The National Academy of Sciences • Engineering • Medicine
Exploring Novel Clinical Trial Designs for Gene-Based Therapies – A Workshop
Washington, DC *13 November 2019*

Session I: Developing First in Human Gene Therapy Clinical Trials

Natural History Studies for Neurodegenerative Disorders

Richard S. Finkel, MD
Nemours Children's Hospital
University of Central Florida Orlando

Disclosures

- **Grant support:** NIH, MDA, SMA Foundation, Ionis Pharmaceuticals, Biogen, Roche, AveXis, Lilly, Sarepta, BMS, Summit, Catabasis, ReveraGen, Cytokinetics, Capricor

- **Advisor:** NIH, SMA Foundation, Cure SMA, SMA REACH UK, SMA Europe, TREAT-NMD, Ionis, Biogen, Roche, AveXis, Novartis, Biomarin, Catabasis, Mitobridge, Capricor, Neurogene

- **DSMB Member:** Nationwide CH scAAV9 P1, Roche Moonfish P1-2 studies

Topics

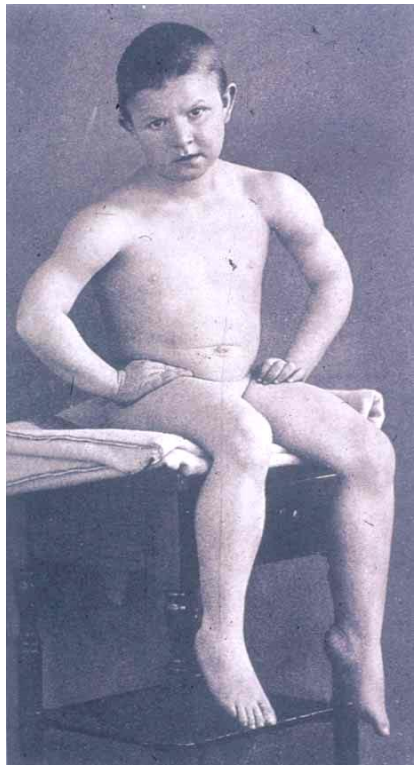
- The pediatric population
- Understanding the true and (un)natural history
- Impact of standard-of-care
- Clinical trial readiness

The Pediatric Population

- Fetus, newborn, infant, child, adolescent – not the same
- Differences in
  - Blood and CSF volume (drug delivery, target engagement)
  - Drug metabolism and excretion (drug exposure, safety)
  - Weight (drug dosing)
  - Pediatric presentation may differ from adults (different outcome measures, study design)
  - Off-target effects may differ in the growing child
- Does the disease in question occur only in the pediatric population?
  - Test first in adults when feasible
  - Children before infants

Understanding the Natural History:
Genotype-Phenotype in Duchenne Muscular Dystrophy

Intragenic differences in DMD and age at loss of ambulation



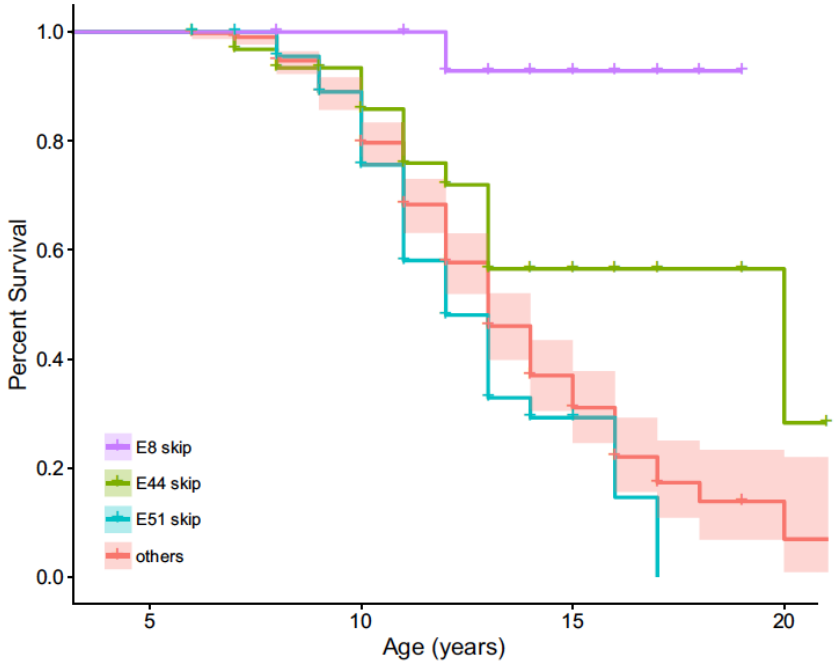
Gowers

Duchenne muscular dystrophy

Incidence: 1: 3,500 boys

Onset: 2-4 years

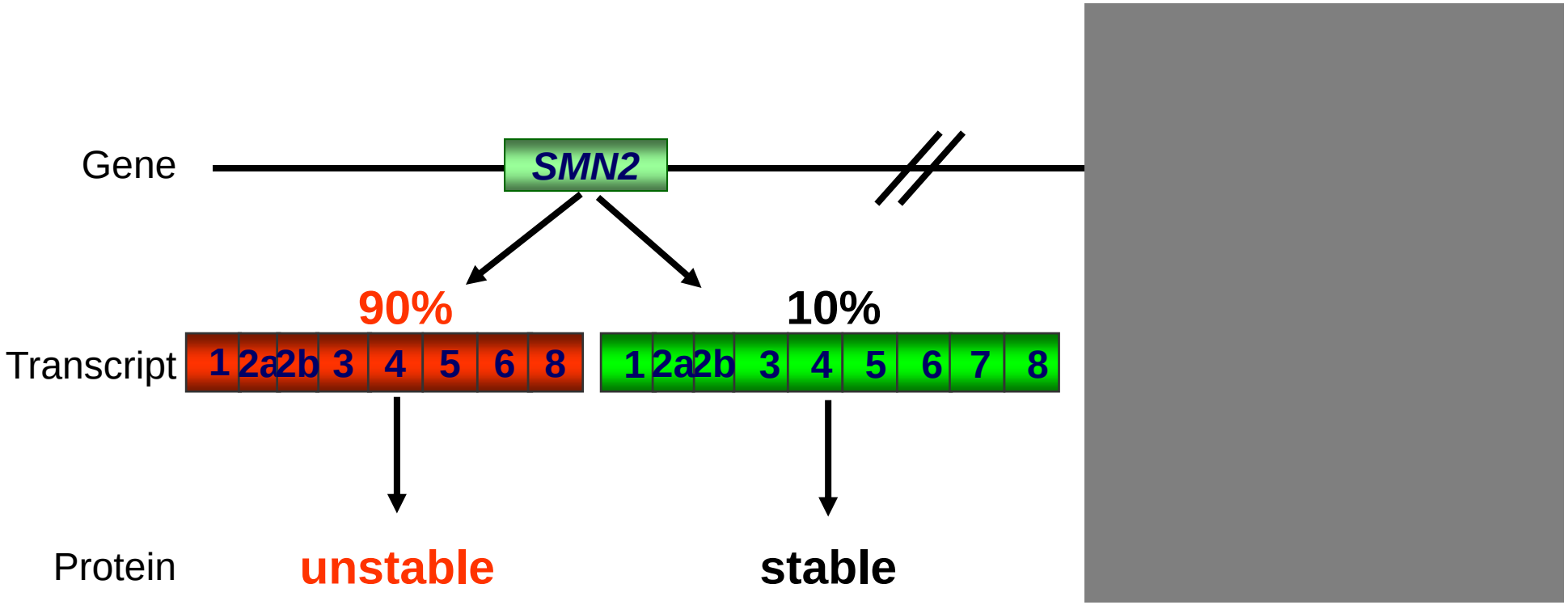
Loss of ambulation:10 years (7-12)



Wang RT et al, Hum Mut, 2018

Spinal Muscular Atrophy

SMN Genes and Protein



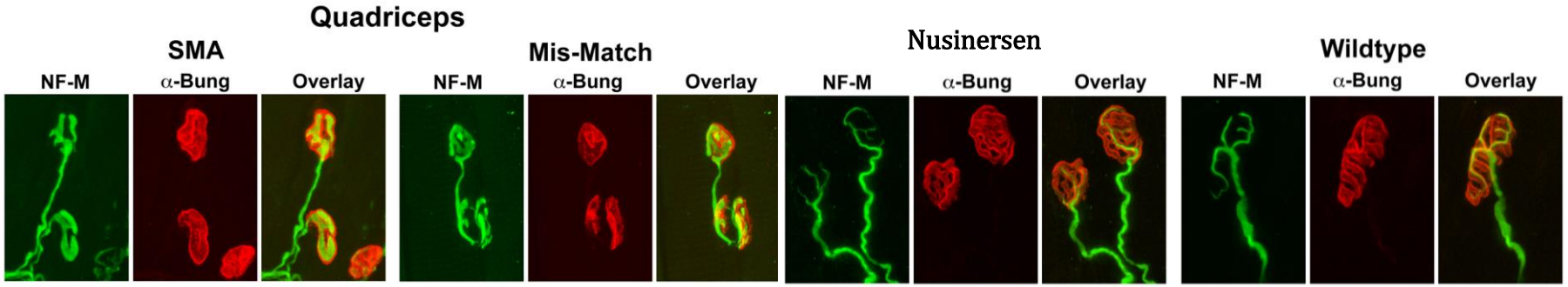
Melke et al, Cell, 1995

Clinical Trial Readiness - 1
Generation of Informative Animal Models

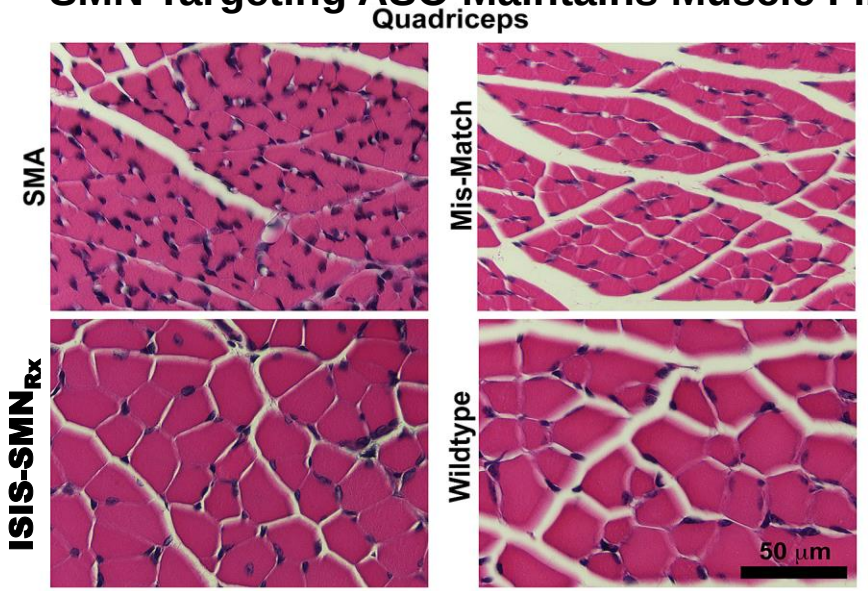
- Mouse – KO with human *SMN2* transgene (A Burghes)
  - **“Delta-7” – Smn$^{-/-}$; human *SMN2*$^{+/+}$; Δ7$^{+/+}$ = severe type 1**
- Zebrafish - knockdown with RNAi (U Fischer)
- Fly – spontaneous missense mutations (M van den Heuvel)
- Pig – knockdown model (A Burghes)

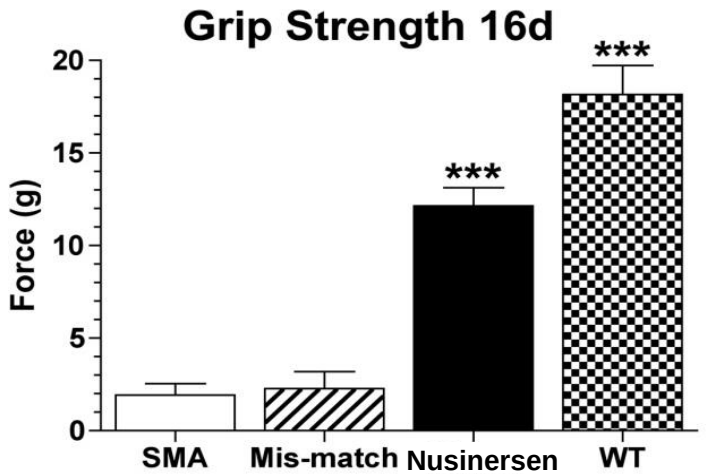
SMN Targeting ASO Preserves Neuron and Muscle Function in a Mouse Model of SMA

SMN Targeting ASO Preserves Neuromuscular Junctions



SMN Targeting ASO Maintains Muscle Fiber Size

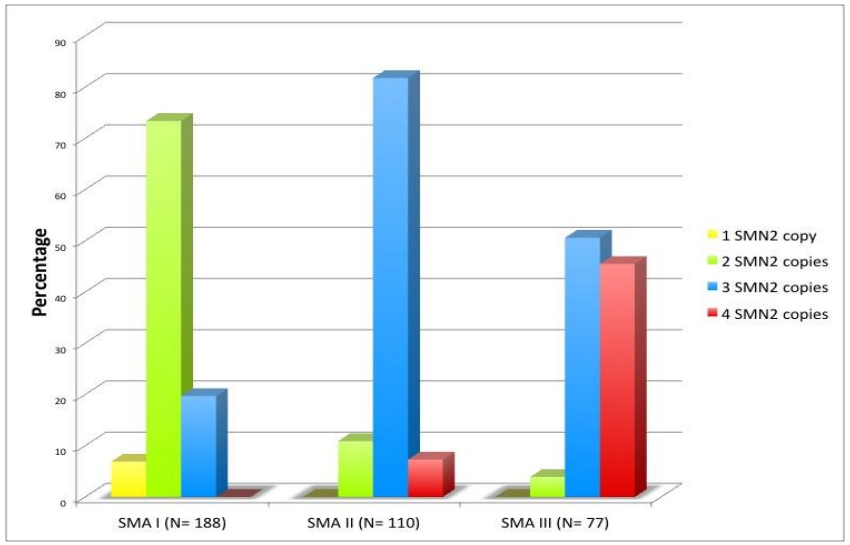




Passini et al. (2011) *Sci Trans Med*.**3**:72ra18

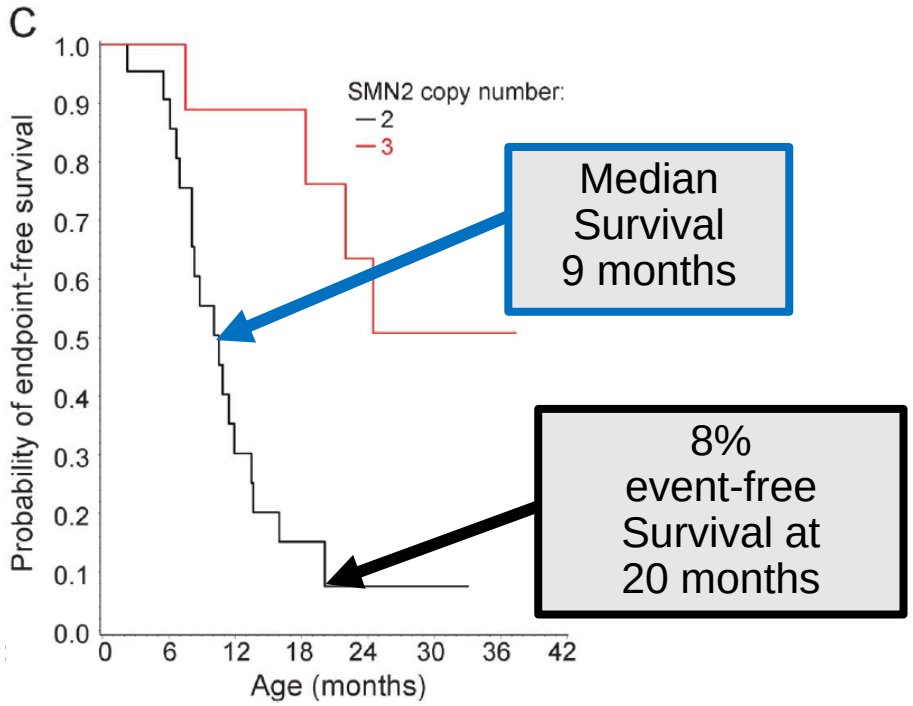
Understanding the Natural History:
Genotype-Phenotype in Spinal Muscular Atrophy

SMN2 copy number and severity of disease



Feldkotter et al. *AJHG,* 2002

SMN2 copy number and survival in SMA type 1

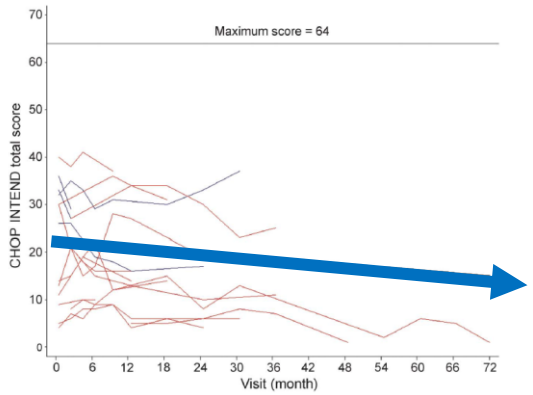


Finkel et al, *Neurology*, 2014

Clinical Trial Readiness – 2
Biomarkers for SMA

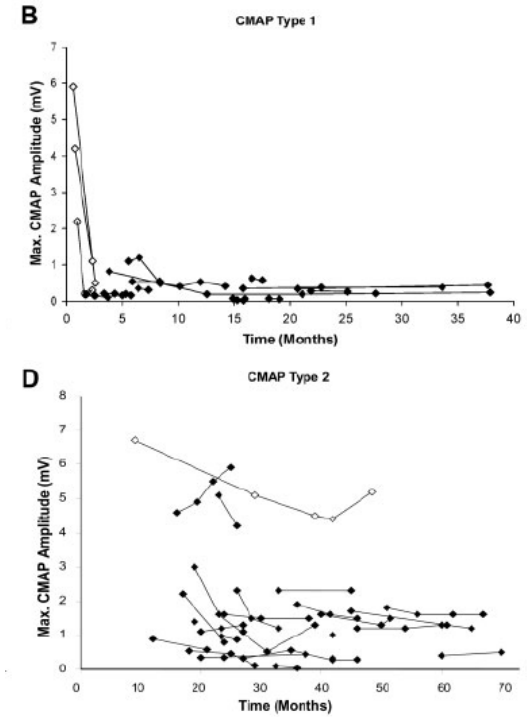
Motor Function Scales

CHOP INTEND
Hammersmith Infant Neurologic Exam
Hammersmith Functional Motor Scale
Revised Upper Limb Module
Motor Function Measure



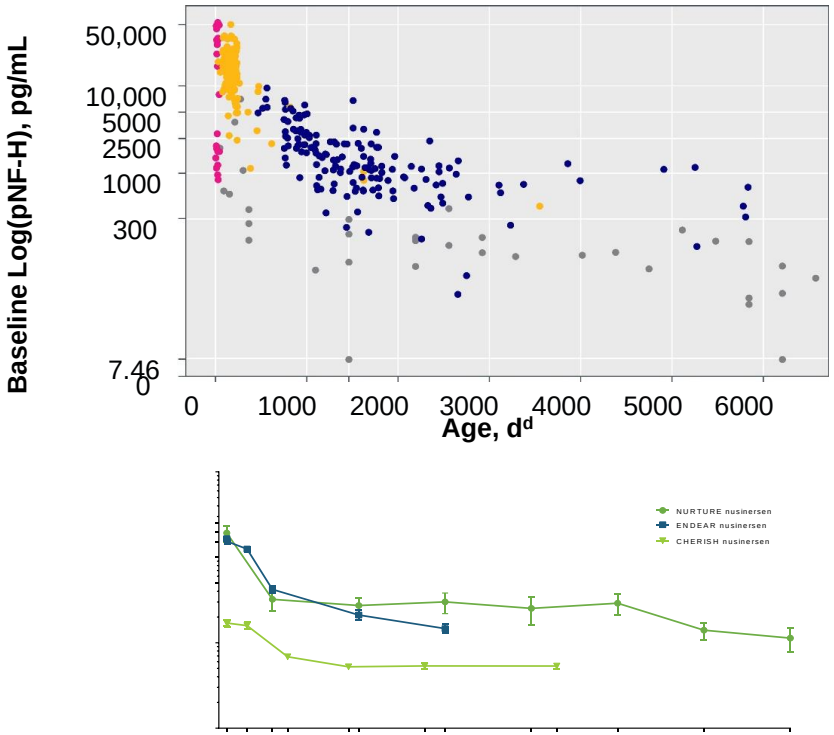
Finkel et al, Neurology, 2014

Electrophysiological: CMAP



Swoboda et al, Ann Neurol, 2005

Neurofilament pNFH



Darras et al, ACTN, 2019

Understanding Trajectories of Change in SMA
Age as an important variable

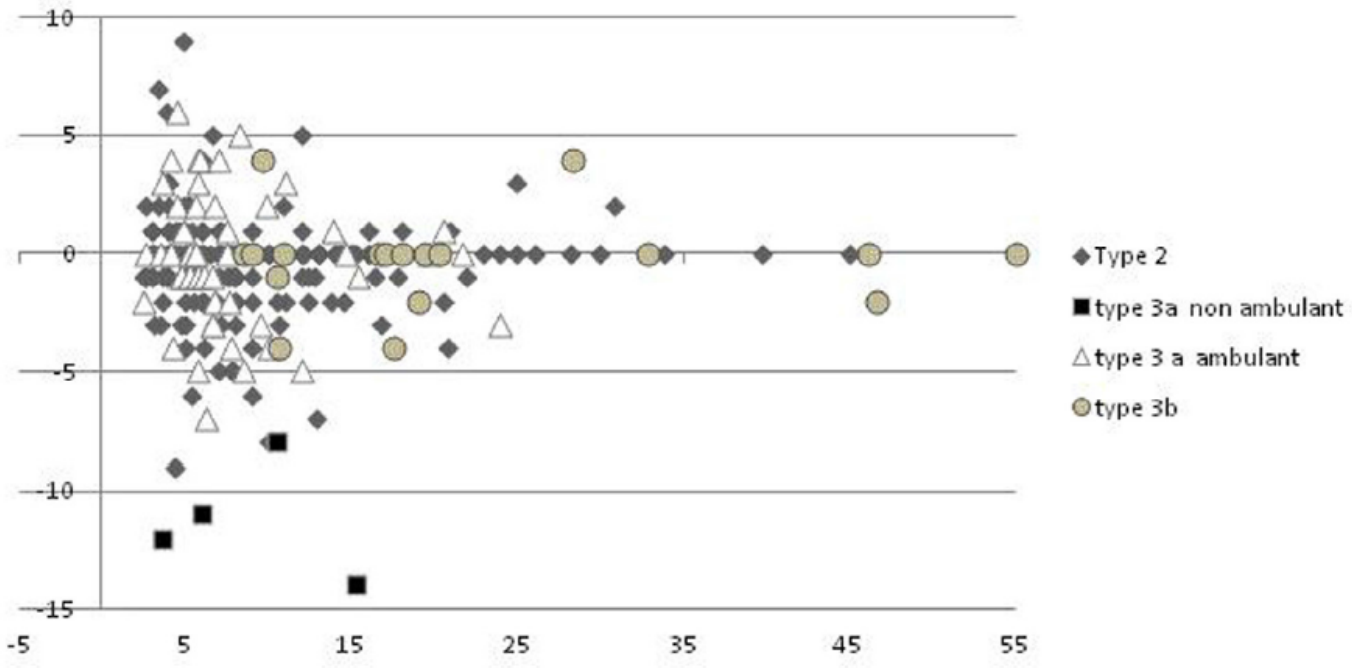


Fig. 1. HFMSE 12-month changes: individual details according to age.

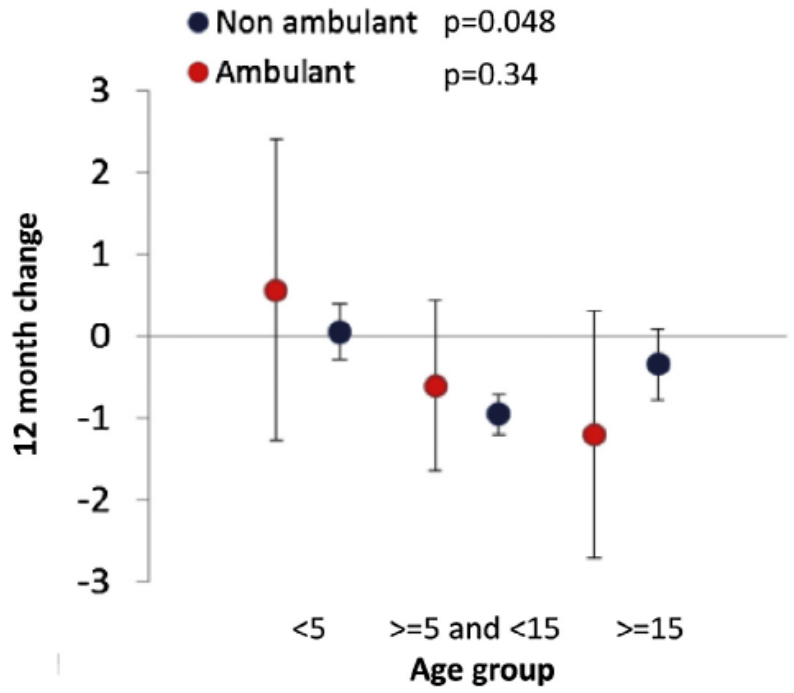
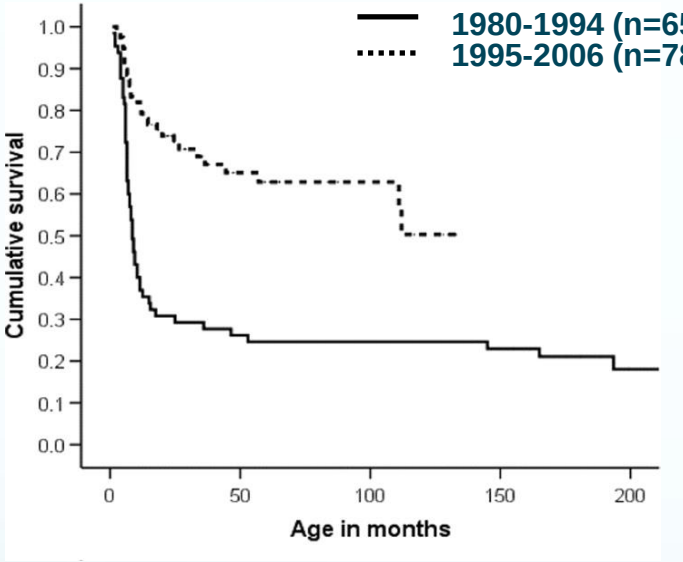


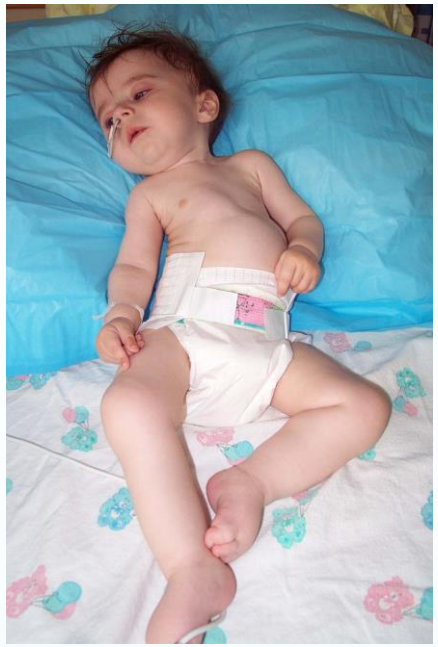
Fig. 4. Average 12-month change of the Hammersmith scale according to age classes and ambulation.

Mercuri E et al, *Neuromusc Disord*, 2016

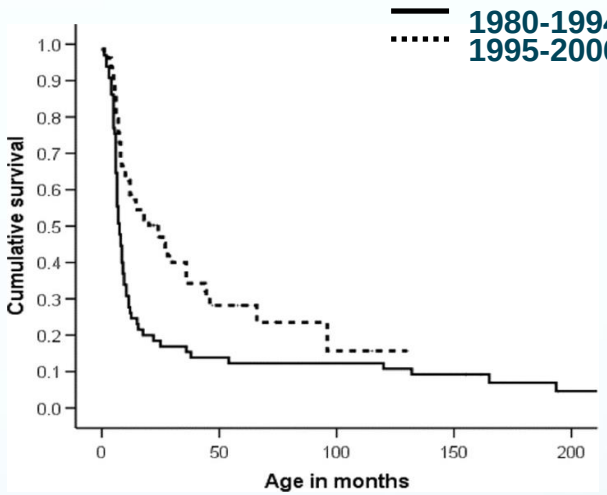
Spinal Muscular Atrophy Type I: Changing Survival and Impact of Standards of Care

Death





Death or Ventilator Dependance for more than 16 hrs.

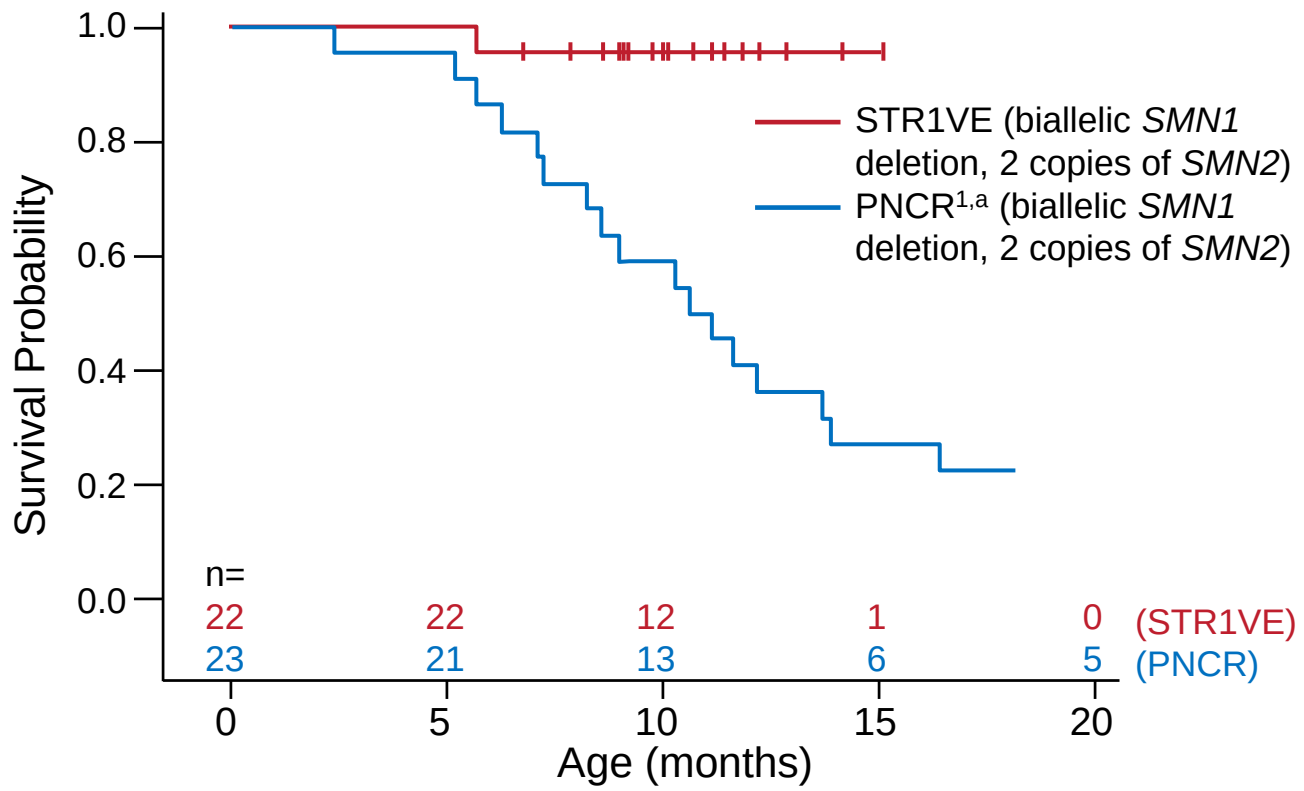


- Retrospective study[2] of 33 infants with SMA type 1, with symptom onset <6 months of age
- Highest motor function score (HINE-2) seen at initial visit
- **Prolongation of survival does not impact (non-) achievement of motor milestones**

Oskoui M, et al. *Neurology*. 2007;69(20):1931-1936.

2. De Sanctis R, et al, *Neuromuscular Disorders*. 2016;26(11):754-759.

Event-Free Survival Response in Patients With SMA1 in STR1VE (AVXS-101 gene replacement therapy)



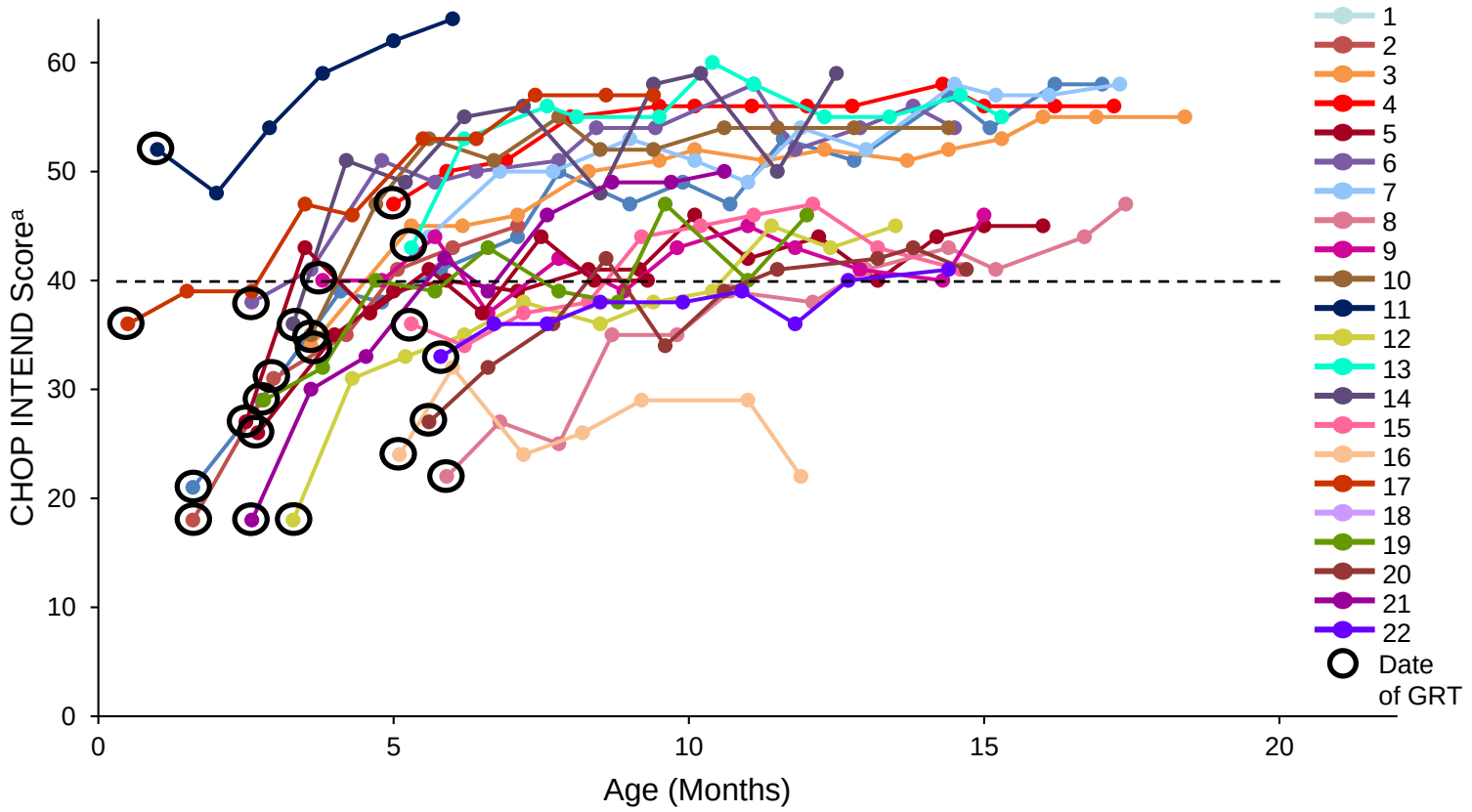
Phase 3, Open-label study
No internal control

Survival was improved compared with natural history among patients who could have reached 13.6 months of age at the datacut

[a]Survival for PNCR[1] = no death, or no need for ≥16-h/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness; n=23 (2 copies of *SMN2*).
[d]One patient died at the age of 7.8 months due to causes unrelated to treatment. [e]One patient withdrew consent at 11.9 months of age.
PNCR, Pediatric Neuromuscular Clinical Research; SMA1, spinal muscular atrophy type 1.
1. Figure adapted from Finkel RS, et al. *Neurology*. 2014;83:810–817.

Day JW et al, presented at WMS 2019

Motor Function Improvement in Patients With SMA1 in STR1VE



95% with score ≥40

A total of 21 (out of 22) patients have reached a CHOP INTEND score ≥40

Black dashed line: According to natural history, SMA1 children do not achieve/maintain CHOP INTEND scores >40 points.[1]
[a]Scores on the CHOP INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
Mar 8, 2019 datacut.
CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; GRT, gene-replacement therapy; SMA1, spinal muscular atrophy type 1.

1. Finkel RS, et al. *Neurology*. 2014;83:810–817.

Day JW et al, presented at WMS 2019

Talk early and often with the FDA and EMA

Development of gene therapies—lessons from nusinersen

L Xu[1], I Irony[1], WW Bryan[1] and B Dunn[2]

The nusinersen development and approval process provide important lessons regarding the pathway to marketing approval for gene therapies. These lessons emphasize rigorous clinical trial design, flexibility in trial design and analysis, a collaborative effort with regular communications between the drug developer and the Food and Drug Administration (FDA), and use of FDA's expedited programs. These lessons are critical to the development of gene therapies for the treatment of serious or life-threatening rare diseases.

Gene Therapy (2017) **24,** 527–528; doi:10.1038/gt.2017.64

Discuss study population, clinical trial design, PKPD, safety, outcome measures, biomarkers, ….

Summary

- Pediatric studies have particular challenges and regulatory requirements
- Understanding the nuances of genotype:phenotype associations can help design an efficient clinical trial
- Provision of standard-of-care is necessary to minimize patient variation, yet adds a second treatment variable

Acknowledgements

The many patients and their parents who bravely participated in these pioneering clinical trials

- Colleagues:
- Pre-clinical: Adrian Krainer, Arthur Burghes, Charlotte Sumner, Brunhilda Wirth
- Clinical: ISMAC Eugenio Mercuri, Francesco Muntoni, Darryl De Vivo, Basil Darras, John Day Thomas Crawford, Kathy Swoboda
- Co-Investigators, study coordinators, clinical evaluators
- Patient Advocacy Groups: MDA, Cure SMA, SMA Foundation, SMA Europe,

Pharma: Ionis (F Bennett), Biogen, AveXis (B Kaspar), PTC/Roche

- FDA and EMA: B Dunn, R Temple, E Unger, W Bryan

Thank you

Questions?