Regulatory Considerations for Trial Design in Myotonic Dystrophy

Myotonic Dystrophy Patient-Centered Therapy Development, September 17, 2015
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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?