Session I: Developing First in Human Gene Therapy Clinical Trials

Natural History Studies for Neurodegenerative Disorders

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- **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

Duchenne muscular dystrophy

Incidence: 1: 3,500 boys
Onset: 2-4 years
Loss of ambulation: 10 years (7-12)

Gowers

Wang RT et al, Hum Mut, 2018
Spinal Muscular Atrophy

SMN Genes and Protein

Gene

SMN2

90%

1 2a 2b 3 4 5 6 8

10%

1 2a 2b 3 4 5 6 7 8

Transcript

Protein

unstable

stable

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

Grip Strength 16d

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

Electrophysiological: CMAP

Neurofilament pNFH

Finkel et al, Neurology, 2014
Swoboda et al, Ann Neurol, 2005
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

- 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**

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

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*Survival for PNCR<sup>1</sup> = 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).

<sup>1</sup>One patient died at the age of 7.8 months due to causes unrelated to treatment. *One patient withdrew consent at 11.9 months of age.

PNCR, Pediatric Neuromuscular Clinical Research; SMA1, spinal muscular atrophy type 1.

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Day JW et al, presented at WMS 2019
Motor Function Improvement in Patients With SMA1 in STR1VE

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

Day JW et al, presented at WMS 2019

Black dashed line: According to natural history, SMA1 children do not achieve/maintain CHOP INTEND scores >40 points.1

*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.

Talk early and often with the FDA and EMA

Development of gene therapies—lessons from nusinersen

L. Xu¹, I Irony¹, WW Bryan¹ and B Dunn²

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.


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
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Thank you

Questions?