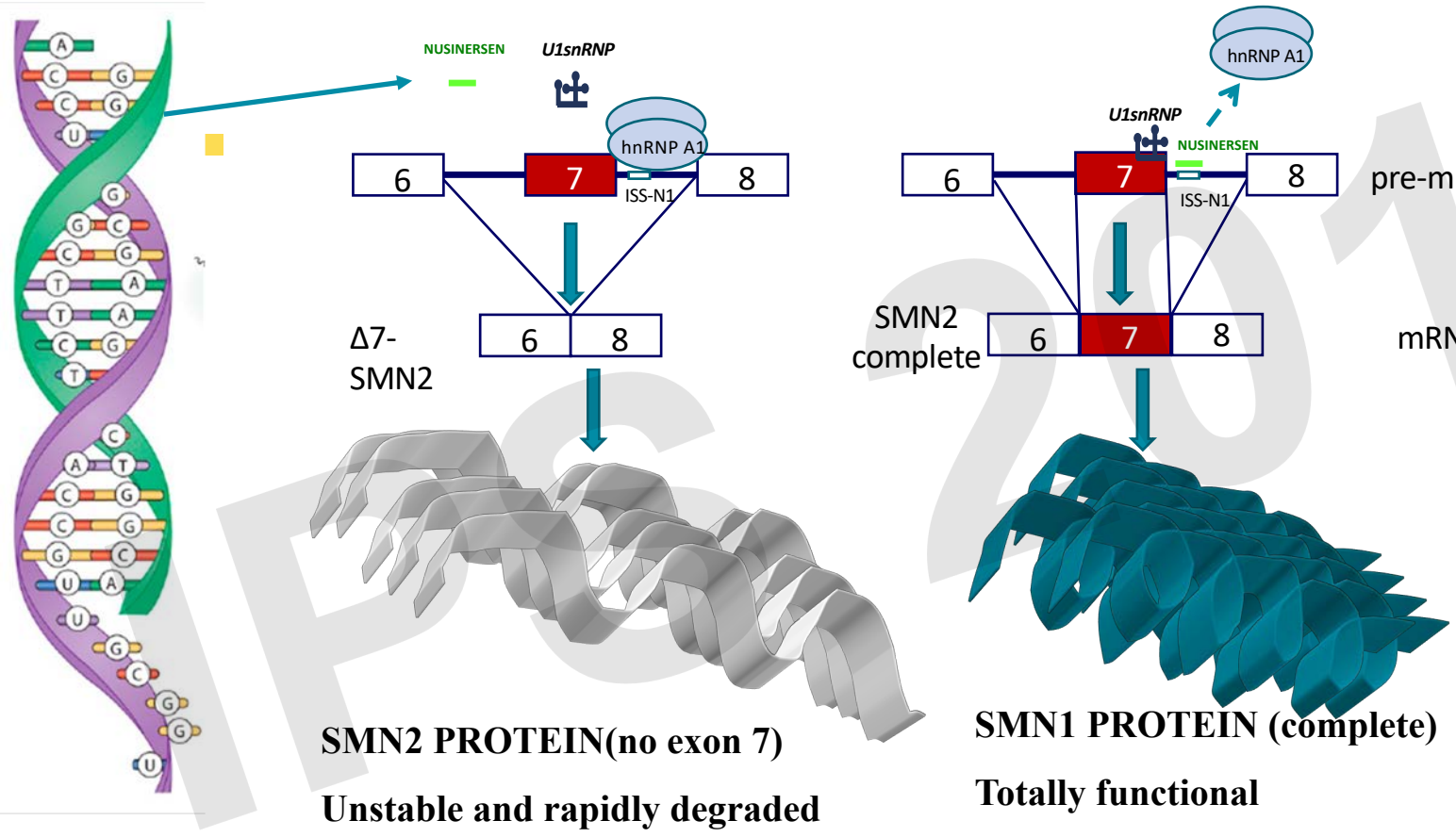


A continuous spectrum of phenotypes in SMA

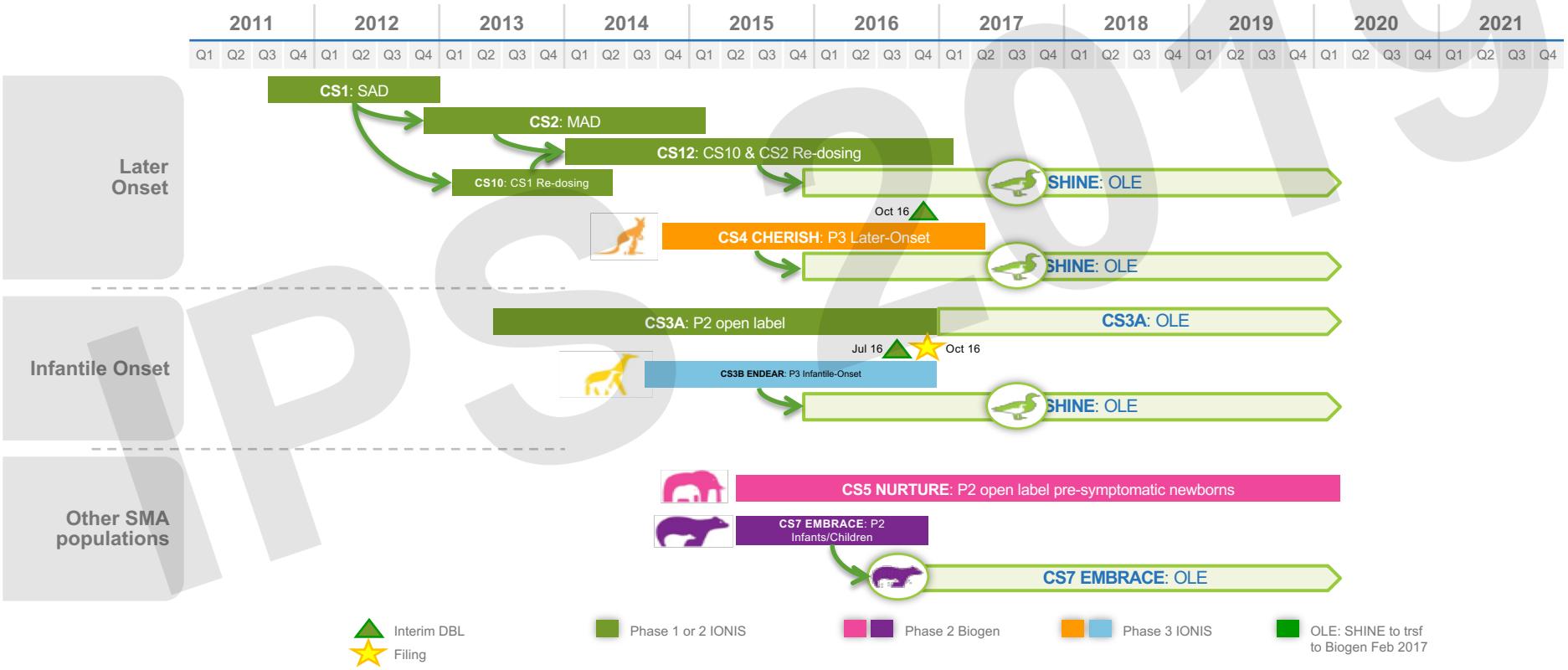


Talbot and Tizzano, Gene therapy, 2017

Simplified mechanism of action of Nusinersen

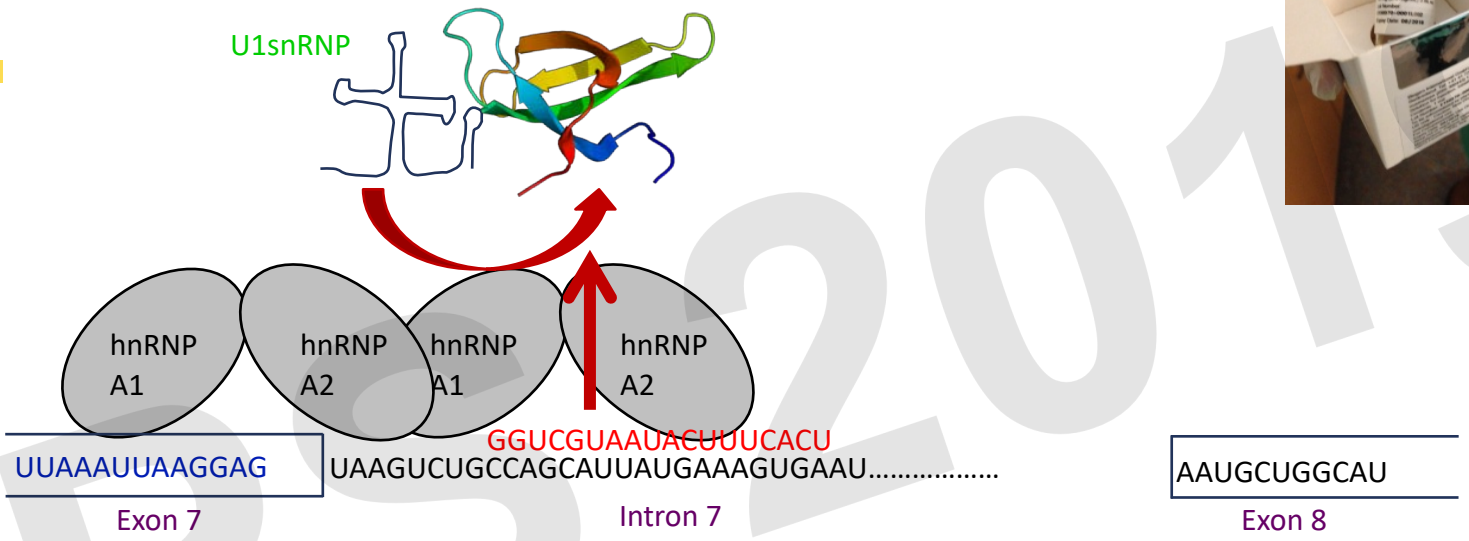


Nusinersen Clinical Development Program



SPINRAZA (nusinersen) 12mg solution for injection

Modulation of SMN2 by Antisense therapy

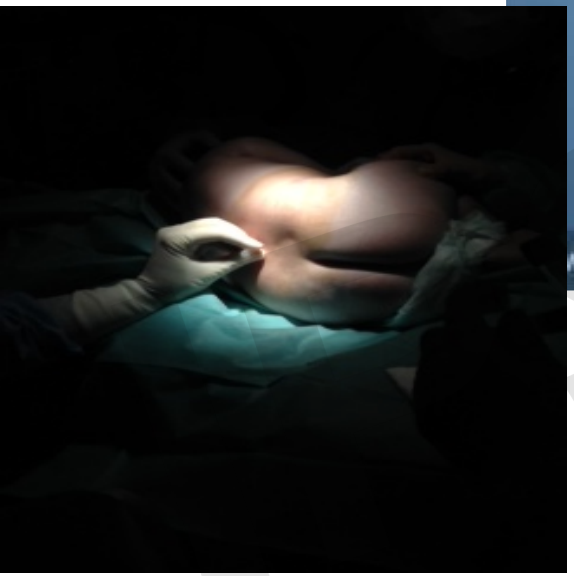


- 2'-*O*-methoxyethyl (MOE) modified antisense drug
- Displaces negative splicing factors on pre-mRNA, promoting inclusion of mis-spliced exon 7
- Promotes synthesis of fully functional SMN protein

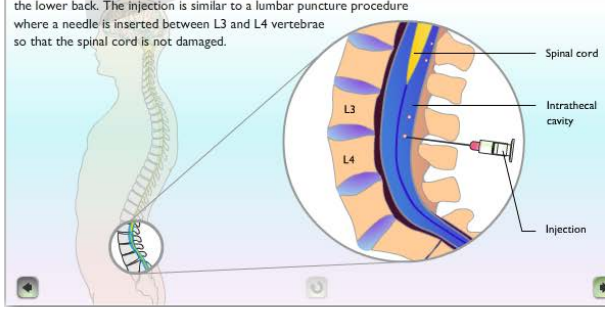
Demonstrates safety and efficacy in different SMA types (FDA (2016) and EMA (2017) approved

SPINRAZA (nusinersen) 12mg solution for injection

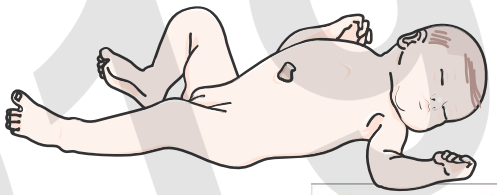
Intrathecal drug delivery



CSF, where it flows through the intrathecal cavity between the vertebrae of the lower back. The injection is similar to a lumbar puncture procedure where a needle is inserted between L3 and L4 vertebrae so that the spinal cord is not damaged.



Intrathecal injection 120 type I patients starting before 6 months



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

ABSTRACT

BACKGROUND

Spinal muscular atrophy is an autosomal recessive neuromuscular disorder that is caused by an insufficient level of survival motor neuron (SMN) protein. Nusinersen is an antisense oligonucleotide drug that modifies pre–messenger RNA splicing of the *SMN2* gene and thus promotes increased production of full-length SMN protein.

METHODS

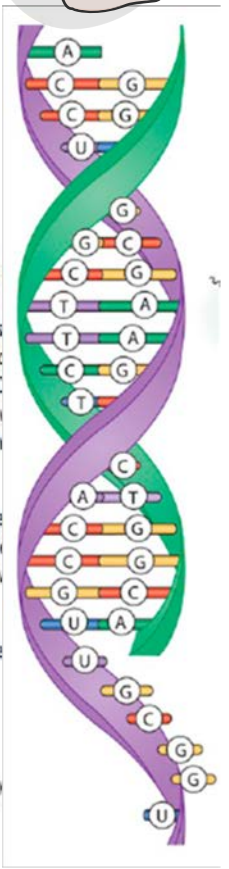
We conducted a randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial of nusinersen in infants with spinal muscular atrophy. The primary end points were a motor-milestone response (defined according to results on the Hammersmith Infant Neurological Examination) and event-free survival (time to death or the use of permanent assisted ventilation). Secondary end points included overall survival and subgroup analyses of event-free survival according to disease duration at screening. Only the first primary end point was tested in a prespecified interim analysis. To control the overall type I error rate at 0.05, a hierarchical testing strategy was used for the second primary end point and the secondary end points in the final analysis.

The authors' full names, academic grees, and affiliations are listed in Appendix. Address reprint requests Dr. Finkel at the Division of Neurolo Department of Pediatrics, Nemours C dren's Hospital, 13535 Nemours Pk 5th Fl., Orlando, FL 32827, or at rich .finkel@nemours.org.

*A complete list of the principal inve gators in the ENDEAR trial is provi in the Supplementary Appendix, av able at NEJM.org.

This article was updated on Novembe 2017, at NEJM.org.

N Engl J Med 2017;377:1723-32.
DOI: 10.1056/NEJMoa1702752



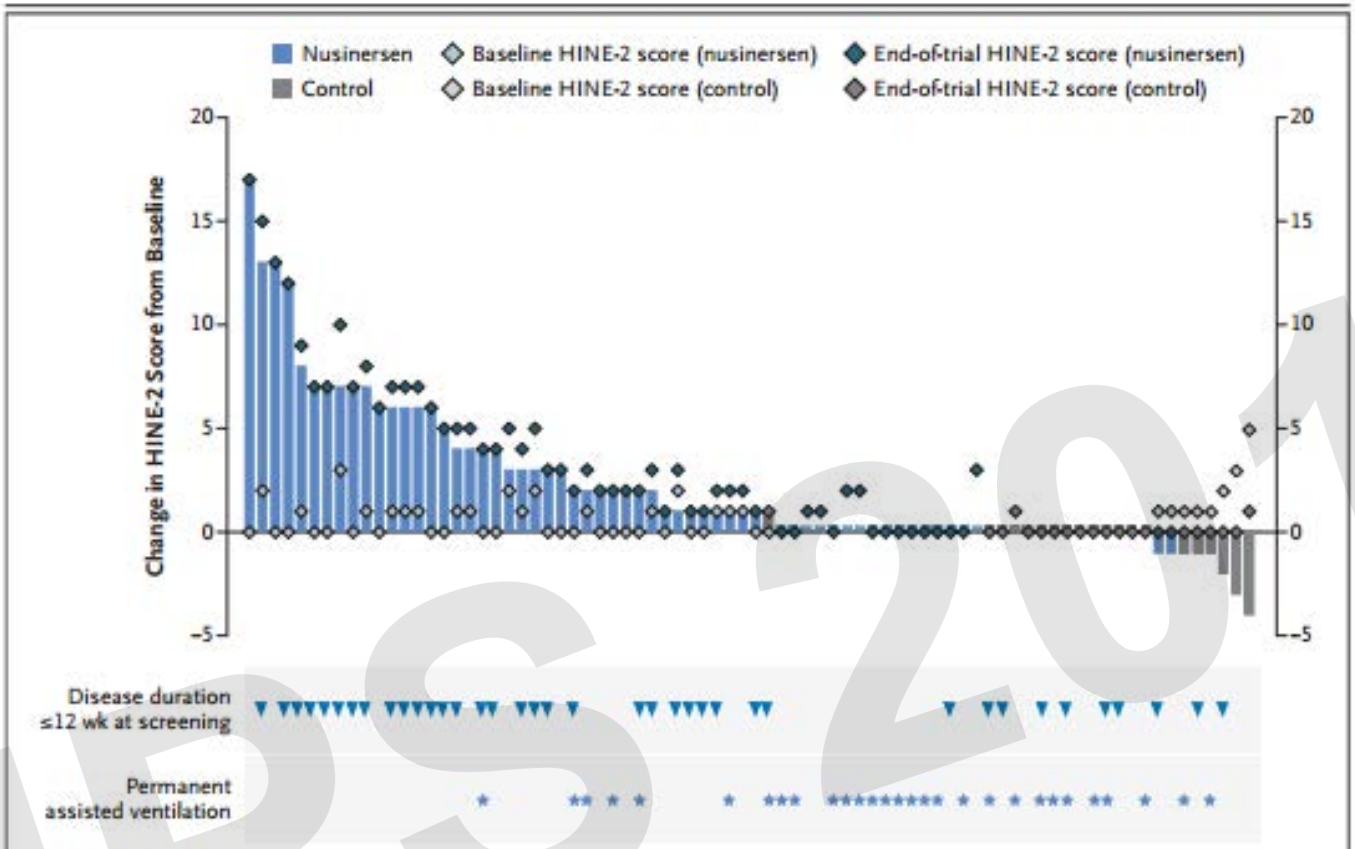


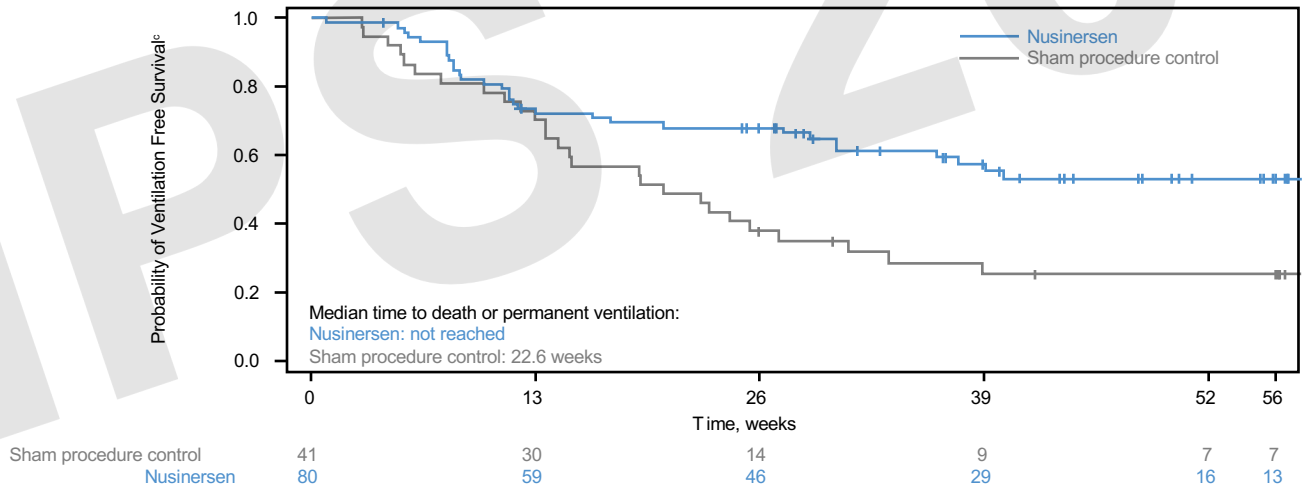
Figure 1. HINE-2 Scores.

Shown are the scores on Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) at baseline and at the end-of-trial visit (on day 183, 302, or 394) (diamonds), as well as the change in HINE-2 score from baseline through the end-of-trial visit (bars), for the 78 infants who were alive, attended an end-of-trial visit, and were included in the final analysis. (Of the 110 infants who were included in the final analysis, 29 died [13 in the nusinersen group and 16 in the control group] and 3 were withdrawn for a reason other than death [2 in the nusinersen group and 1 in the control group] and therefore were not included in this analysis.) The HINE-2 assesses the development of motor function through the achievement of motor milestones; scores on the HINE-2 range from 0 to 26, with higher scores indicating better motor function. The scores shown here account for seven of the eight motor-milestone categories, excluding voluntary grasp. For the infant in the control group who had a 1-point increase, the increase was in the score for kicking, and therefore the infant was not considered to have a motor-milestone response. The shortest bars indicate a value of 0. Triangles indicate infants who had a disease duration of 12 weeks or less at screening. Stars indicate infants who received permanent assisted ventilation during the trial.

Event-Free Survival at End of Study

- Significantly prolonged event-free survival[a] in nusinersen-treated infants (HR, 0.53; *P*=0.0046[b])

Outcome	Sham procedure control	Nusinersen
Death or permanent ventilation, n (%)	28 (68%)	31 (39%)
Alive and no permanent ventilation, n (%)	13 (32%)	49 (61%)



Nusinersen: 61%

Sham procedure control: 32%

All infants randomized who received at least one dose of nusinersen or sham procedure were included in the analysis. [a]Event-free survival = time to death or permanent ventilation (permanent ventilation was defined as tracheostomy or ≥16 hours ventilatory support per day for >21 days in the absence of acute reversible event in the determination of an independent endpoint adjudication committee). [b]Log-rank statistical test stratified by disease duration. [c]Estimated from the Kaplan-Meier method. HR = hazard ratio.

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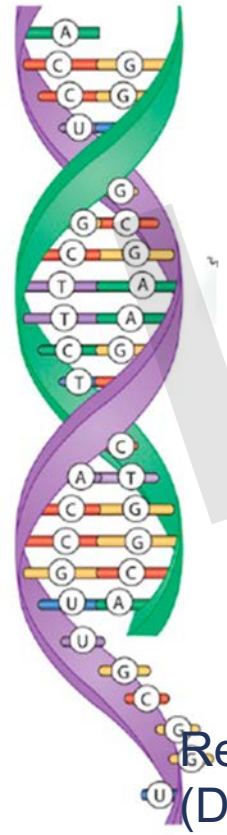
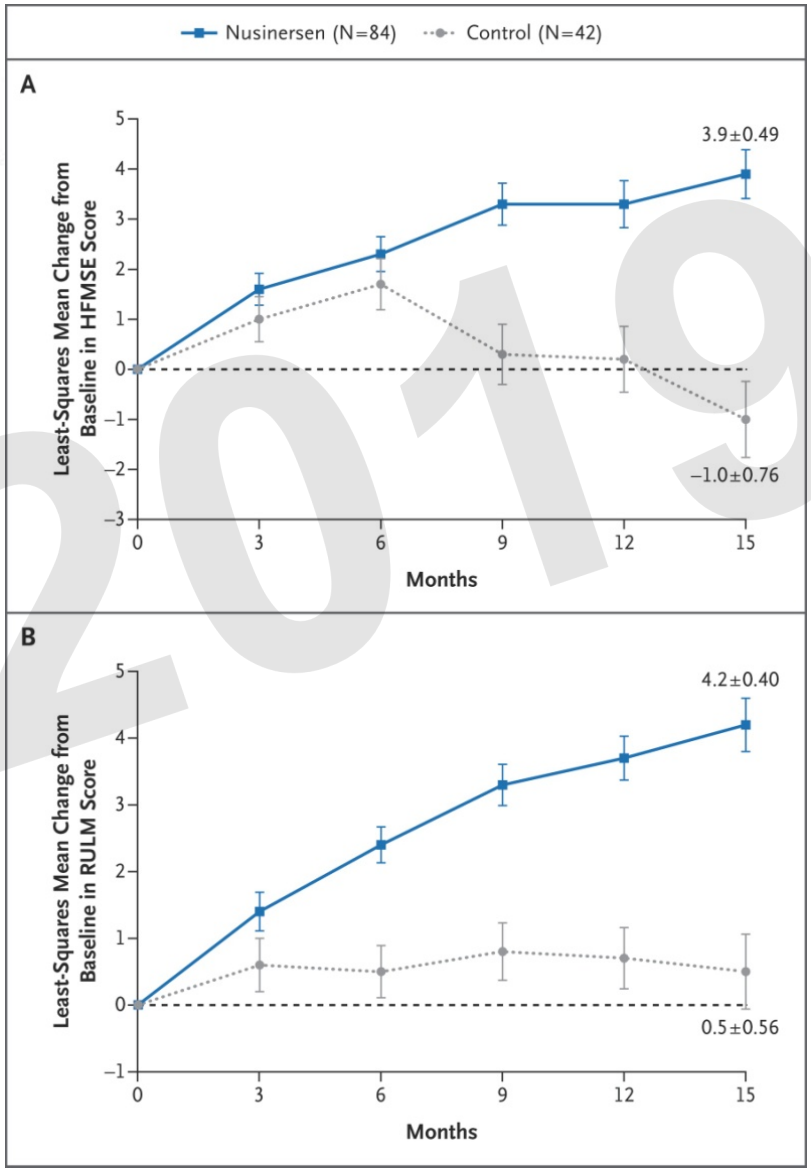
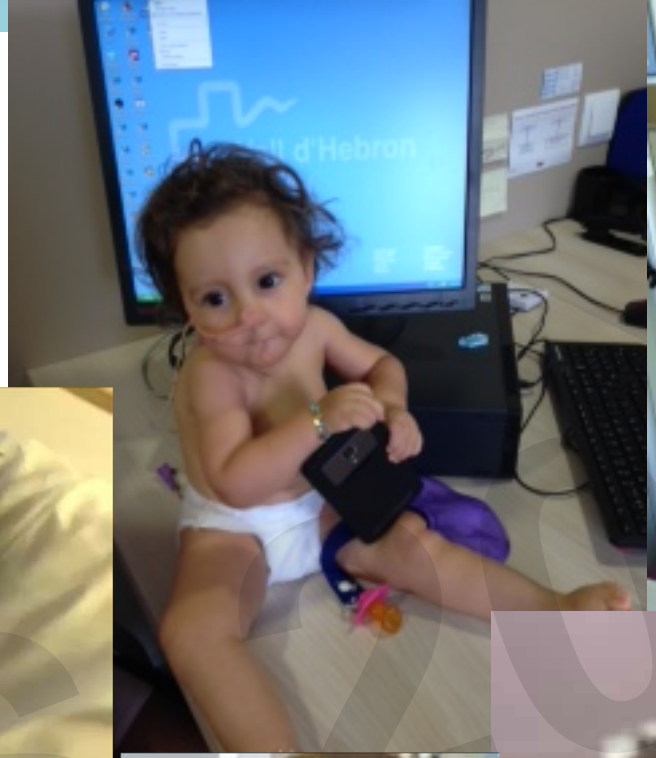


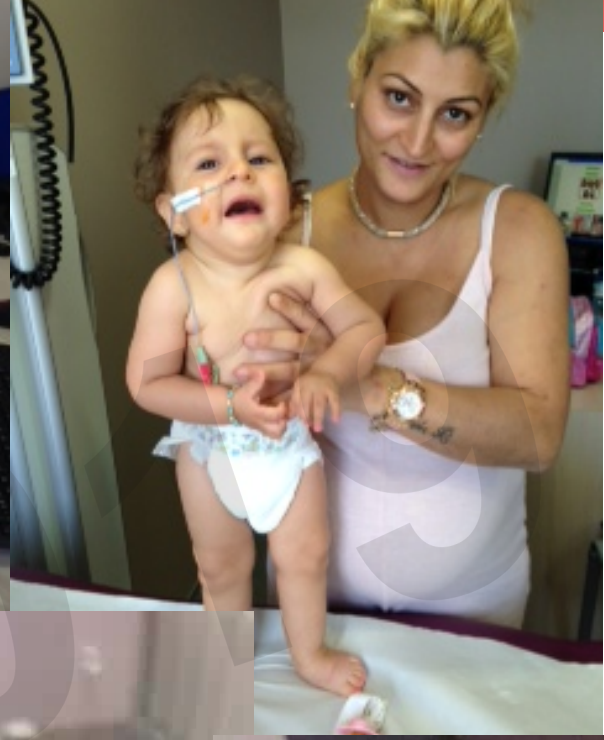
Intrathecal injection in 120 type II and III Non ambulant patients

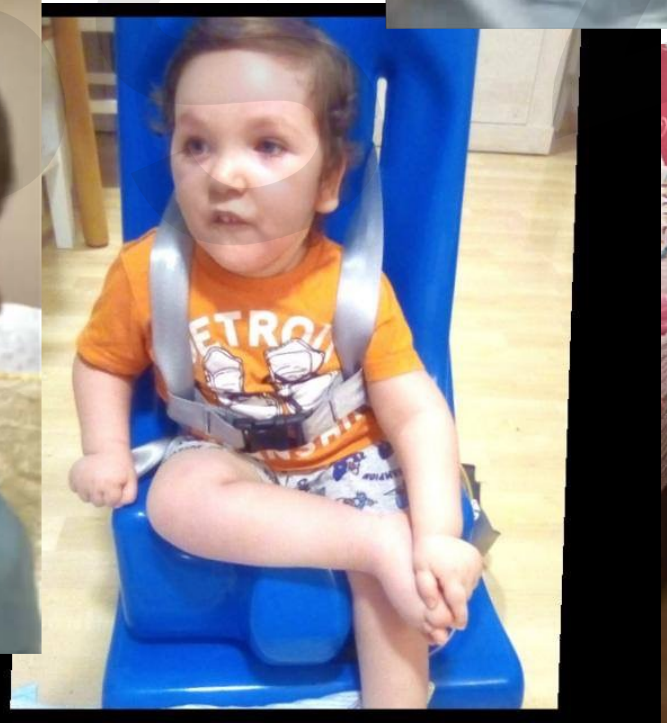


Results of these two clinical trials resulted in approval by FDA (Dec 2016) and EMA (June 2017)

SPINRAZA (nusinersen) 12mg solution for injection








YOU ROLL

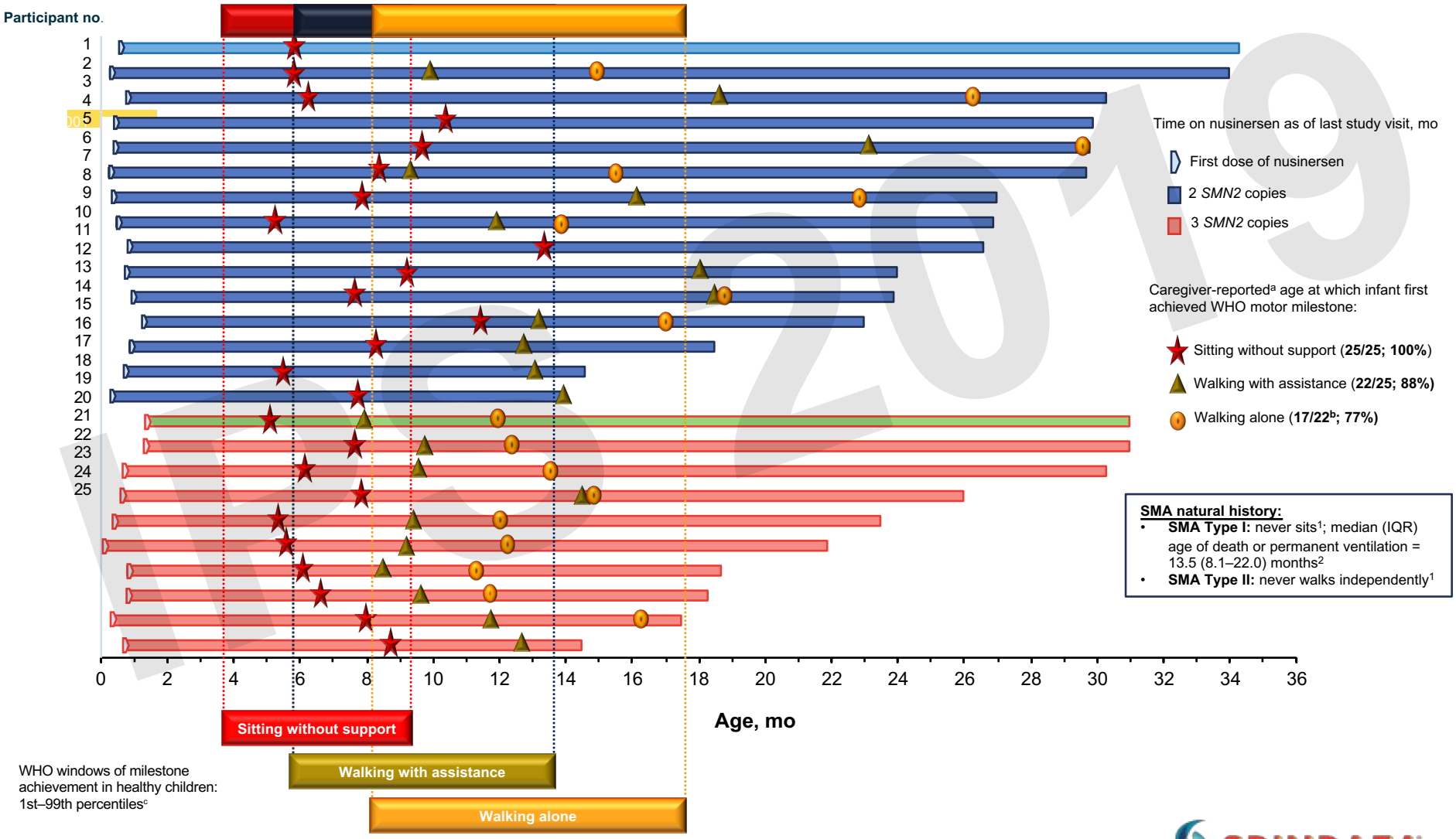
Pre-symptomatic SMA

Considerations regarding the definition of pre-symptomatic SMA in genetically confirmed neonates

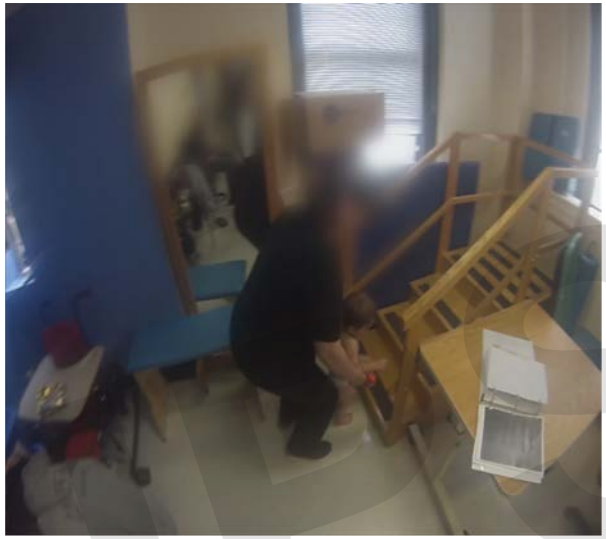
- No weakness or hypotonia
- Presence of tendon reflexes
- No tongue fasciculations
- No diaphragmatic paradoxical breath
- No bell shaped thorax
- No hypoxemia
- No hypercapnia
- No swallowing or feeding problems
- CMAP more than 1.5 mv
- CHOP Intend score more than 40
- Biomarkers under study (miRNAs; SMA-MAP; Neurofilament)

- *Tizzano E and Zafeiriou D, EJPN, 2018*

Participants Are Alive Without Permanent Ventilation and Achieving WHO Motor Milestones – Many in Timeframes Consistent With Normal Development



Day 700 study visit
2 *SMN2* copies



- First infant enrolled in study
- Age in video = 24 months
- Age at first dose = 9 days
- Plasma pNF-H at baseline = 2,060 pg/mL
- CHOP INTEND at baseline, last visit = 57, 64
- 1 sibling with SMA Type II
- Highest motor function achieved by sibling = standing with support at 14 months

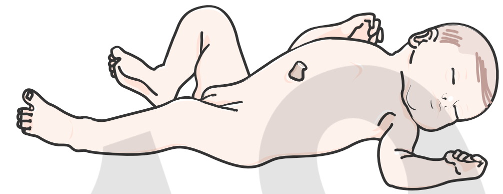
Day 659 study visit
2 *SMN2* copies

- Age in video = 23 months
- Age at first dose = 12 days
- Plasma pNF-H at baseline = 44,800 pg/mL
- CHOP INTEND at baseline, last visit = 44, 58
- 1 sibling with SMA Type I
- Highest motor function achieved by sibling = bring arms to mouth at 24 months

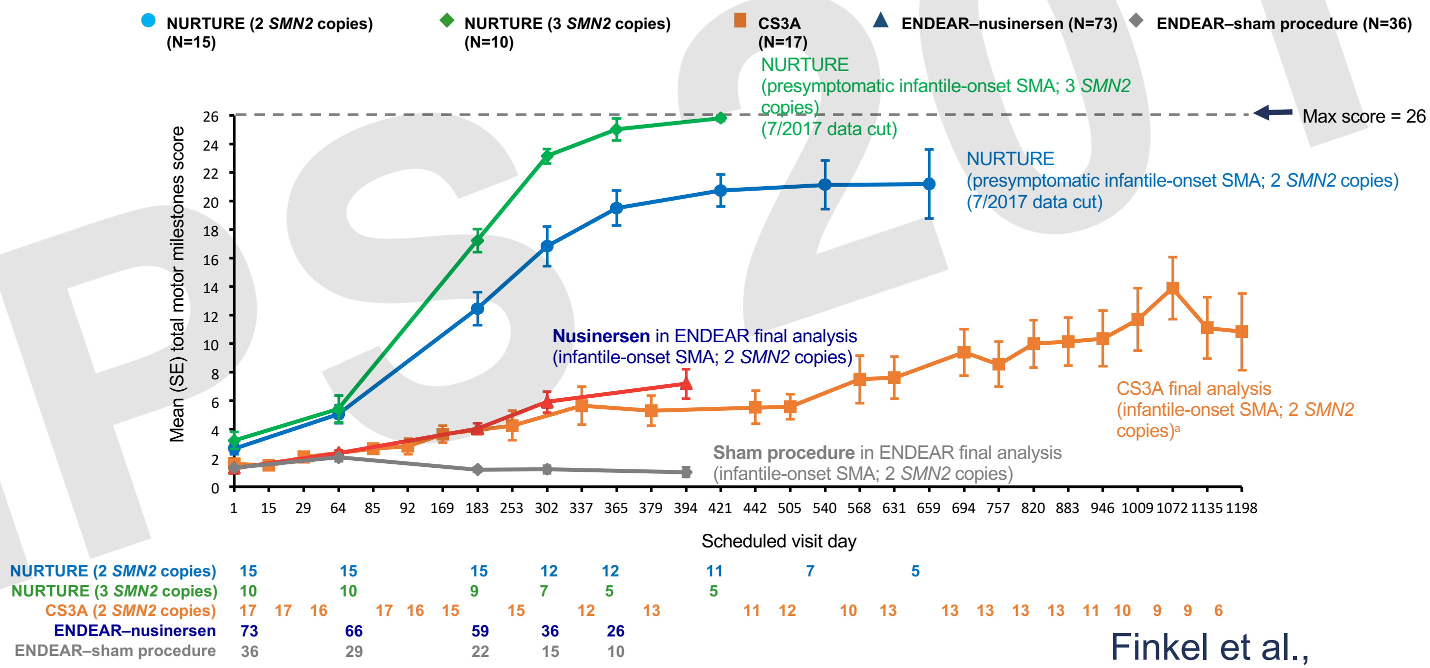
Day 659 study visit
3 *SMN2* copies

- Age in video = 24 months
- Age at first dose = 42 days
- Plasma pNF-H at baseline = 1,770 pg/mL
- CHOP INTEND at baseline, last visit = 56, 61
- 1 sibling with SMA Type II
- Highest motor function achieved by sibling = sitting without support at 7 months

HINE Motor Milestone Scores Over Time Across Studies



- The greatest improvements in total HINE Section 2 motor milestones were observed in infants treated with nusinersen in the presymptomatic stage of SMA in NURTURE



NURTURE study interim analysis data cutoff date: July 5, 2017. [a]CS3a end of study data for the cohort of infants with 2 *SMN2* copies.

Finkel et al.,
Lancet 2016,NEJM,2017
De Vivo et al., Cure SMA 2018

SPINRAZA
(nusinersen) 12mg solution for injection

Rationale for pre-symptomatic screening

There has been considerable debate about the justification for newborn screening in SMA but as we enter a new therapeutic era this is changing…

Early detection and treatment of SMA may enable:

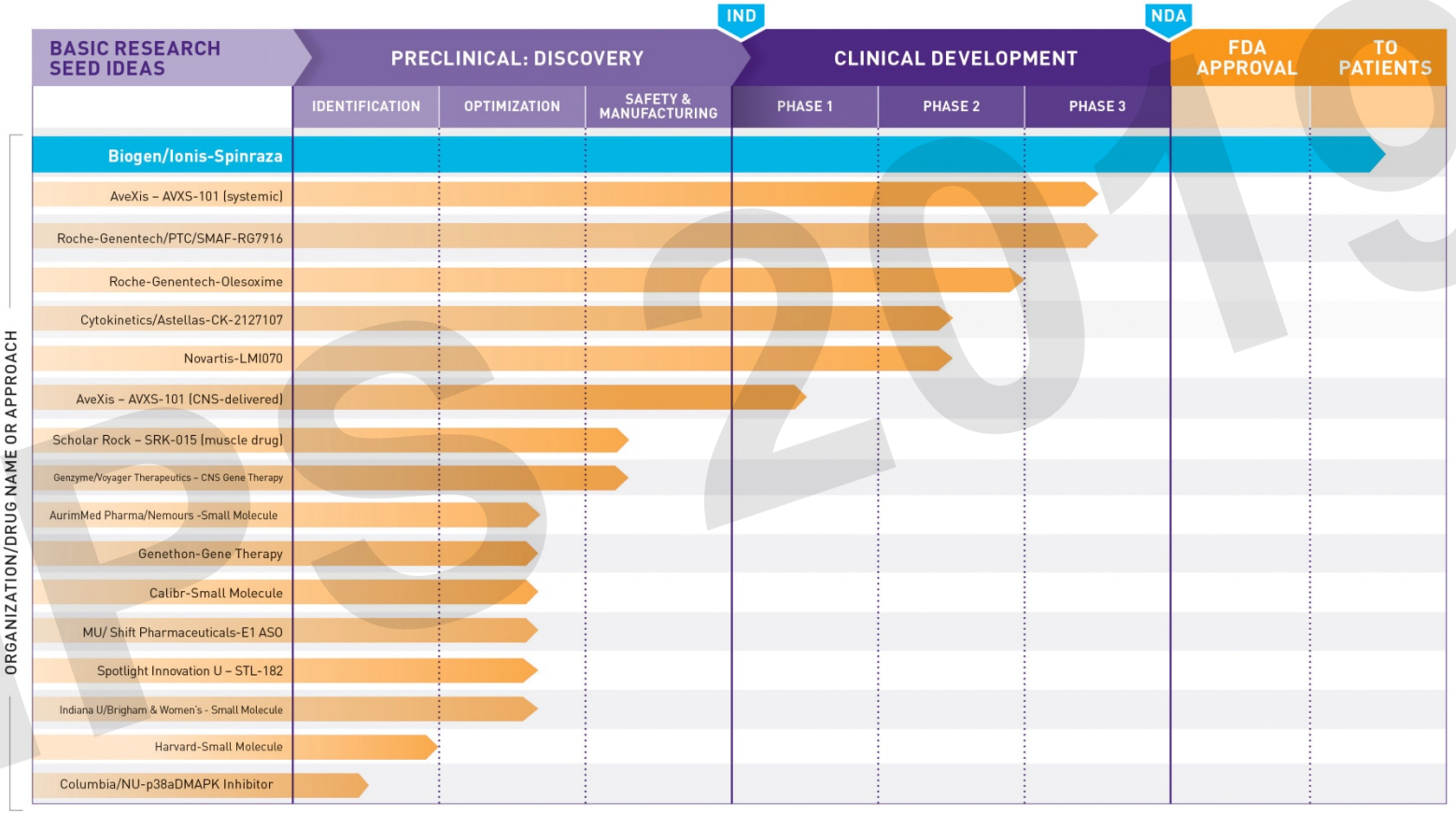
- Better incidence and prevalence estimates
- Improved family planning and genetic counseling[1]
- Early diagnosis and intervention[2]
- Prevention or reduction in the development of disease[2]
- Improved survival and quality of life[2]

SMA, spinal muscular atrophy.

1. Serra-Juhe C and Tizzano EF. Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors. Submitted for publication. 2019. 2. Phan HC, et al. Semin Perinatol. 2015;39(3):217–229.

SMA DRUG PIPELINE

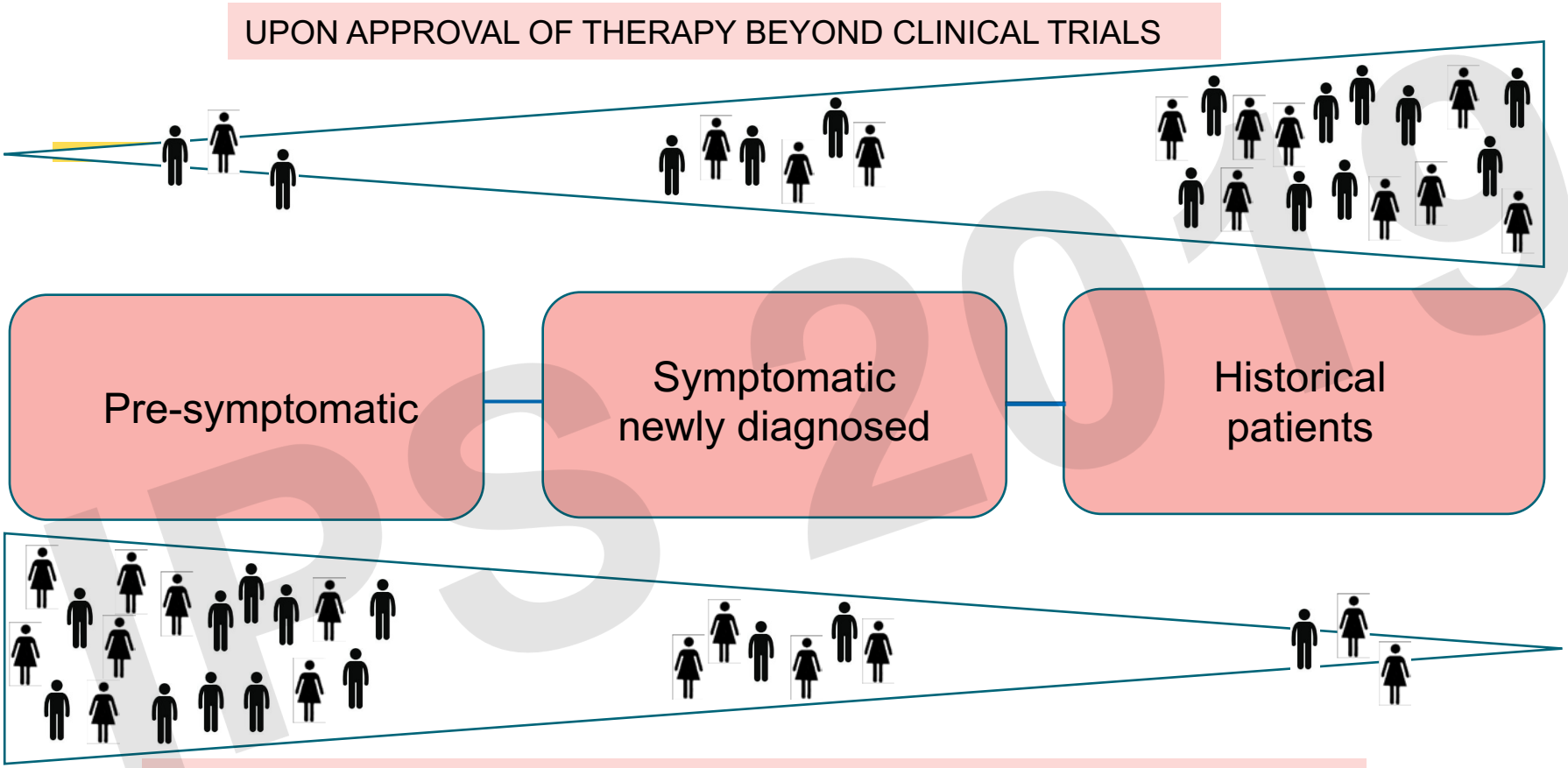
We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue 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: January 2018

Envisaged scenario of SMA treatment



SMA, spinal muscular atrophy.

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SPINRAZA® (nusinersen) 12mg solution for injection

- Spinraza is now registered and available in UAE
- Biologix is helping in the diagnosis of SMA by offering free testing (Please consult Biologix booths)

 References are placed here

Vall d'Hebron Hospital

Vall d'Hebron Barcelona Campus Hospitalari

Vall d'Hebron Institut de Recerca

SMA Clinical Trial Group

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David Gomez/Ana Felipe
Esther Toro / Bernat Planas
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Marta Gómez
Mercedes Gallardo
Carla Aguilar/Gisela Gili/Maria Jose Perez

Department of Clinical and Molecular Genetics
Rare Diseases Unit
Hospital Vall d´Hebron
Medicine Genetics Group VHIR

Back up slides

SOME CONSIDERATIONS ABOUT EMERGING PHENOTYPES

Response of the neuromuscular phenotype may not be initially symmetrical or similar depending on motor neuron compromise and topographic concentration of medication:

- **Intrathecal injection technique (initial lumbar concentrations? Bolus better than slow)**
- **Different distribution in the motor neurons**

Manifestations of the disease with new therapies, new phenotype

- **It is the first time that we treat these patients, be prepared for the unexpected**
- **ASO effects in other CNS cells? Systemic therapy?**

Other organ involvement beyond the neuromuscular phenotype (type I patients)

Delay in appearance of complications (type II patients)

Rescue or reverse of the phenotype in older patients

Definition of a type I sitter (or type II) or a type II walker (or type III)

Spinal muscular atrophy: A changing phenotype beyond the clinical trials

Eduardo F. Tizzano [a,1], Richard S. Finkel [b,c,1,*]

Neuromuscular Disorders 27 (2017) 883–889

To resolve

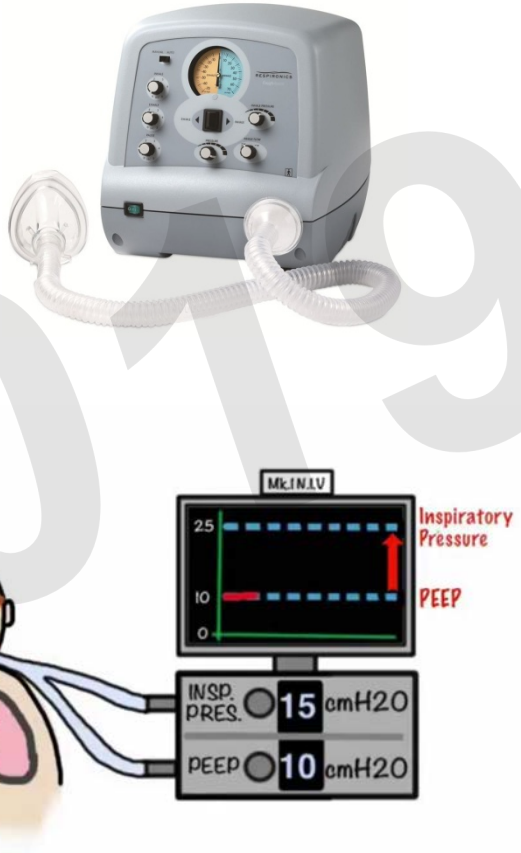
Respiratory problems

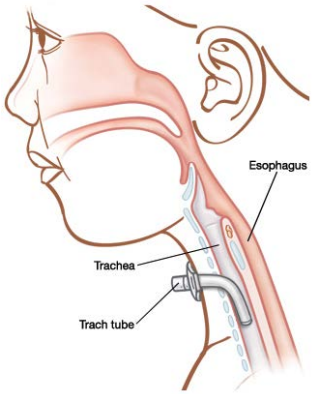
Impaired cough resulting in poor clearance of lower airway secretions

Hypoventilation during sleep

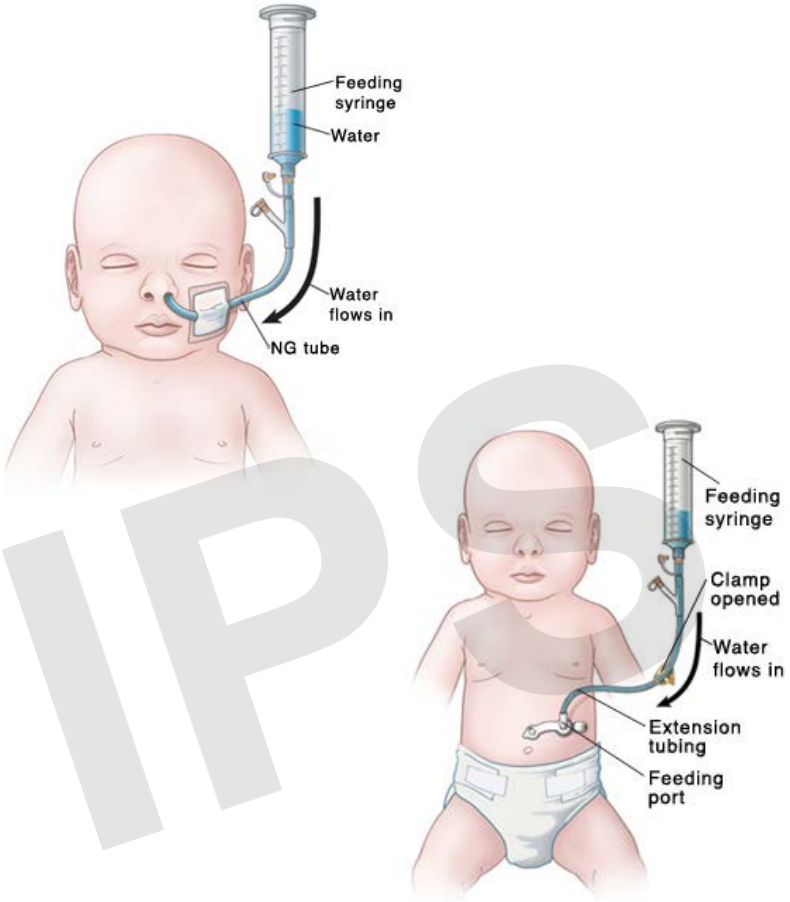
Chest wall and lung underdevelopment

Recurrent infections that exacerbate muscle weakness.





To resolve



Nutritional and GI problems

Feeding and swallowing difficulties

Gastroesophageal reflux

Constipation

Abdominal distension and bloating.

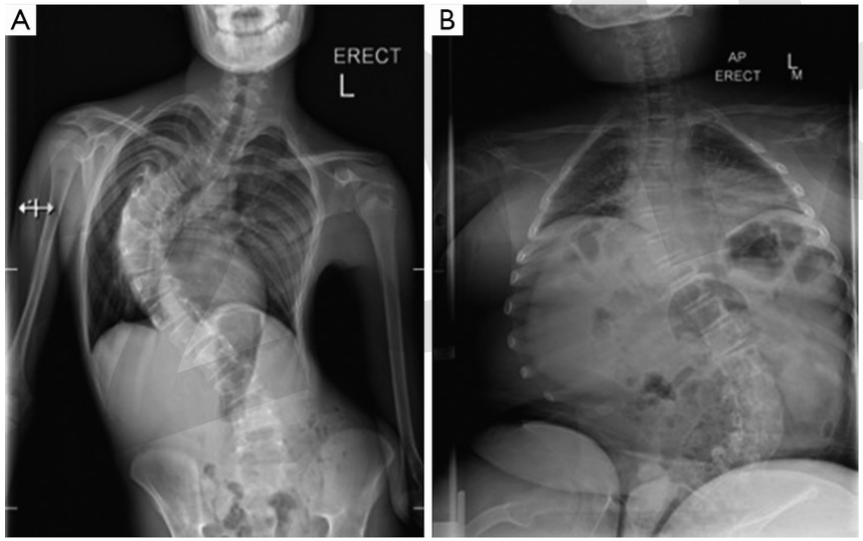
Growth

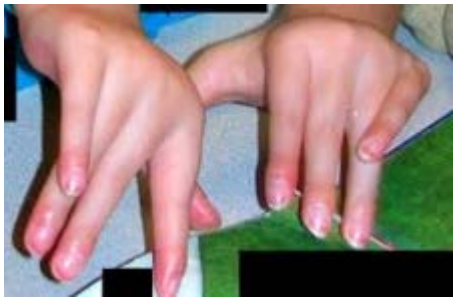
Undernutrition/Overnutrition

To resolve

Orthopedic Care

- Postural deformities
- Contractures
- Scoliosis





MULTIDISICPLINARY TEAM

- Coordinator or leader (pediatric *and* adult)
- Faculty members and specialists
- Case Manager
- Psychologist
- Administrative support
- Trained social worker
- Capacity to integrates medical, paramedical, psychological and social environment patient.

Profiles of the professionals that participate in the experience

Patient

Educationists

Medical specialists

Psychologists

Psychopedagogs

Multidisciplinary follow-up

PATIENT

Clinical Genetics Counselling

Psychology

Cardiology

Nutrition and metabolics

Speech therapist

Traumatology

Swallowing control and Image Rx

Neurosurgery

Neurologist

Palliative care

Pulmonology

Foniatrics

Rehabilitation

ADOLESCENCE
Follow up Transition optimization
Review of protocols

INFANCY

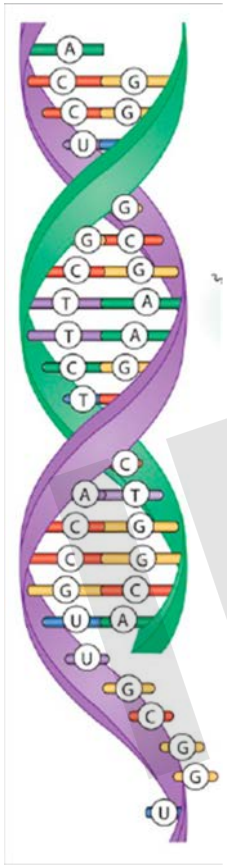
TRANSITION

BIRTH
Initial diagnosis
Pediatric follow up protocol

ADULT LIFE
Follow up protocol by adult team

E TIZZANO Hosp. V. Hebron Barcelona Spain

ADVANCED THERAPIES IN SPINAL MUSCULAR ATROPHY



SMN 2

SMN 2

SMN 1

SMN 1

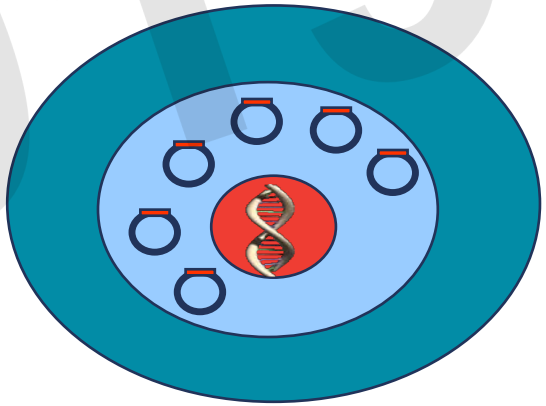
EXON 6 — EXON 7 — EXON 8

EXON 6 — EXON 8

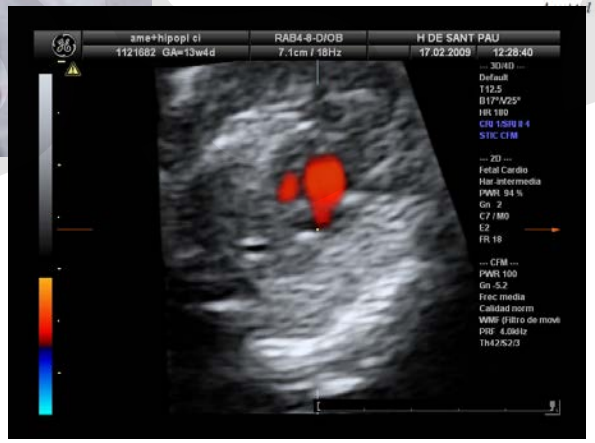
Delta7 SMN protein: unstable and rapidly degraded

Antisense oligonucleotide SPLICING MODIFIER

GENE transfer and replacement



The most severe forms of type I SMA: arthrogryphosis, cardiac malformation and digital necrosis



Original article

Congenital heart disease is a feature of severe infantile spinal muscular atrophy

S Rudnik-Schöneborn,[1] R Heller,[2] C Berg,[1] C Betzler,[2] T Grimm,[3] T Eggermann,[1] K Eggermann,[1] R Wirth,[2] B Wirth,[2,4,5] K Zerres[1]

DIGITAL NECROSES AND VASCULAR THROMBOSIS IN SEVERE SPINAL MUSCULAR ATROPHY

SABINE RUDNIK-SCHÖNEBORN, MD,[1] SILKE VOGELGESANG, MD,[2] SVEN ARMBRUST, MD,[3] LUITGARD GRAUL-NEUMANN, MD,[4] CHRISTOPH FUSCH, MD,[5] and KLAUS ZERRES, MD[1]

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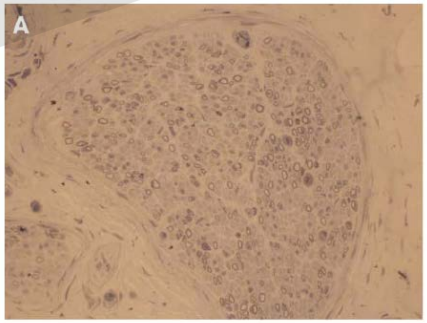
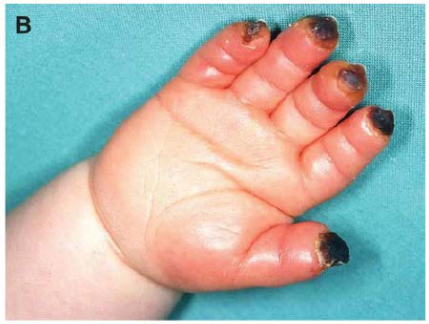
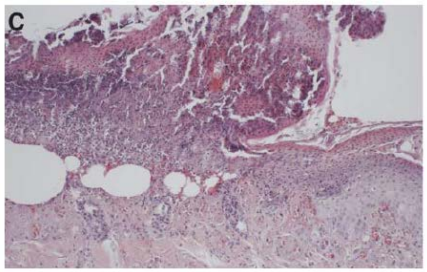
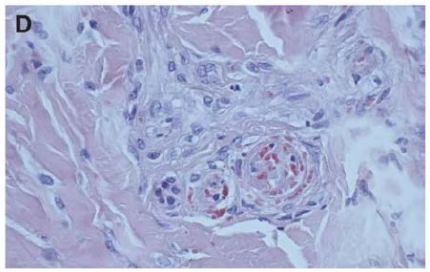
[2] Department of Neuropathology, University of Greifswald, Greifswald, Germany
[3] Department of Pediatric Cardiology, University Hospital Schleswig-Holstein, Kiel, Germany
[4] Institute of Human Genetics, Charité Campus Virchow, Berlin, Germany
[5] Children's Hospital, University of Greifswald, Greifswald, Germany

10 December 2009









Spinal Muscular Atrophy: a changing phenotype beyond the clinical trials

- SMA has evolving phenotypes due to improved standard of care and new treatments.
- The clinician should be alert to identify new patterns of motor development in SMA.
- Cognitive development in patients with SMA type 1 warrants further study.
- Other organ systems may develop signs of dysfunction as these patients live longer.
- Early diagnosis and intervention including presymptomatic newborn screening have to be considered
- Combined therapeutic strategies targeting central nervous system and peripheral tissues are envisaged.

Spinal muscular atrophy: A changing phenotype beyond the clinical trials
Eduardo F. Tizzano [a,1], Richard S. Finkel [b,c,1,*]
Neuromuscular Disorders 27 (2017) 883–889

SMA type	ONSET	MAXIMUM MOTOR MILESTONES	EVOLUTION, NATURAL HISTORY, COMPLICATIONS	Prevalent SMN2 copies
1A (Also referred as type 0)	Prenatal/ Congenital	none	Death in weeks Contractures Cardiopathy Vascular problems	1
1B	<3M	Poor or none cephalic control	Feeding and respiratory problems Linear declination	2
1C	>3M	Cephalic control	Feeding and respiratory problems Plateau in first two years	3

	Nusinersen	AVXS-101	Risdiplam (RG7916)
Type of therapy	Antisense oligonucleotide specific to ISSN1 ASO –ISSN1	Self complementary adeno associated virus with human SMN1 scAAV9.CB.SMN1	Increase binding of U1snRNP
Intracellular place of action	Pre-mRNA in nuclei to include exon 7	Incorporates in nuclei as episomes	Pre-mRNA in nuclei to include exon 7
Mechanism of action	Increase amount of complete SMN protein from SMN2	Production of SMN protein from SMN1	Increase amount of complete SMN protein from SMN2
Administration route	Intrathecally (IT)	Intravenously	Oral
Dose and frequency of administration	Loading dose (12 mg each) and maintenance every 4 months	One dose of 2.0E14 vg/kg	5 mg /day or 0.25mg /kg
Cell Target	Motor neurons and other CNS cells	All non-dividing cells of the organism	All cells of the organism
Pipelines	Phase 3 trials completed	Phase 1-2 trial completed	Phase 1 completed, phase 2-3 ongoing
Type of SMA patients treated	**Type I and II and presymptomatic (n=25)**	**Type I (type II IT ongoing) presymptomatic ongoing**	**Type I-type II- type III presymptomatic ongoing**
Number of patients treated to date	CT 285 EAP 843 Prescription >5,000	15+20 plus other programmes	Approx 170
Approval	FDA (Dec 2016) EMA (June 2017)	Expanded CTs ongoing	CTs ongoing