Regulatory Considerations for Trial Design in Myotonic Dystrophy

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Disclosures

The views presented here do not necessarily reflect those of the Food and Drug Administration

Overview

- Efficacy and safety requirements
- Endpoints
- Useful study design approaches
- Biomarkers and accelerated approval

Efficacy Evidence in Rare Serious Diseases

- Study size determined mainly by statistical power considerations
- Small efficacy studies can be acceptable, but must be rigorously designed, conducted, and analyzed
- "Independent substantiation" critical; can be provided in many different ways, e.g.
  - studies in other disease phases or in related diseases
  - particularly well-understood pharmacological effect

Safety Evidence in Rare Serious Diseases

- FDA is flexible about size of safety database necessary to support approval
- Efficacy trials combined with other types of exposure (e.g. PK studies) might be enough
- Depends in part on size of benefit and potential risks

Safety Data for Early Development

- FDA can be flexible about the type, size, and duration of nonclinical studies required at each phase of development for rare serious diseases

- Principle remains that nonclinical studies needed to avoid unreasonable risk to patients

Duration of Efficacy Studies

- 3 months can be adequate for symptomatic drugs
  - Not required to show effect on disease progression
- If effect size expected to increase over time, longer studies advantageous for statistical power
  - 12 months often selected by sponsors, but FDA recommends 18 or 24 months if more realistic for power

Clinical Endpoints

- FDA is flexible about clinical efficacy endpoints in DM
  - Measure how patients feel, function, or survive
- No minimum size of benefit to support approval, so long as significant enough to be of perceptible benefit to patient in everyday life

No specific clinical endpoint preferred in DM

- One or more symptoms that affect daily function
  - Weakness, myotonia, GI, respiratory, GI, cardiac, CNS, etc.
  - Do not need to improve all or even most symptoms, although in polysymptomatic disease is desirable
  - Composite endpoints of key symptoms may be advantageous if multiple symptoms expected to improve
- Should include both objective and subjective endpoints

- Straightforward endpoints, including Patient-Reported Outcomes (PRO's), often acceptable in a form similar to that proposed
  - ***"select a relatively small number of items (e.g., from an existing disease-specific instrument) that measure important disease-related symptoms that you would expect to see improvement in due to treatment"***

- FDA is flexible about validation necessary for endpoints in DM

- Instruments commonly used in the clinic may *not* be well suited for efficacy studies, e.g.
  - Overly long recall period
  - Hypothetical not actual abilities
  - Floor and ceiling effects
  - Overly broad or nonspecific
  - Problematic to combine signs and symptoms
    - *FDA interested in both, but measured separately*
    - *Correlation between signs and symptoms observed in natural history can be altered by drug*

Useful study design approaches

- Multiple FDA Guidance Documents can help guide study design
  - Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products
  - Adaptive Design Clinical Trials for Drugs and Biologic
  - Statistical Principles for Clinical Trials (ICH E9)
  - Dose-Response Information to Support Drug Registration (ICH E4)

And others…

Enrichment

- Clinical trials randomized, but *not* done in a random sample of the population. Make sure:
  - Patients have disease and/or subtype drug treats
  - Change can occur in endpoint being measured…
  - …in the period of time of the study
  - Endpoint can be reproducibly measured in each patient
  - Enrichment can also be based on patients that preliminary evidence suggests are responsive
    - Clinical or biomarker evidence

- *In rare serious diseases, no requirement to enroll patients who are less likely to respond*
- An important benefit will not be delayed to obtain information about other patient subgroups
- But clearly of great interest to study as soon as possible

Designs to Increase Data from Available Patients

- Crossover studies
  - Each patient serves as their own control, increasing study power
  - e.g. used to study periodic paralysis
- Parallel-arm + randomized withdrawal
  - Same patients in each; 2 separate studies
  - Can use biomarker-based enrichment
  - e.g. used to study “Non 24” (N = 20)

Adaptive Design

- Many well-understood approaches, e.g.
  - Adjust sample size, endpoints, statistical analysis, etc. based on blinded analysis of ongoing study
  - High-dose arm with unacceptable toxicity can often be dropped after unblinded analysis with no statistical penalty
  - Early stopping for efficacy or futility

Endpoints for Accelerated Approval

- adequate and well-controlled clinical trials establishing that drug has effect on a surrogate endpoint reasonably likely, based on evidence, to predict clinical benefit
- ***or*** an effect on a clinical endpoint other than survival or irreversible morbidity.
- requirement to verify and describe clinical benefit or ultimate outcome

Biomarkers vs Surrogate Endpoints

- Same types of measures
  - e.g. lab tests, histology, imaging
- Biomarkers useful in development even if evidence insufficient to support use as surrogate endpoint
  - Demonstrate pharmacodynamic activity
  - Dose-finding
  - Can provide important supportive evidence of efficacy even if not surrogates

Biomarker Assay Development

- Technical performance of assays is critical
  - reliably measuring what it's designed to measure
- A separate issue from potential clinical meaning
- Important no matter how biomarker used in drug development, from lead generation through surrogate endpoint

Assay Considerations

- The specific use determines the necessary assay characteristics and methods
  - e.g. might be acceptable if semi-quantitative or based on expert readers
- Objectives of assay should be established as early in development as possible

Assay Considerations

- Adequate controls
  - both positive and negative
- Adequate blinding
  - May need more formal process than used in most basic science laboratories
- Similar to clinical studies, need to pre-specify statistical analysis if intend to provide evidence to support approval

Assay Considerations

- In some basic research settings, may be common to dismiss negative results as “technical failure” and repeat assay without consideration of multiple-testing bias
- To provide support for FDA approval, reasonable technical reliability should be established first, and all subsequent data should be included in analyses
- Documentation of procedures and results should be at similar level as for clinical results

Thank You

Questions?