

Design Considerations for Clinical Trials in Rare Diseases

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Regulatory Education for Industry (REdI) – June 2022

Learning Objectives

- Describe the general design considerations for efficient clinical development of cell and gene therapy (CGT) products for rare diseases
- Describe the use of natural history studies in the clinical development of CGT products for rare diseases
- Describe the regulatory requirements to provide substantial evidence of effectiveness and safety of CGT products for treatment of rare diseases

Overview



- Efficient Development of CGT Products
- Use of Natural History Studies in Clinical Development of CGT for Rare Diseases
- Substantial Evidence of Safety and Effectiveness of CGT Products for Treatment of Rare Diseases
- Example of GT Clinical Development Program for Rare Disease

EFFICIENT DEVELOPMENT OF CELLULAR AND GENE THERAPY PRODUCTS

Orphan Drug Act (1983)



- Rare disease: a disorder or condition that affects less than 200,000 persons in the United States.
- Incentives to make developing drugs for rare diseases financially viable:
 - Orphan product development grants
 - Protocol assistance
 - Tax credits equal to the qualified clinical testing expenses
 - Waiver of Prescription Drug User Fee Act (PDUFA) marketing application fee
 - Seven-year marketing exclusivity once the drug is approved by FDA

Efficient Clinical Development



Preparation

- Early Collaboration between basic scientists and clinicians
- When preclinical studies are beginning, draft the design of Phase 1, 2, and 3 studies
- Design and conduct Natural History studies, with banking of DNA samples

Collaboration

- Collaboration between all stakeholders
- Early and regular communications with FDA
- Formal regulatory meetings: INTERACT, PreIND and EOP meetings

Expectation

- Design first-in-human clinical trial to provide evidence of effectiveness (e.g., include randomized, concurrent controls)
- Resolve manufacturing issues, as much as possible, before first-in-human clinical trial

Design of Early-Phase Trials

- Multi-purpose trials:
 - Safety, tolerability, feasibility, disease pathophysiology
 - Dose-exploration, biomarker exploration, preliminary efficacy
- Choice of control:
 - Concurrent control arm: standard of care and placebo
 - Natural history

Design of Early-Phase Trials, cont.



- Standard of care (SOC) for all subjects
- No subject should be denied effective therapies in order to be randomized to a placebo-only arm
- Add-on designs: All subjects receive standard of care (SOC), then be randomized to the added GT product or placebo (e.g., muscular dystrophy trials)

Design of Early-Phase Trials, cont.



- Many rare diseases
 - Have poorly understood etiology and/or pathophysiology
 - Are poorly characterized or have highly variable natural history
- Consider randomized, concurrent-controlled (e.g., placebo, sham-procedure), double-blind clinical trials, even for FIH studies
 - Aid data interpretation
 - Especially important for rare diseases
 - Maximize the use of valuable resources
 - May provide sufficient evidence of effectiveness to support a marketing application.

Dose Selection and Product Delivery



- Early Phase studies: dose ranging
 - Initial dose
 - Supported by preclinical studies and/or available clinical information
 - Reasonably safe and have therapeutic potential
- Substantial dose exploration throughout clinical development
- Invasive surgical procedure
 - Staged approach
 - Unilateral first, then bilateral (i.e., delivery into eyes, brain)
 - Detailed description of delivery procedure and devices used

Safety Considerations



- Monitor risks associated with GT product and the administration procedure:
 - Standard safety monitoring
 - Immune response: immunoassays measuring cellular and humoral immune responses to both the vector and the transgene-encoded protein
 - Potential insertional carcinogenesis

Safety Monitoring Duration



- Duration of monitoring
 - Sufficient to cover expected duration of effect
 - Depends on information from preclinical studies, and experience with related products
- Long term follow-up required for certain GT products
 - e.g., 15 years of follow-up for integrating viral vector-based products
 - Clinical development can continue while long term follow-up of early phase trial subjects is ongoing

Endpoints



- Encourage exploration of a wide spectrum of endpoints in early phase trials
- Early recognition of the need to develop a new assessment tool, or to modify an existing one, for use as a clinical trial endpoint
- Primary efficacy endpoints in trials supporting BLA:
 - Clinically meaningful endpoints - directly measure how patients feel, function or survive, or
 - Surrogate endpoints - reasonably likely to predict a clinical benefit

USE OF NATURAL HISTORY STUDIES IN CLINICAL DEVELOPMENT OF CGT PRODUCTS FOR TREATMENT OF RARE DISEASES

Natural History Studies



Knowledge about the disease's NH can inform important aspects of drug development including:

- Defining the disease population
- Description of the full range of disease manifestations
- Identification of important disease subtypes
- Understanding and implementation of critical elements in clinical study design, such as study duration and choice of subpopulations

Natural History Studies



- Developing and selecting outcome measures that are more specific or sensitive to changes in the disease or more quickly demonstrate efficacy than existing measures
- Developing new biomarkers that may provide proof-of-concept (POC) information, guide dose selection, allow early recognition of safety concerns, or provide supportive evidence of efficacy
- NH data should be collected for a sufficient duration to capture clinically meaningful outcomes and determine variability in the course of the disease

Use of NH as External Controls



- External, historical controls may be appropriate if all criteria are met:
 - An unmet medical need
 - A concurrent control: not practical or ethical
 - Disease course: well-documented, highly predictable
 - Study population and historical controls: suitably comparable
 - Expected effect: large, self-evident, and temporal to the intervention

Use of NH as External Controls



- Historical controls may be inadequate
 - Heterogenous disease/condition
 - NH unknown
 - Lack of consistent assessments in historical controls to allow interpretation of treatment effect
- Generally, use of external, historical controls in place of a concurrent comparator group is not encouraged

SUBSTANTIAL EVIDENCE OF EFFECTIVENESS OF CGT PRODUCTS FOR TREATMENT OF RARE DISEASES

Regulatory Requirements



- Approval of all drugs – for both rare and common conditions – must be based on substantial evidence of effectiveness and sufficient evidence of safety.
- Evidence of effectiveness should be obtained from adequate and well-controlled studies.
- Certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases.
- FDA regulations provide flexibility in applying regulatory standards.

Regulatory Flexibility

- FDA “**exercise[s] its scientific judgment**” in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs.
- This **flexibility** extends from early phases of development to design of adequate and well-controlled studies required to demonstrate safety and effectiveness to support marketing approval.

21 CFR 314.105

Evidence of Effectiveness



- No specific minimum number of subjects to establish effectiveness and safety of a treatment for any rare disease
- Case-by-case determination of adequacy of sample size, based on the:
 - Persuasiveness of data (e.g., comprehensiveness and quality)
 - Nature of the clinical benefit
 - Length of treatment or exposure
 - Target patient population
 - Concern for potential of harm from the treatment

Substantial Evidence of Effectiveness



- General requirement of more than one adequate and well-controlled (AWC) clinical trials to provide the substantial evidence of effectiveness necessary to support a future marketing application.
- Consistency of results across two AWC trials greatly reduces the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a product is effective.

Reliance on Single AWC Clinical Investigation Plus Confirmatory Evidence



- Reliance on a single AWC trial in situations that a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible
- Important considerations:
 - Persuasiveness of the single trial
 - Robustness of the confirmatory evidence
 - Seriousness of the disease
 - Size of the patient population
 - Whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation

CLINICAL DEVELOPMENT OF ZOLGENSMA FOR SPINAL MUSCULAR ATROPHY (SMA)

Onasemnogene Apeparvovec (Zolgensma)



- AAV9-vector based GT
- FDA approved in 2019
- Single intravenous (IV) infusion: 1.1×10^{14} vg/kg* of body weight
- Children < 2 years of age with SMA with bi-allelic mutations in *SMN1*
- BLA approval based on data from the ongoing Phase 3 trial and the completed Phase 1 trial in patients with infantile onset SMA (SMA1)



Ongoing Phase 3 Trial

- Primary evidence of effectiveness
- Open-label, single-arm trial
- Natural history data as control
- n=21
- All received from 1.1×10^{14} vg/kg*

* vg/kg: vector genome per kilogram body weight

Endpoints - Phase 3 Trial



- Co- Primary efficacy endpoints:
 - The proportion of patients achieving the milestone of sitting without support for at least 30 seconds at 18 months of age
 - Survival at 14 months of age, defined by avoidance of the combined endpoint of either (a) death or (b) permanent ventilation
- Secondary efficacy endpoint: the proportion of patients who are independent of ventilatory support at 18 months of age.

Study Population: Infantile Onset SMA (SMA1)



- Onset of clinical symptoms before age 6 months
- Genetically-confirmed bi-allelic deletions of *SMN1*; two copies of *SMN2*
- Well-defined natural history
 - No patients meeting the study entry criteria would be expected to attain the ability to sit without support
 - ~25% expected to remain alive without permanent ventilation beyond 14 months of age

Ongoing Phase 3 Trial- Results

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

*At the time of BLA review, only 13 of 19 remaining subjects had reached age 14 months.

Completed Phase 1 Trial



- Supportive evidence of effectiveness
- Open-label, single-arm, ascending dose design
- n=15
 - Low dose cohort, n=3
 - High dose cohort, n=12
- Clear dose-response relationship
- Uncertainty in the administered dose

Completed Phase 1 Trial- Results



Endpoint	Natural History Controls [N = 23]	Low-Dose Cohort, n (%) [N = 3]	High-Dose Cohort, n (%) [N = 12]
Survival at 20 months	8%	3 (100%)	12 (100%)
Sitting for ≥ 30 seconds	0	0	9 (75%)
Standing	0	0	2 (17%)
Walking	0	0	2 (17%)

Clinical Development of GT for SMA



- **Nontraditional Clinical Development Program**
 - Open-label trials
 - Dose-escalation control
 - Natural-history controls
 - Unmet medical need
 - Well-characterized disease course
 - Historical controls are suitably comparable
 - Large treatment effect
 - Concurrent control not practical/ethical for the Phase 3 study



Benefit / Risk Justification

The benefit-risk profile was deemed favorable, and onasemnogene abeparvovec was approved in 2019.

Challenge Question #1



Which of the following statements is **NOT** true?

- A. FDA requires sponsors to conduct natural history studies in early stages of clinical development, to help in designing an efficient drug development program for rare diseases.
- B. Well-designed natural history studies can help the investigators and sponsors design more efficient drug development programs.
- C. FDA encourages the sponsors to resolve the product's manufacturing issues, as much as possible, before initiating the first-in-human clinical trial.
- D. Use of external, historical controls in place of a concurrent comparator group is not recommended.

Challenge Question #2



Which of the following statements is true?

- A. In rare, serious and life-threatening diseases with unmet medical need, the use of placebo as a comparator should not be considered.
- B. Randomized, placebo-controlled clinical trials may be the most efficient means to demonstrate product effectiveness
- C. FDA must not exercise any scientific judgment in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs.
- D. A concurrently controlled, randomized first-in-human early phase trial for rare diseases is not necessary or recommended because the objective of such a study is to assess safety.

Summary

- Approval of drugs and biologics must be based on **substantial evidence of effectiveness** and sufficient evidence of safety.
- Evidence of effectiveness should be obtained from **adequate and well-controlled clinical trials**.
- Certain aspects of product development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide **flexibility** in applying regulatory standards (21 CFR 314.105).

Guidance for Industry



- Cellular and Gene Therapy Guidances
<https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances>
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), 2020
<https://www.fda.gov/media/113760/download>
- Potency Tests for Cellular and Gene Therapy Products, 2011
<https://www.fda.gov/media/79856/download>
- Preclinical Assessment of Investigational Cellular and Gene Therapy Products, 2013
<https://www.fda.gov/media/87564/download>
- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry, 2015
<https://www.fda.gov/media/106369/download>
- Long Term Follow-up After Administration of Human Gene Therapy Products, 2020
<https://www.fda.gov/media/113768/download>

Guidance for Industry



- [Rare Diseases: Natural History Studies for Drug Development, Draft Guidance for Industry](#) March 2019
- [Human Gene Therapy for Rare Diseases, Guidance for Industry](#) January 2020
- [Rare Diseases: Common Issues in Drug Development, Guidance for Industry](#) February 2019

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- **OTAT Learn Webinar Series:**
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm

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Acknowledgements

- Larissa Lapteva, MD, MHS
- Tejashri Purohit-Sheth, MD, FACAAI, CQIA
- Anne Rowzee, PhD
- Lei Xu, MD, PhD

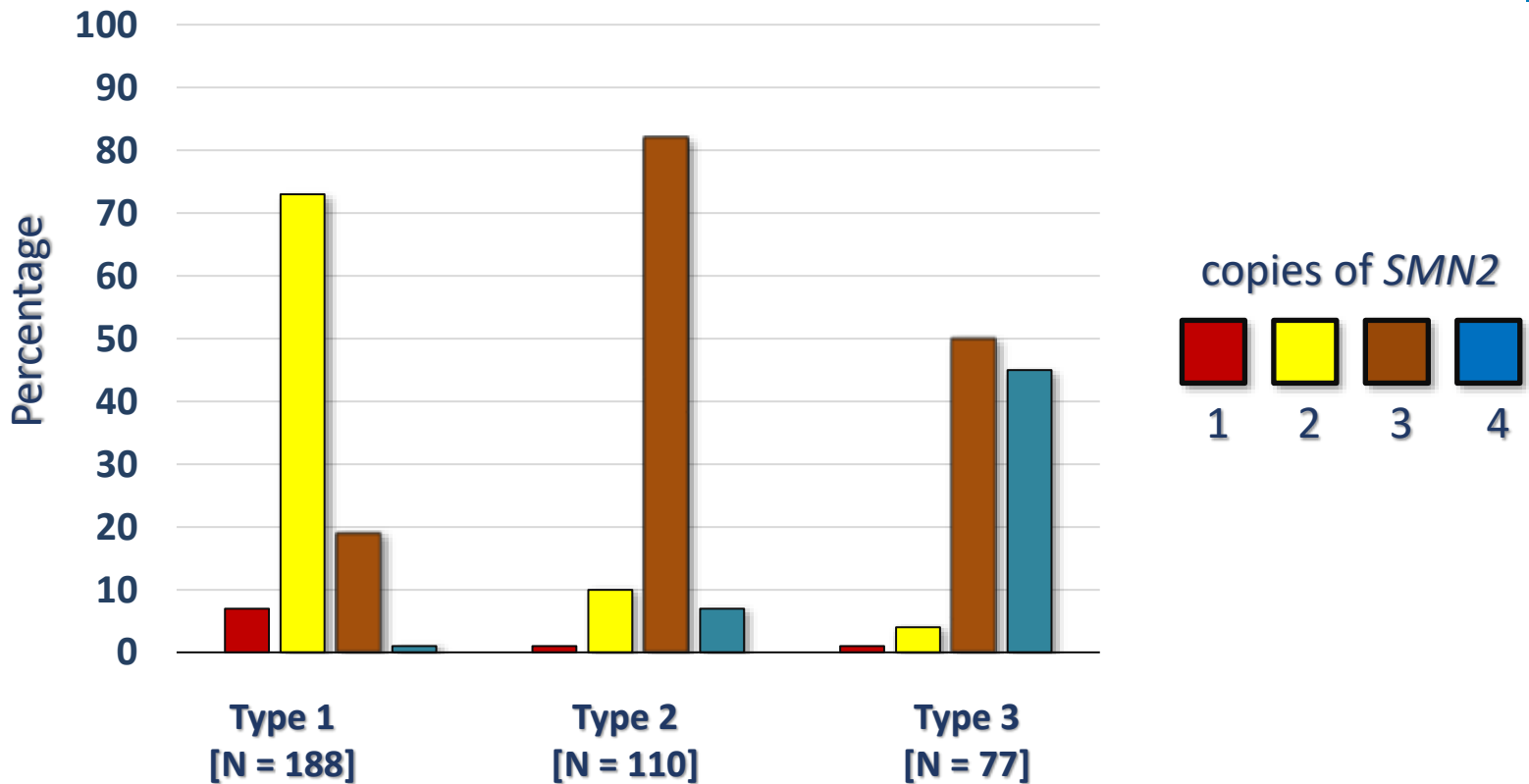


Back Up Slides

Confirmatory Evidence of Effectiveness

- Existing AWC clinical investigation(s) that demonstrated effectiveness of the drug for its other, closely related approved indication(s)
- Data that provide strong mechanistic support
- One AWC trial with compelling results, supported by additional data from the natural history of the disease
- Scientific knowledge about the effectiveness of other drugs in the same pharmacological class

SMA Genotype and Phenotype



Indication Statement

INDICATIONS AND USAGE

ZOLGENSMA (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene. ([1](#))