

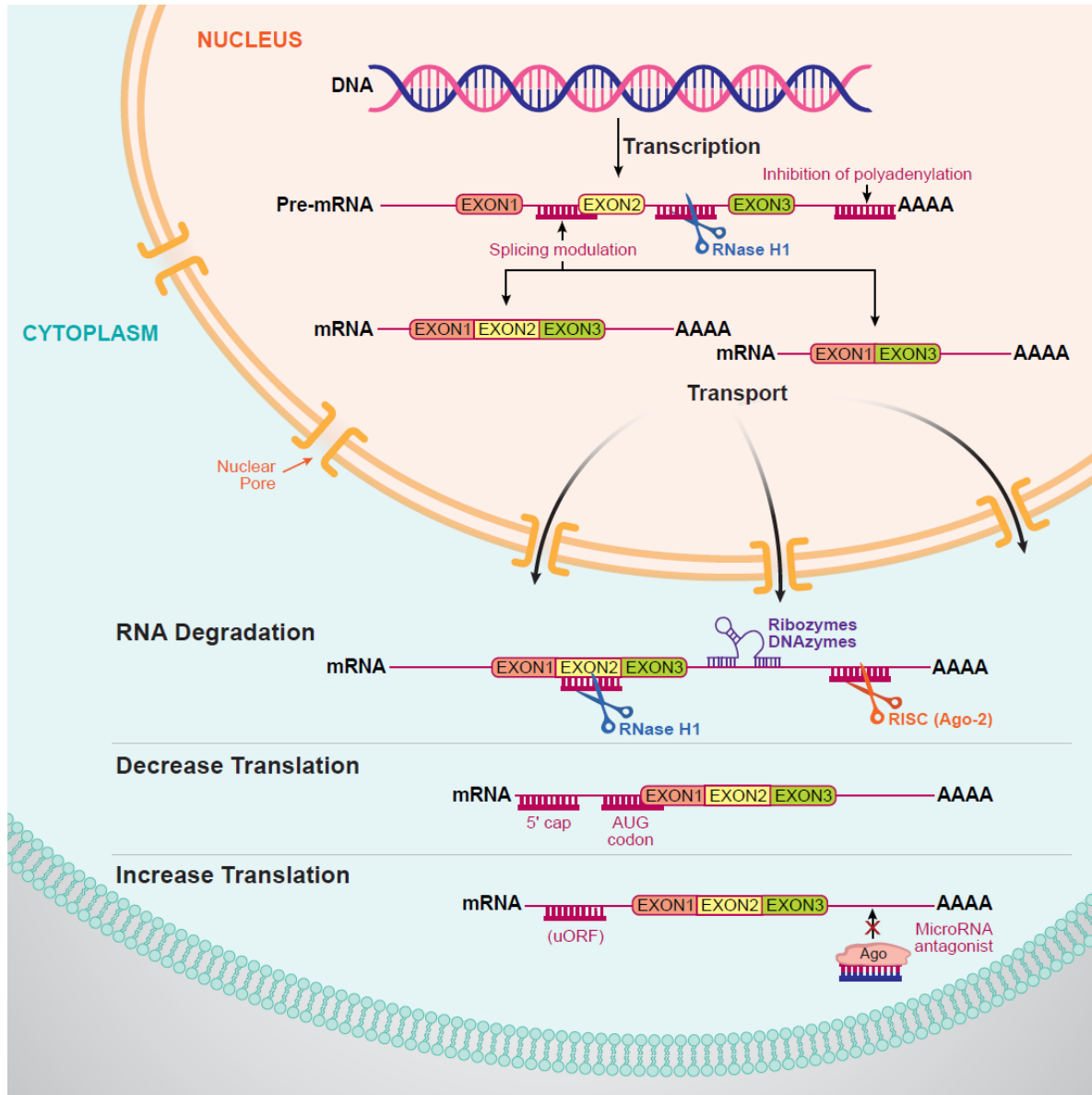


ASO Therapy For SMA

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Different Antisense Mechanisms



6 Antisense Drugs

Have Been Approved by the FDA to Treat Patients (All for Rare Diseases)

Fomiversen
Viral Infection



Mipomersen
High Cholesterol



Nusinersen
Spinal Muscular Atrophy



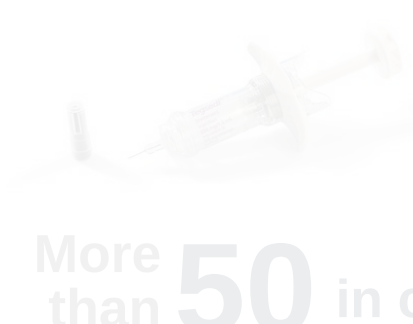
Eteplirsen
Duchenne
Muscular Dystrophy



Patisiran
TTR Polyneuropathy



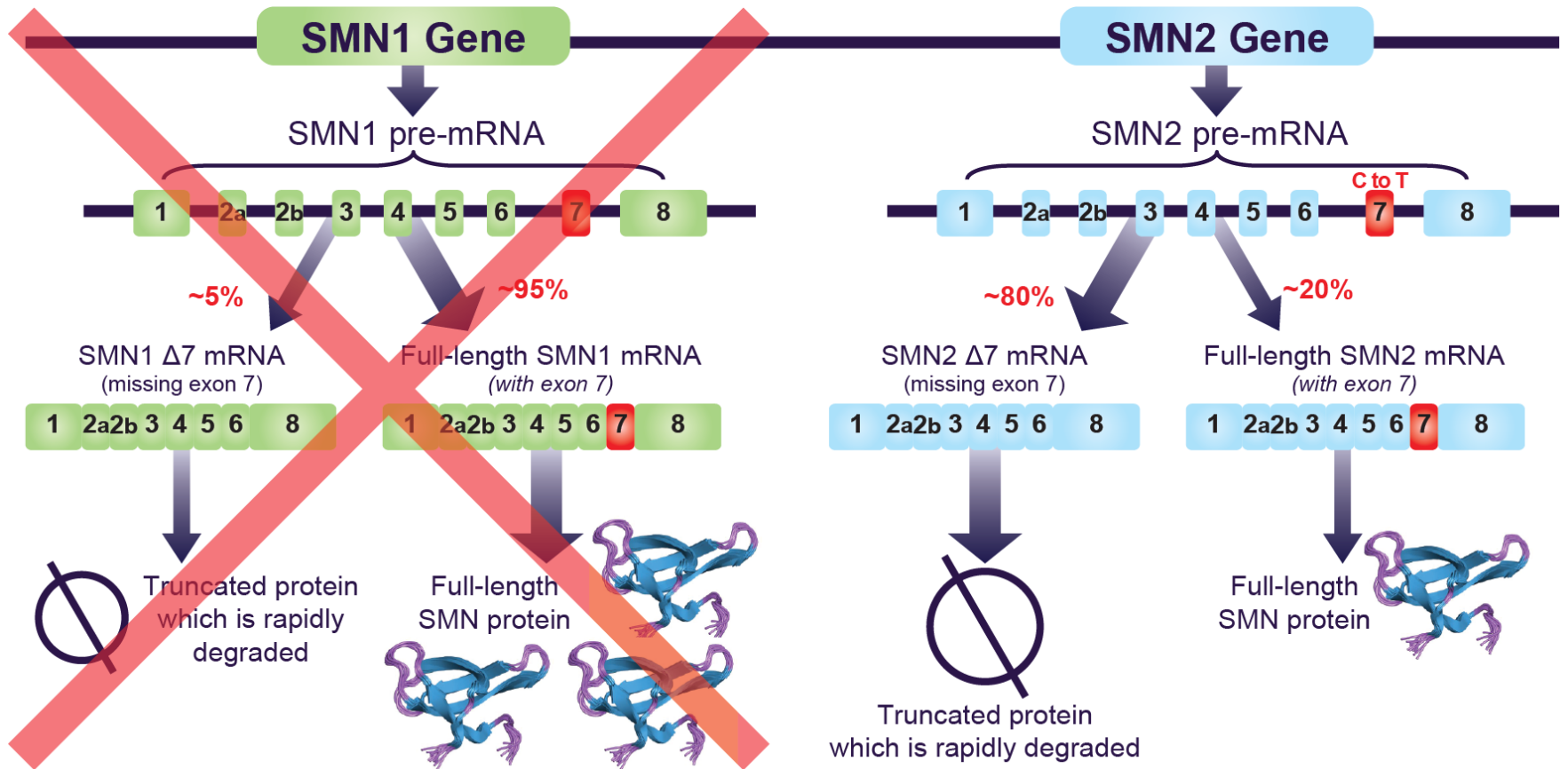
Inotersen
TTR Polyneuropathy



More than **50** in clinical trials

SMA Disease Mechanism

SMA Patient



SMN Protein Deficiency

SMA: Broad Spectrum of Disease Severity Correlates with Copy Number of SMN2 Gene



Type 1 Infantile-onset

- Most severe form of SMA
- Age of symptom onset ≤ 6 months
- Very short life expectancy
- Recent natural history studies show the median event-free survival is 6.1¹-10.5 months²
- Never able to sit
- Most have 2 copies of SMN2 gene



Type 2 Later-onset

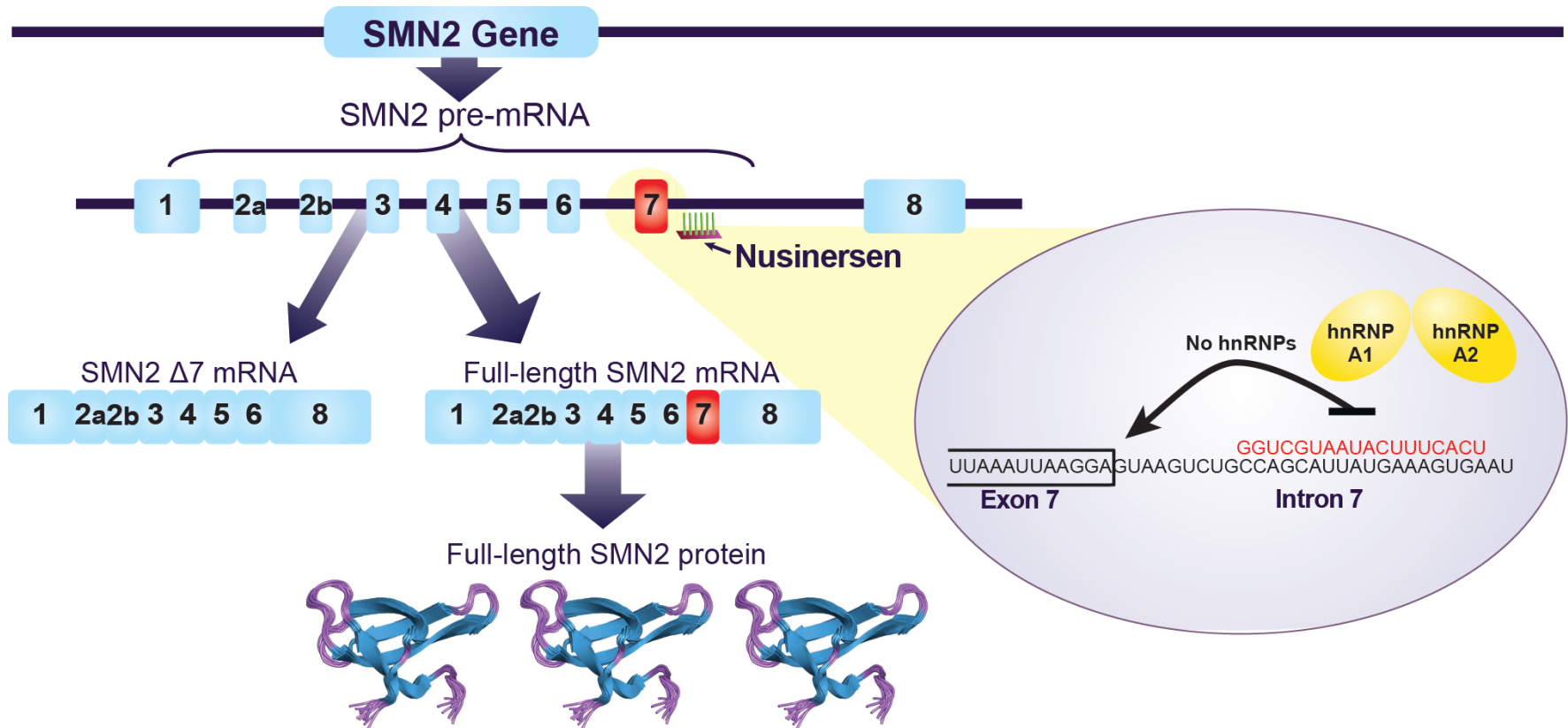
- Age of symptom onset > 6 months
- Shortened life expectancy
- Able to sit or stand, but not walk
- Muscle weakness/skeletal deformities
- Most have 3 copies of SMN2 gene



Type 3 Later-onset

- Age of symptom onset > 6 months
- Close to normal life expectancy
- Ability to walk declines over time to a non-ambulatory state
- Muscle weakness/skeletal deformities
- Most have 3-4 copies of SMN2 gene

Nusinersen- Mechanism of Action



Preclinical Studies with Nusinersen Created a Solid Foundation Supporting Clinical Trials

- **Proof of mechanism** in cell culture and in transgenic mice
- **Proof of biology** in multiple transgenic mouse models of SMA
- **Optimized delivery** methods and route
- **Determined PK/PD relationship** in transgenic mice and non-human primates to support human dose selection
- **Completed comprehensive toxicology studies** to support human clinical trials
- **Published results**

Bogdanik et al., 2015. *Proc Natl Acad Sci U S A* **112**: E5863-72

Hua et al., 2015. *Genes Dev* **29**: 288-97

Hua et al., 2010. *Genes Dev* **24**: 1634-44

Hua et al., 2011. *Nature* **478**: 123-6

Hua et al., 2007. *PLoS Biol* **5**: e73

Hua et al., 2008. *Am J Hum Genet* **82**: 834-48

Jangi et al. 2017. *Proc Natl Acad Sci U S A* **114**: E2347-E56

Passini et al., 2011. *Sci Transl Med* **3**: 72ra18

Rigo et al., 2014. *J Pharmacol Exp Ther* **350**: 46-55

Rigo et al., 2012. *Nat Chem Biol* **8**: 555-61

Sahashi et al. 2012. *Genes Dev* **26**: 1874-84

Sahashi et al., 2013. *EMBO Mol Med* **5**: 1586-601

Sheng et al., 2018. *Hum Mol Genet* **27**: 486-98

Staropoli et al., 2015. *Genomics* **105**: 220-8

Natural History Studies Were Critical for the Design of the Clinical Program

Prospective cohort study of spinal muscular atrophy types 2 and 3

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Jonathan Marra, MA
Benjamin Koo, BS
Darryl C. De Vivo, MD
On behalf of the Muscle Study Group (MSG), The Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy (PNCRA)

ABSTRACT

Objective: To characterize the natural history of spinal muscular atrophy type 2 and type 3 (SMA 2/3) beyond 1 year and to report data on clinical and biological outcomes for use in trial planning.

Methods: We conducted a prospective observational cohort study of 79 children and young adults with SMA 2/3 who participated in evaluations for up to 48 months. Clinically, we evaluated motor and pulmonary function, quality of life, and muscle strength. We also measured SMN2 copy number, hematologic and biochemical profiles, muscle mass by dual x-ray absorptiometry (DXA), and the compound motor action potential (CMAP) in a hand muscle. Data were analyzed for associations between clinical and biological/laboratory characteristics cross-sectionally, and for change over time in outcomes using all available data.

Results: In cross-sectional analyses, certain biological measures (specifically, CMAP, DXA fat-free mass index, and SMN2 copy number) and muscle strength measures were associated with motor function. Motor and pulmonary function declined over time, particularly at time points beyond 12 months of follow-up.

Conclusion: The intermediate and mild phenotypes of SMA show slow functional declines when observation periods exceed 1 year. Whole body muscle mass, hand muscle compound motor action potentials, and muscle strength are associated with clinical measures of motor function. The data from this study will be useful for clinical trial planning and suggest that CMAP and DXA warrant further evaluation as potential biomarkers. *Neurology*® 2012;79:1889-1897

GLOSSARY

AUC = area under the curve; CMAP = compound motor action potential; DXA = dual x-ray absorptiometry; FFMI = fat-free mass index; GMFM = Gross Motor Function Measure; HFMS = Hamman-Richardson Functional Motor Scale; HFMS-E = Expanded Hamman-Richardson Functional Motor Scale; NHANES = National Health and Nutrition Examination Survey; FVC = forced vital capacity; SMA = spinal muscular atrophy.

Spinal muscular atrophy (SMA), the second most common recessive lethal pediatric disease,¹ causes proximal muscle weakness, atrophy, and respiratory and orthopedic complications. The severity of the clinical phenotype is heterogeneous with the most severe form (SMA type 1) beginning in infancy. The intermediate (SMA type 2) and mild (SMA type 3) forms cause less severe motor disability.²

Almost all patients have a homozygous deletion of the survival of motor neuron gene (*SMN1*).³ The phenotype is modified by the *SMN2* copy number. *SMN2* partially compensates for the lack of *SMN1* explaining the inverse relationship between disease severity and *SMN2* copy number.⁴

Observational study of spinal muscular atrophy type I and implications for clinical trials

ABSTRACT

Objectives: Prospective cohort study to characterize the clinical features and course of spinal muscular atrophy type I (SMA-I).

Methods: Patients were enrolled at 3 study sites and followed for up to 36 months with serial clinical, motor function, laboratory, and electrophysiologic outcome assessments. Intervention was determined by published standard of care guidelines. Palliative care options were offered.

Results: Thirty-four of 54 eligible subjects with SMA-I (63%) enrolled and 50% of these completed at least 12 months of follow-up. The median age at reaching the combined endpoint of death or requiring at least 16 hours/day of ventilation support was 13.5 months (interquartile range 8.1-22.0 months). Requirement for nutritional support preceded that for ventilation support. The distribution of age at reaching the combined endpoint was similar for subjects with SMA-I who had symptom onset before 3 months and after 3 months of age ($p = 0.58$). Having 2 *SMN2* copies was associated with greater morbidity and mortality than having 3 copies. Baseline electrophysiologic measures indicated substantial motor neuron loss. By comparison, subjects with SMA-II who lost sitting ability ($n = 10$) had higher motor function, motor unit number estimate and compound motor action potential, longer survival, and later age when feeding or ventilation support was required. The mean rate of decline in The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders motor function scale was 1.27 points/year (95% confidence interval 0.21-2.33, $p = 0.02$).

Conclusions: Infants with SMA-I can be effectively enrolled and retained in a 12-month natural history study until a majority reach the combined endpoint. These outcome data can be used for clinical trial design. *Neurology*® 2014;83:1-8

GLOSSARY

CHOP INTEND = The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; CI = confidence interval; CMAP = compound motor action potential; IQR = interquartile range; MUNE = motor unit number estimate; SMA = spinal muscular atrophy; SMN1 = survival of motor neuron 1, telomeric.

Proximal spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disorder with an incidence of 1:11,000 live births.¹ Mutations in the survival of motor neuron 1, telomeric (*SMN1*) gene cause SMA.² A nearly identical gene, *SMN2*, harbors an exonic splicing enhancer

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Nusinersen Clinical Program Overview

Phase 1

CS1: Open label single IT dosing in childhood onset SMA

Phase 2

CS2: Open label multiple IT dosing in childhood onset SMA

CS3a: Open label multiple IT dosing in infantile onset SMA



nurture

Open label multiple IT dosing in pre-symptomatic Infants



embrace

Sham controlled multiple IT dose in infantile or childhood onset SMA

Phase 3



cherish

Sham controlled multiple IT dose in later onset SMA (most likely to have Type 2 SMA)



endear

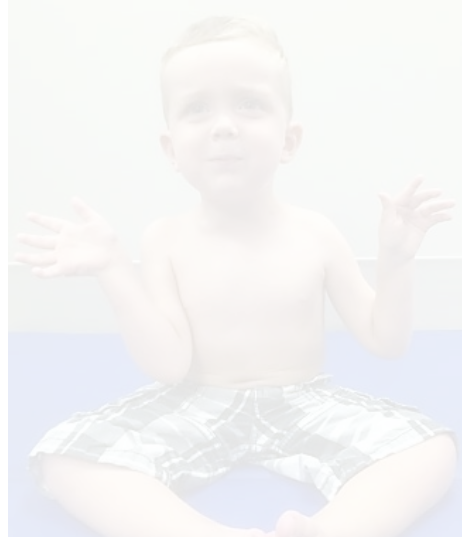
Sham controlled multiple IT dose in Infantile onset SMA

SMA: Broad Spectrum of Disease Severity Correlates with Copy Number of SMN2 Gene



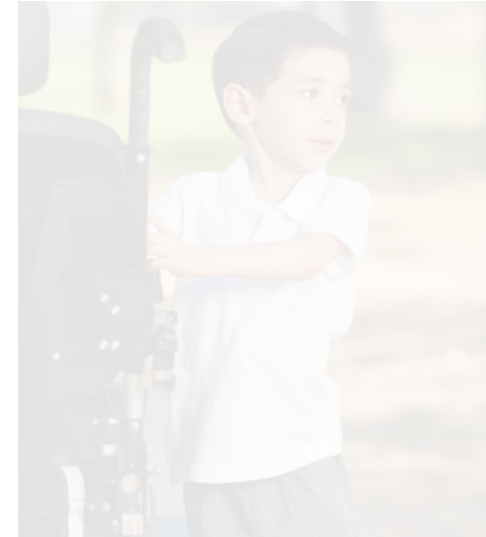
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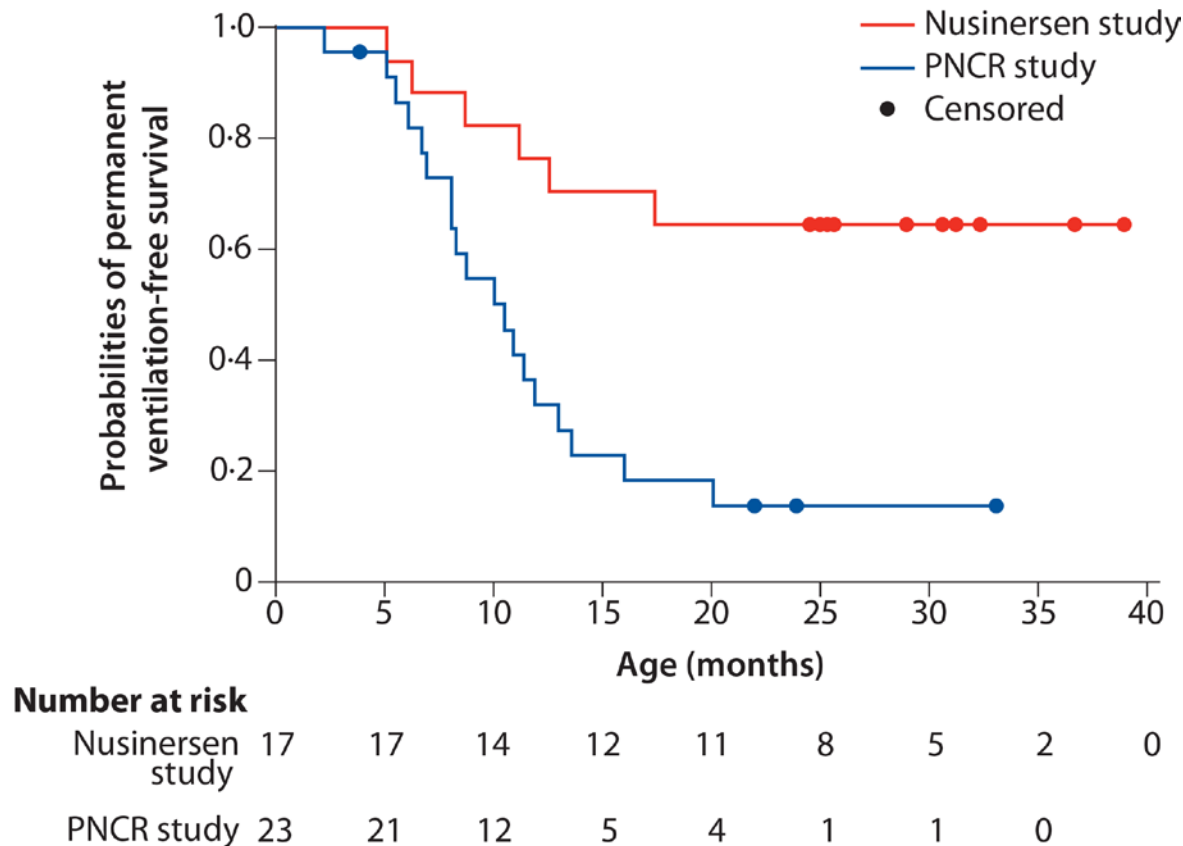
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- Age of symptom onset > 6 months
- Close to normal life expectancy
- Ability to walk declines over time to a non-ambulatory state
- Muscle weakness/skeletal deformities
- Most have 3-4 copies of SMN2 gene

Increased Event-Free Survival in Nusinersen-Treated Infants with SMA Compared to Natural History (PNCR)

As of January 26, 2016

Increased Permanent Ventilation-free Survival



All infants continuing in study are older than 2 years of age

Median event-free age has not been reached in the Phase 2 nusinersen study

Complicating Issues with PNCR Network Natural History Study in Type 1 SMA Patients

**Time
Period**

RESULTS All ages are listed in months. Descriptive results for several variables are expressed as median and interquartile range (IQR). Seventy-nine subjects (34 SMA-I and 45 SMA-II) were enrolled between May 2005 and April 2009. The baseline subject characteristics are summarized in table 1, and longitudinal data are summarized in table 2.

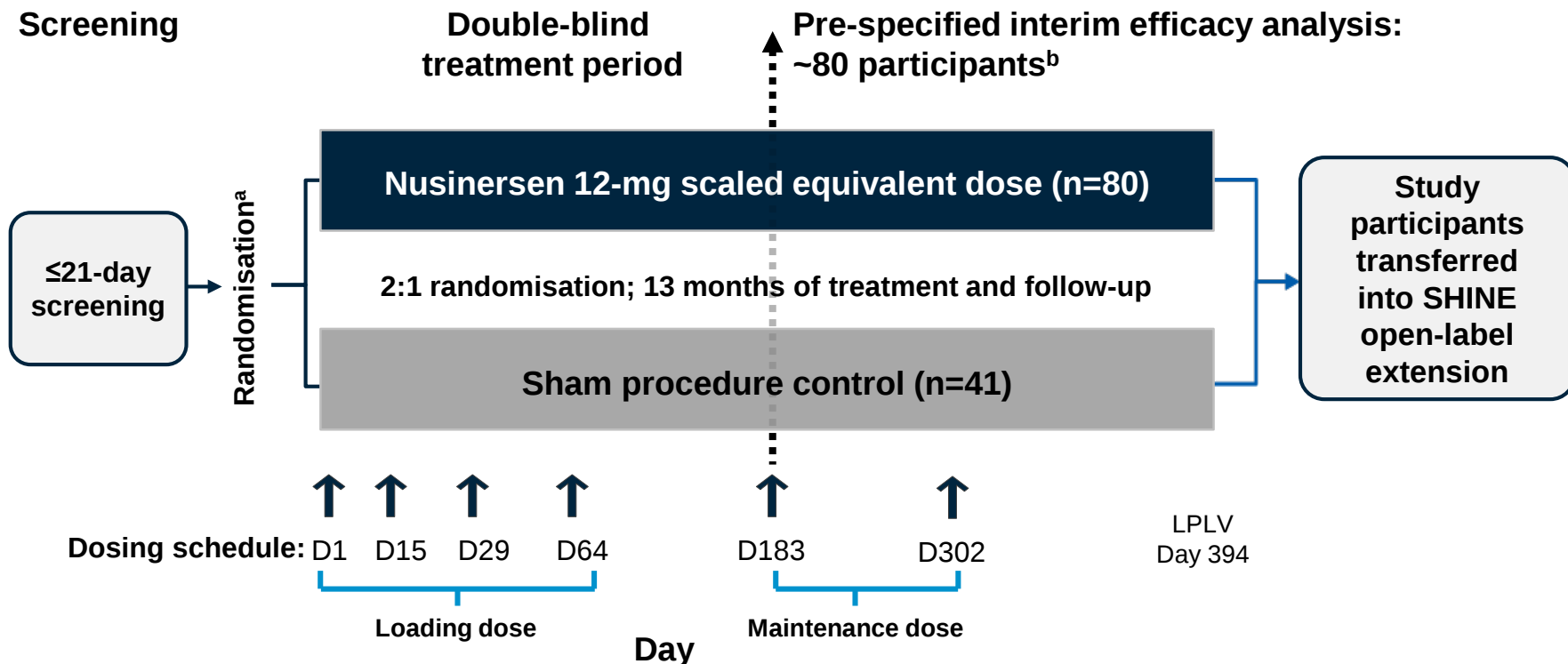
Table 1 Baseline demographic and clinical characteristics of study participants

	Type IB		Type IC		Type II	
	Recent	Chronic	Recent	Chronic	Type IIA	Type IIB
No.	8	10	6	10	10	35
Sex, M/F, n	2/6	4/6	5/1	8/2	2/8	16/19
Age at symptom onset, mo, median (IQR)	1.5 (1-2.5)	3.0 (2-3)	4.0 (4-5)	4.0 (4-6)	11.0 (7-12)	8.5 (6-12)
Age at clinical diagnosis, mo, median (IQR)	3.5 (1.8-6)	6.0 (4-7)	5.5 (5-7)	6.0 (6-8)	11.5 (9-14)	13.0 (10-18)
Age at enrollment, mo, median (IQR)	5.0 (2.5-6.5)	59 (17-184)	6.5 (6-8)	30.5 (22-78)	200 (137-298)	64 (38-90)



The majority of type 1 patients enrolled in the study were older than the median age of survival at time of enrollment

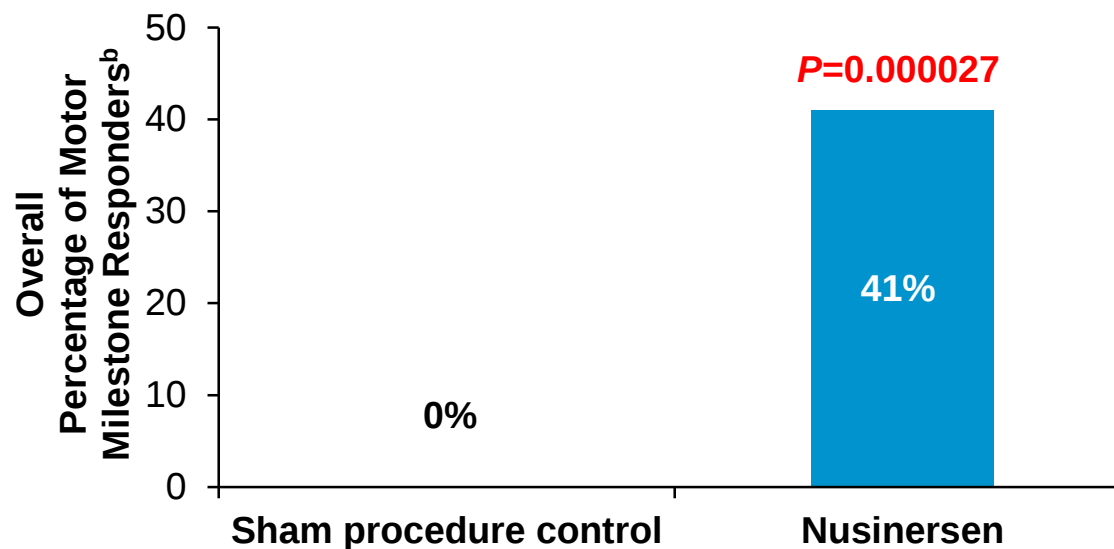
ENDEAR Study Design



- **ITT and safety population:** randomised and received ≥ 1 dose of study drug
- **Interim efficacy population:** ITT participants who received nusinersen dose/sham procedure control ≥ 6 months before cutoff date for interim efficacy analysis and/or were assessed at any of the Day 183, 302 or 394 visits

Motor Milestone Responders: IES Population

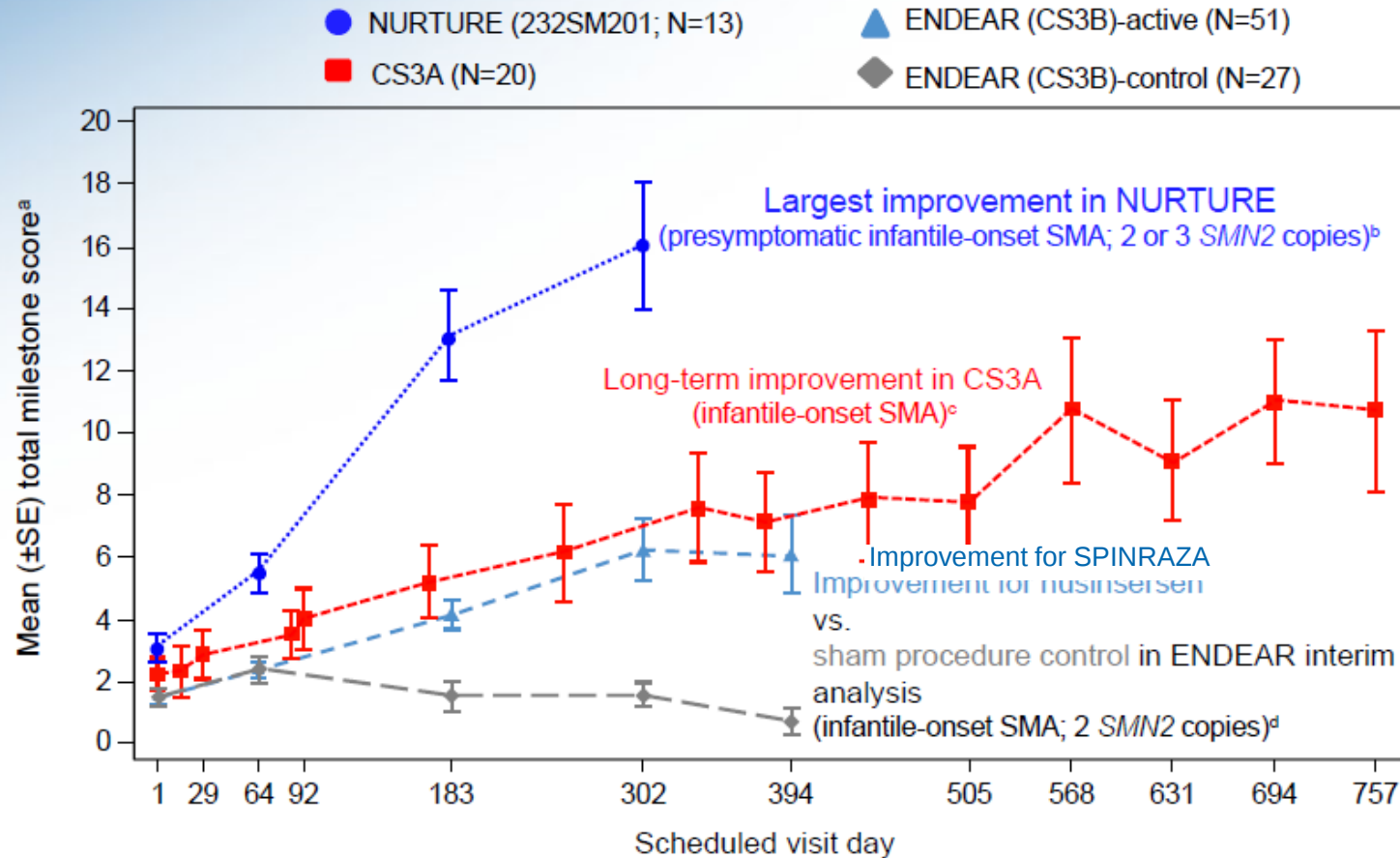
Highly clinically and statistically significant percentage of motor milestone responders^a



Motor milestone responders, %	Sham procedure control	Nusinersen	P-value
6 month visit (n=78)	7	39	0.0032
10 month visit (n=55)	0	47	0.0002
13 month visit (n=34)	0	43	0.0135

^a The interim efficacy analysis was conducted on 15 June 2016, once ~80 participants had the opportunity to be assessed at Day 183 visit. bn=78. IES = Interim efficacy set.

Consistent Changes in HINE Motor Milestone Scores Across Multiple Studies



232SM201	13	13			10		5													
CS3A	20	20	19		19	18		17		17		14	15		13	14	11	11	10	7
CS3B-active	51		45					40					25		16					
CS3B-control	27		20					18					12		7					

Populations: NURTURE (232SM201) = interim efficacy set, CS3A = all dosed infants; ENDEAR (CS3B) = interim efficacy set. For each study, visits with n<5 are not plotted.

a Maximum total milestone score = 26. b Median (range) age at first dose: 19.0 (8–42) days. c Median (range) age at enrolment: = 155 (36–210) days. d Median (range) age at first dose: 175.0 (30–262) days.

Lessons Learned from Nusinersen Clinical Studies

SMA is a treatable disease

Most symptomatic patients continue to improve with continued treatment

Early treatment results in best outcomes

- Most infants treated before symptom onset obtain motor milestones at age appropriate windows

Published natural history studies were important for the design of the studies and interpretation of clinical results

- A contemporaneous prospective natural history study may have accelerated approval and negated the need for a controlled clinical trial

Going forward well designed NHS and access to source data will continue to be important for development of drugs for rare diseases

THANK YOU

to My Colleagues and Partners in this Endeavor



Cold Spring Harbor Laboratory

Dr. Adrian Krainer
Dr. Yimin Hua



Dr. Daryll DeVivo
Dr. Claudia Chiriboga
Dr. Jackie Montes



Dr. Basil Darras



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Katie Alexander
Kathie Bishop



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