Zolgensma

(onasemnogene abeparvovec-xioi)

Gene Therapy:
Probing Regulatory Precedents

ISCTM

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Disclosures

- Former Director of the Office of Tissues and Advanced Therapies (OTAT) in the FDA's Center for Biologics Evaluation and Research (CBER)

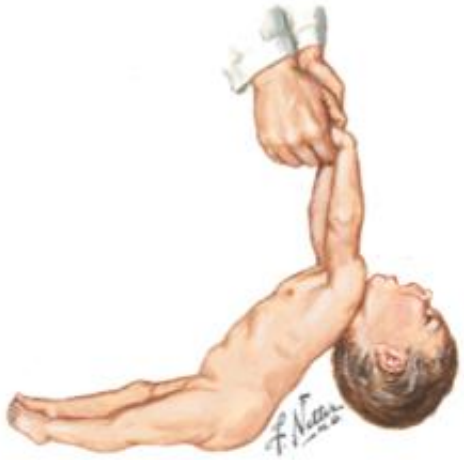
- I have no financial interest in any product mentioned in this presentation, nor in any of its competitors.

Gene Therapy: Scientific Advances

- Human Genome Project
  - Completed in October 2003
  - 99% of human genes sequenced to 99% accuracy
- Development of new vectors
  - Adeno-associated virus (AAV)
  - Lentivirus
  - Nanoparticles
- Genome editing / base editing

Spinal Muscular Atrophy (SMA) Type 1

- Severe form
- Onset before 6 months of age
- Usually presents with poor nursing ability, reduced swallowing, and respiratory failure
- Unable to sit without assistance or su
- Incidence: ~1 / 10,000 live births



[Wikimedia Commons; Iannaccone (1998) Sem Neurol 18:19-26; *Netter's Neurology*]

Zolgensma: Phase 1 Clinical Trial

- Low dose: 3 subjects
- High dose: 12 subjects
- Substantial evidence of effectiveness?

- Change from academic to commercial manufacturing would require new study

[Wikimedia Commons; Iannaccone (1998) Sem Neurol 18:19-26; *Netter's Neurology*]

Zolgensma: Phase 3 Clinical Trial

Endpoint	Natural History Controls [N = 23]	Study Subjects, % (n) [N = 21]
Survival at 14 months	**25%**	**67% (13*)**
Sitting for ≥ 30 seconds	**0**	**47% (10)**

*Only 13 of 19 remaining subjects had reached age 14 months by March 8, 2019

[Modified from US FDA SBRA; Finkel et al. (2014) Neurology 83:810-817]

Summary

- Scientific advances have spurred recent growth in development of gene therapies.
- Gene therapies can be life-changing and life-saving.
- If the effect size is large, then marketing approval may be based on data from a small number of subjects.
- First-in-human studies can be sufficient to support marketing approval.
- Natural history (NH) controls, based on small numbers of NH subjects, are feasible for some rare diseases.
- CMC (manufacturing) often delay development of gene therapies.

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