U.S. FOOD & DRUG ADMINISTRATION
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OFFICE OF CLINICAL PHARMACOLOGY

Model-Informed Approach Supporting Drug Development and Regulatory Evaluation in Rare Diseases

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Supplement Article

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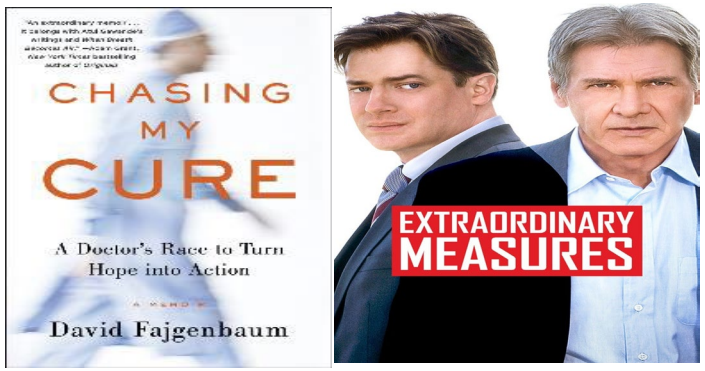
*: Ruo-Jing Li, Lian Ma, Fang Li, Liang Li, Youwei Bi, Ye Yuan, Yangbing Li, Yuan Xu, Xinyuan Zhang, Jiang Liu, Venkatesh Atul Bhattaram, Jie Wang, Robert Schuck, Michael Pacanowski, Hao Zhu. Model-Informed Approach Supporting Drug Development and Regulatory Evaluation for Rare Diseases. J Clin Pharmcol. 2022 Dec; 62 Suppl 2: S27-S37. doi: 10.1002/jcph.2143.

Outline

- Introduction
  - Challenges in Drug Development for Rare Diseases
- Use of MIDD Approaches to Support New Drug Development for Rare Diseases
- Case Examples
  - Optimizing Dose Regimen
  - Informing Clinical Trial Design
  - Selecting End Point
- Take Home Messages

Challenges for Drug Development in Rare Disease



Rare Diseases

↓

Small patient population

↓

Rare Diseases

- Rare: (< 200,000 in the US)
- Prevalent: (accumulatively affecting 10% of the population)
- Complicated: (~ 7,000 recognized rare diseases)
- Severe: (life-threatening)
- Fragile: (~50% in pediatrics)

Lack of Mechanistic Understanding of the Disease

Insufficient Knowledge on Disease Progression

Challenges in Enrolling Patients in Clinical Trials

Incentivizes drug development to treat rare diseases

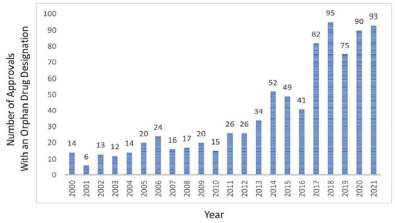
Orphan Drug Act 1983

→

Increased new drug development for rare diseases

Development Pipeline

→



Approval

→

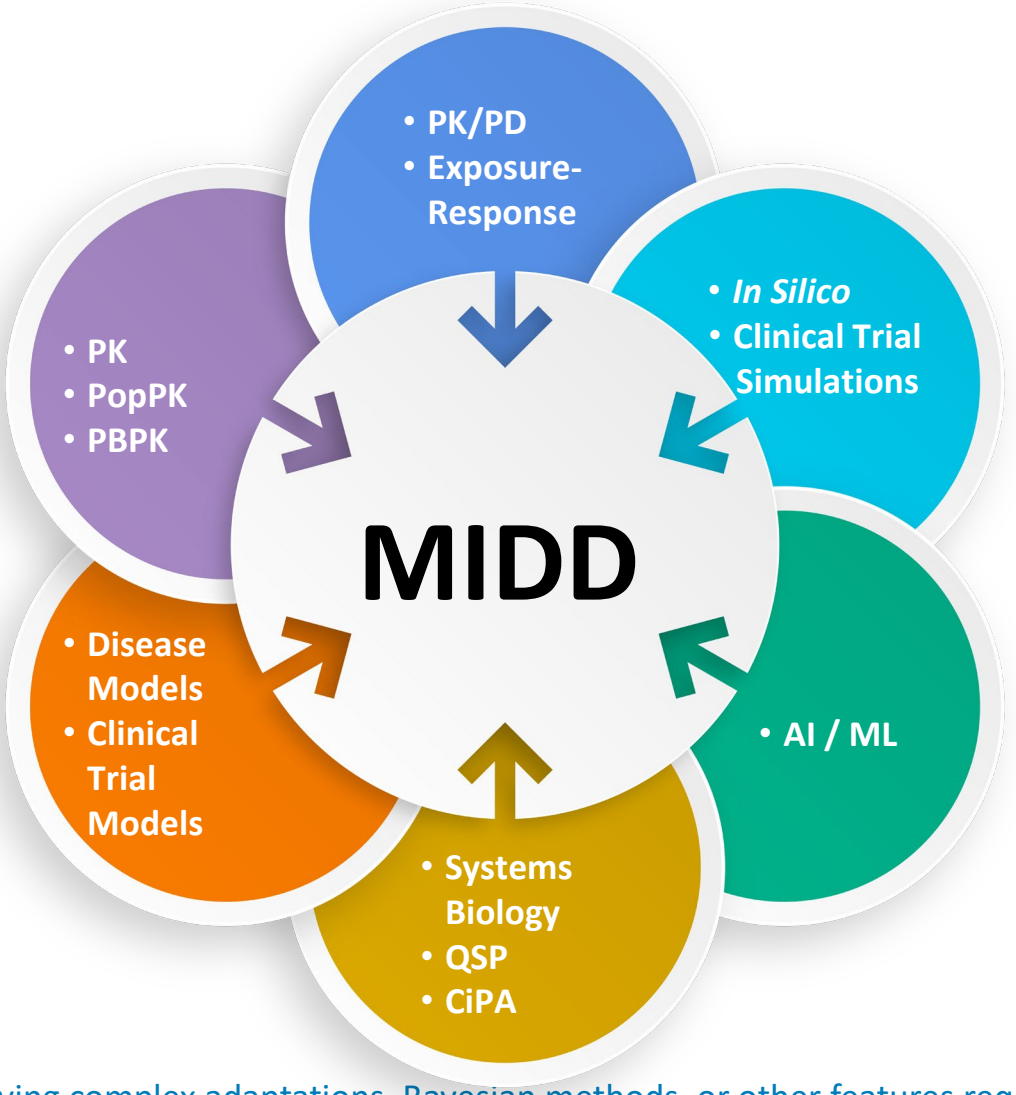
Unmet Medical Needs

< 10% of the recognized rare diseases have an FDA-approved treatment

Novel/Innovative Tools

Model-Informed Drug Development

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*



To support new drug development and regulatory decision making

* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.

MIDD for Rare Disease (1)

MIDD:
To efficiently obtain evidence / information in clinical programs with limited sample size

Optimizing Dose Regimen

- Extensive dose-finding trials are infeasible.
- Less optimal dosing may be assessed in pivotal trials.

MIDD

- Leverage data/information from various sources for dose selection in late phase trials.
- Recommend untested dosing for final approval.

Pediatric Dose following Extrapolation

- Small sample size
- Reluctance of many parents and caregivers to enroll pediatric patients in an experimental trial

MIDD

- Minimize the needed sample size in a trial by using innovative approaches.
- Support pediatric extrapolation for suitable/appropriate cases.

Informing Clinical Trial Design

- Due to small sample size, optimize trial design becomes critical
  - to effectively obtain information
  - to select dose closer to the target.

MIDD

- Optimize starting dose.
- Minimizing sampling (frequency and total volume)
- Natural history and disease model supports patient selection and stratification strategy.

MIDD for Rare Disease (2)

MIDD:
To efficiently obtain evidence / information in clinical programs with limited sample size

Providing Confirmative Evidence

- Challenges for conducting two randomized, well-controlled clinical trials in patients with rare diseases.

MIDD

- Provide confirmative evidence.
- Identify appropriate pharmacodynamic markers.

Emerging Therapeutic Modalities

- Emerging therapeutic modalities bring both opportunities and challenges in drug development for rare diseases.

MIDD

- Factor in unique features of new modalities to streamline new drug development.

Case Examples

- Case 1: Determining Dose - Adalimumab
- Case 2: Improving Trial Design – Disease Modeling
- Case 3: Selecting Endpoint – Tofersen

Case 1: Determining Dose - Adalimumab

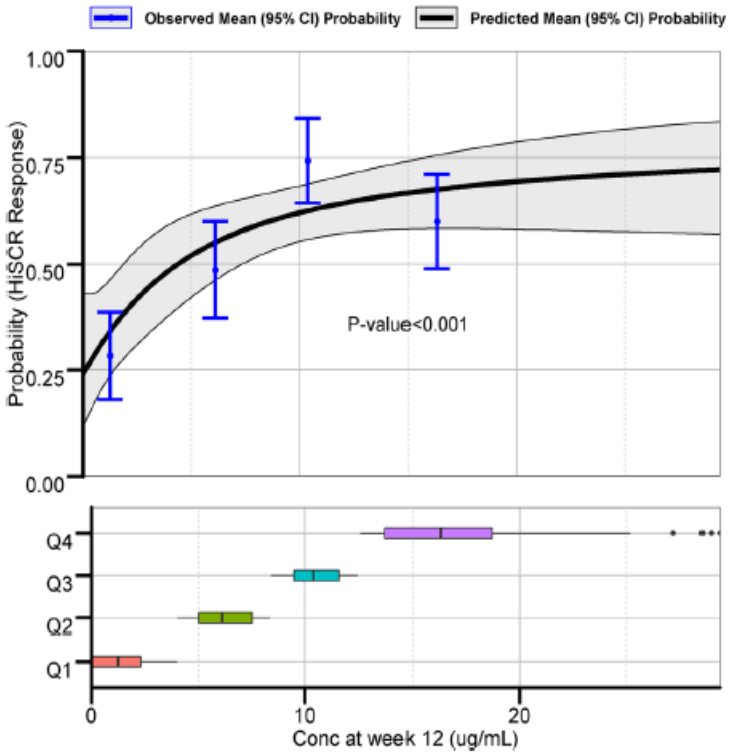
- Adalimumab (Humira ®) is a tumor necrosis factor (TNF) inhibitor indicated for RA, JIA, PsA, AS, CD, UC, Ps, UV

Hidradenitis Suppurativa (HS):

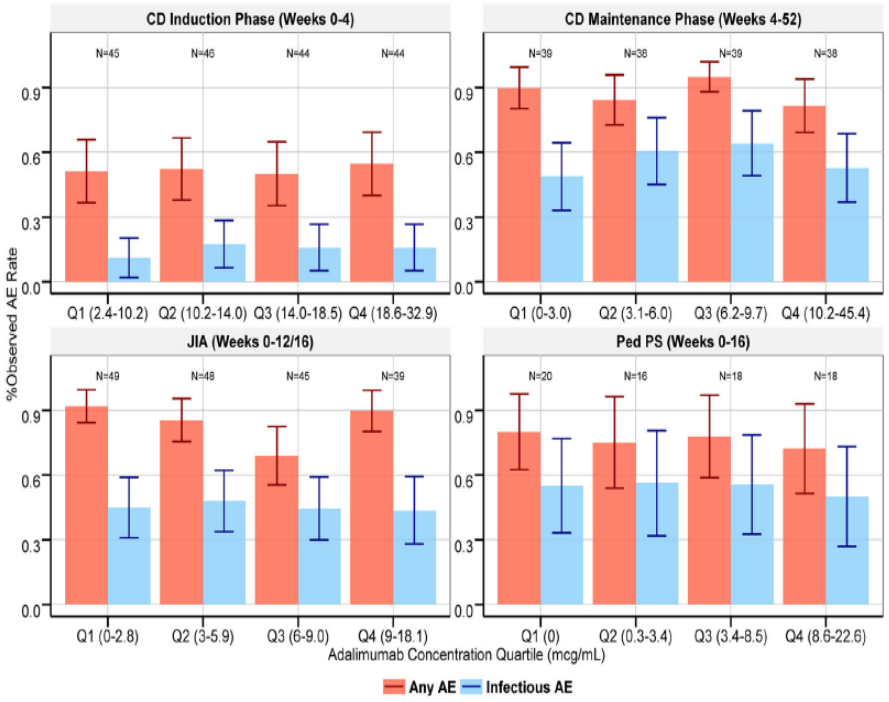
- HS prevalence in the US adults is ~ 0.1%.
- HS prevalence in pediatric patients are: 0.002%, 0.027%, and 0.114% age groups < 9 years, 10-14 years, and 15-17 years. It is challenging to enroll pediatric patients into a study.
- Current knowledge supports similar disease progression and clinical response between pediatric and adult patients with HS. Thus pediatric extrapolation is feasible.

*: Youwei Bi[1], Jiang Liu[2], Jie Wang[1], Roselyn E Epps[3], David Kettl[3], Kendall Marcus[3], Shirley Seo[1], Hao Zhu[1], Yaning Wang[1] Model-Informed Drug Development Approach Supporting Approval of Adalimumab (HUMIRA) in Adolescent Patients with Hidradenitis Suppurativa: a Regulatory Perspective. AAPS J. 2019 July 19; 21 (5):91. doi: 10.1208/s 12248-019-0363-5

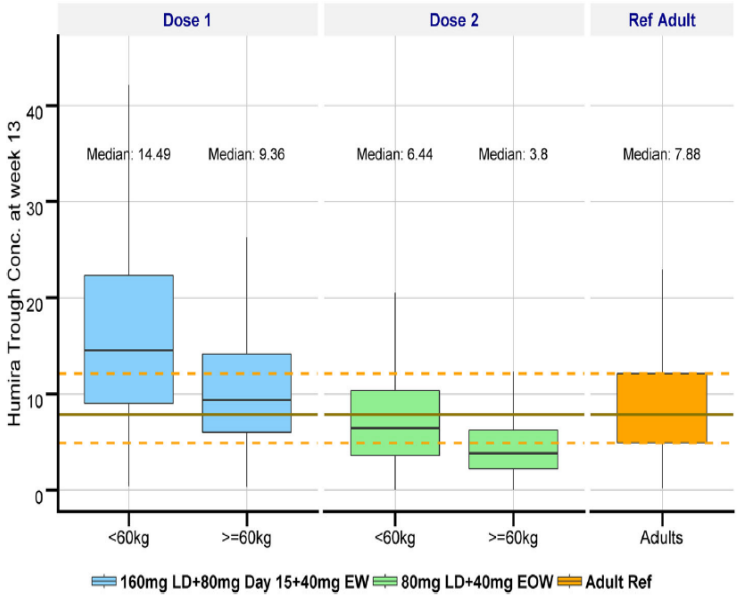
Model Informed Dose Selection for HS



Positive ER for efficacy in adult HS



Flat ER for safety in pediatric CD, JIA, and PsO

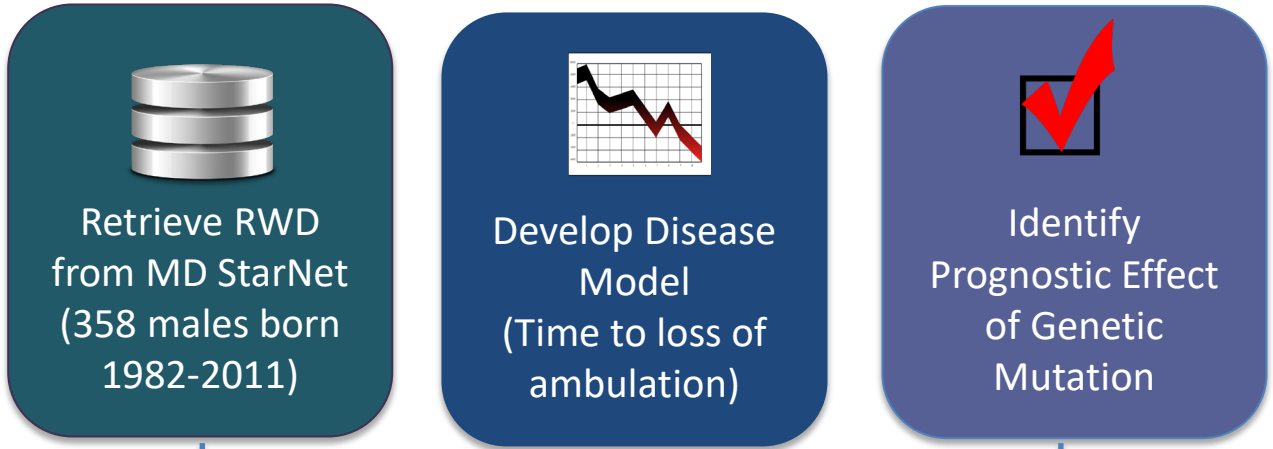


Exposure-matching for Dose Selection

MIDD Approaches

- Totality of evidence supports the new dosing regimen:
  - High exposure is the target:
    - Positive exposure-response relationship on efficacy at Week 8 and Week 52
    - Flat exposure-response relationship on safety
  - Simulation was conducted to match the high exposure.
  - Other clinical data and benefit-risk evaluation

Case 2: Informing Trial Design – Disease Modeling



Joint effort from federal/state government & academia

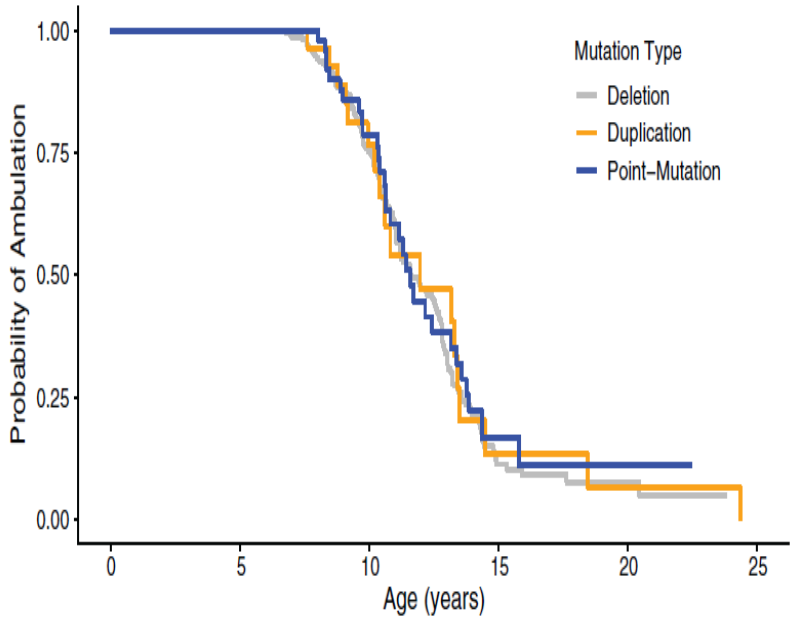
Model Building

New Protocol Design

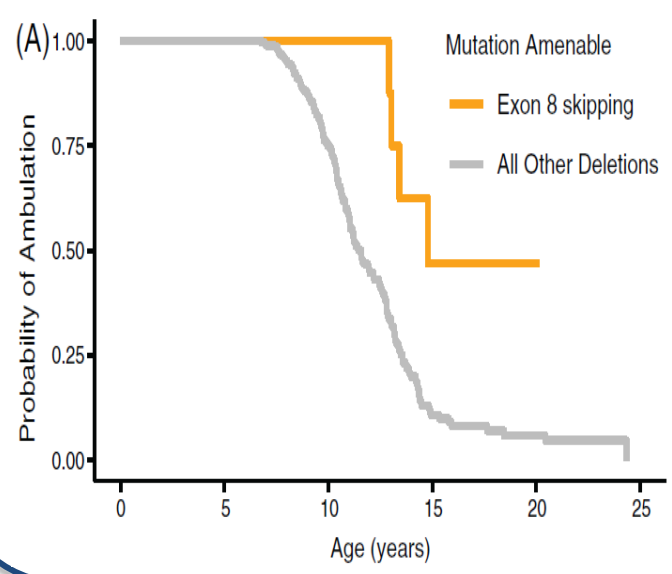
Identify Prognostic Effect of Genetic Mutation

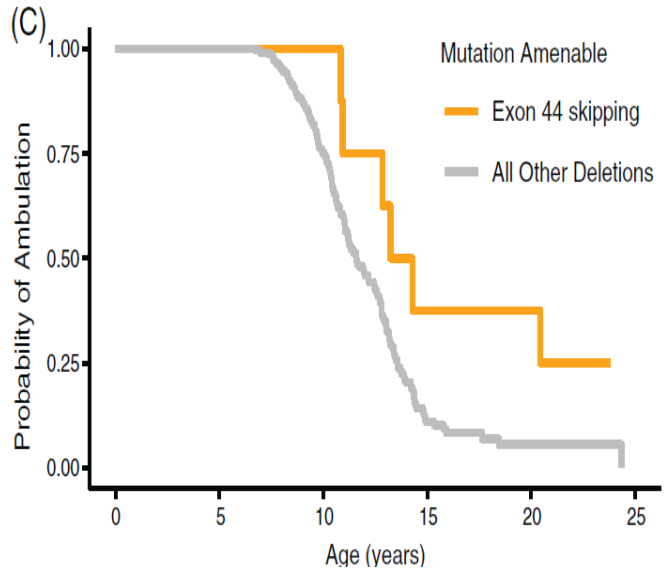
Disease Model with Covariate Effect

No Difference in Disease Progression by Genetic Mutation Type



Exon 8 and 44 Skippable Subgroups Showed Lower Risk of LoA Relative to Other Amenable Subgroups



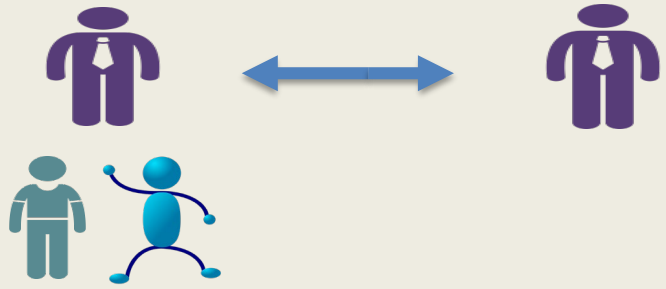


Gregory Haber Kristin M Conway, Pangaja Paramsothy, Anindya Roy, Hobart Rogers, Xiang Ling, Nicholas Kozauer Natalie Street, Paul A Romitti, Deborah J Fox, Han C Phan, Dennis Matthews, Emma Ciafaloni Joyce Oleszek, Katherine A James, Maureen Galindo Nedra Whitehead, Nicholas Johnson, Russell J Butterfield, Shree Pandya Swamy Venkatesh, Venkatesh Atul Bhattaram **Association of genetic mutations and loss of ambulation in childhood-onset dystrophinopathy.** Muscle Nverve. 2021 Feb;63(2):181-191. doi: 10.1002/mus.27113. Epub 2020 Nov 17

Improve Patient Enrichment, Randomization, and Matching

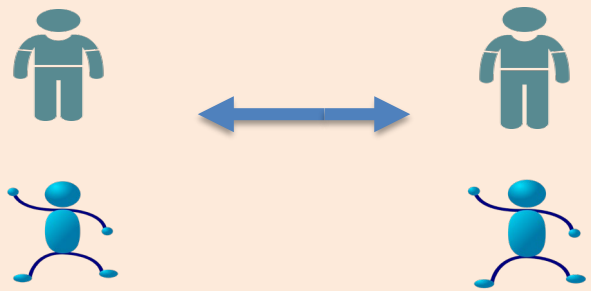
Duchenne Muscular Dystrophy

Matching Strategy



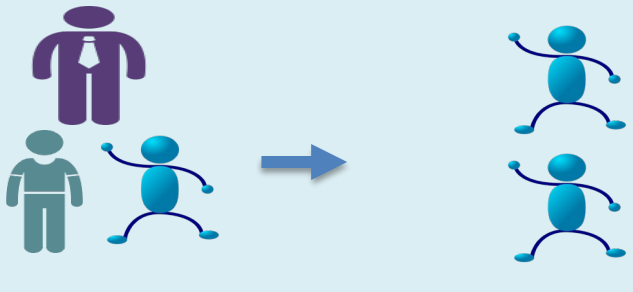
Using historical control subjects as a supplement to the placebo arm (Phase 2)

Randomization by Strata



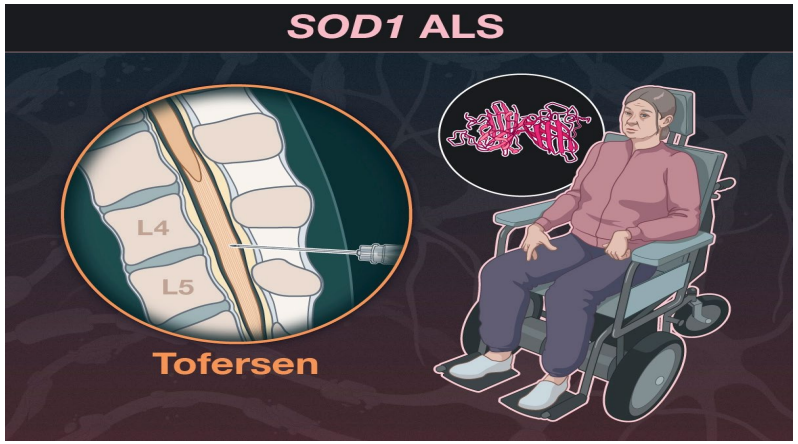
Randomization by strata to ensure consistent disease progression in different arms.

Patient Enrichment



Enrich patients to reduce variability.

Case 3: Selecting Endpoint - Tofersen



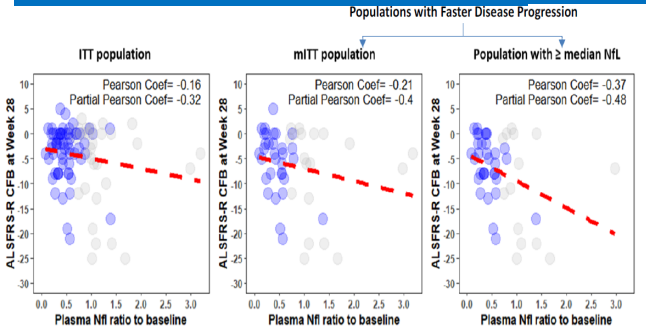
- Accelerated approval in April, 2023.
- Antisense oligonucleotide indicated for treatment of ALS in adults with a mutation in the superoxide dismutase 1 (SOD1) gene.

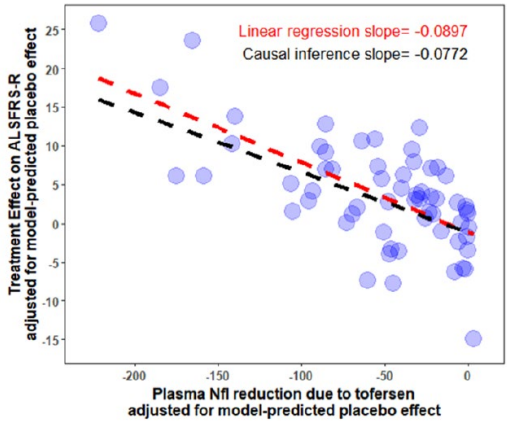
- ALS is a rare disease.
- SOD1-ALS accounts for 2% of the ALS patient population. The estimated patients are < 500 in the US.

*: US package insert: <https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215887Orig1s000Correctedlbl.pdf>

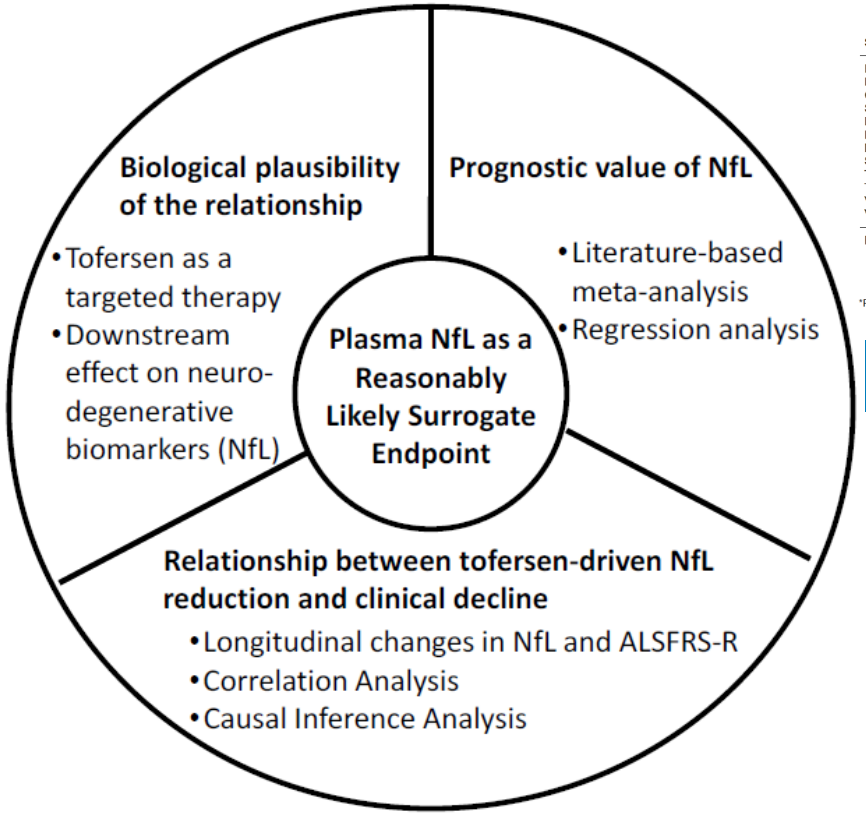
Endpoint Selection

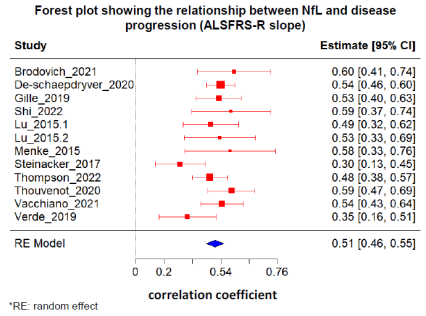
Can NfL be considered as a reasonably likely surrogate endpoint for accelerated approval of tofersen for treating SOD1-ALS?

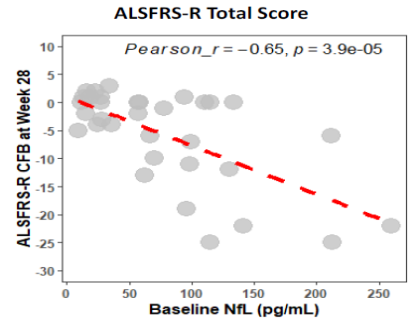




Relationship: Biomarker and clinical Outcome Changes

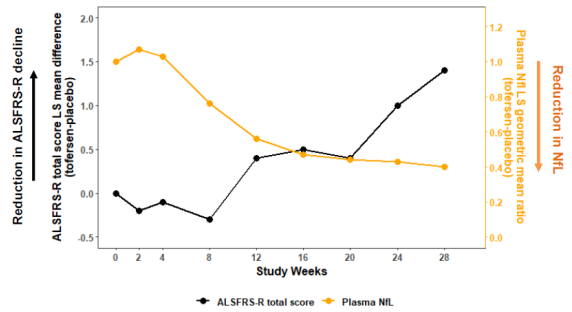






Reported Cases

Clinical Program



The values for **ALSFRS-R** and **NfL** changes are shown on left- and right-side Y-axis respectively

Temporal Relationships

*: FDA Presentation at the AC meeting <https://www.fda.gov/media/166392/download>

Take-Home Messages

- The main challenge in drug development for rare diseases is lack of prior knowledge and experience. In addition, the sample size is small in the clinical program due to challenges in enrollment.

- MIDD allows integration of information with various sources, providing an efficient tool to support drug development in rare disease area.

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- Dr. Vishnu Sharma
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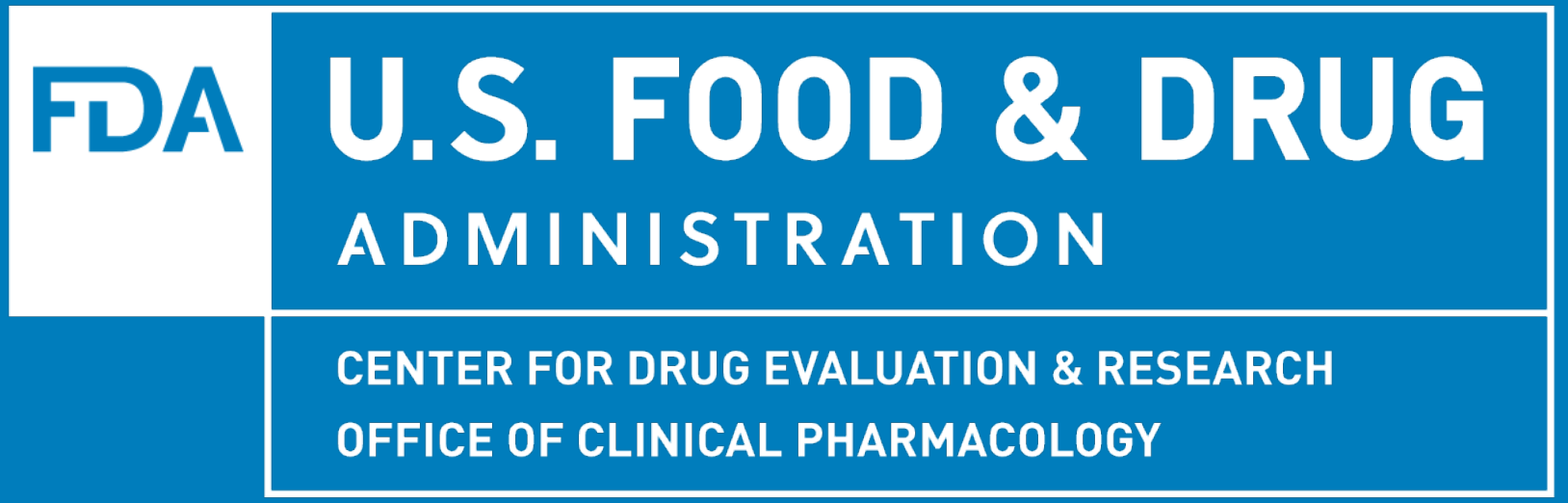
- DPM and OCP colleagues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