Selection of Efficacy Endpoints for Optical Imaging Agents

Louis Marzella, MD , PhD
Director
Division of Medical imaging Products
CDER/FDA

Overview

- Regulatory considerations for efficacy studies applicable to medical imaging drugs in general
  - Strategic plan
  - Clinical trial development
  - Interactions with FDA
- Efficacy endpoints for optical imaging drugs

Strategic Planning Objectives

- maximize efficiency of studies and value of data
  - minimize bias
- enhance communications with regulators
- expedite drug development process

Clinical Development Plan

Overall strategy for clinical studies needed at the very early stages of drug development

- Begin with proposed indication for use
- Define indicated patient population, assessment of outcomes that demonstrate clinical utility
- Identify study population
  - Phase 1, 2 minimize heterogeneity, reduce variability
  - Phase 3 expand patient population , generalize

Clinical Development Plan

Clinical trial design and analysis considerations

- Selection of endpoints
  - efficacy e.g. precision and accuracy, diagnostic performance relative to reference standard
  - pharmacodynamic and biomarker of activity
- Pre-specified hypotheses, sample size, analysis plan

Selection of Efficacy Endpoints

Criteria to be considered

- Benefit: implied, shown through clinical outcomes
- Assay sensitivity
- Statistical efficiency
  - Variability of outcome, duration of assessment
- Trial phase

Efficacy Trial Endpoints

- Exploratory
  - development of hypotheses, pharmacodynamic measurements
- Primary
  - demonstration of efficacy
- Secondary
  - supportive of efficacy, provide information in subgroups for safety and efficacy

Considerations for Imaging in Phase 3 Clinical Trials

- Efficacy assessment
  - Anatomic or functional outcomes in trials of therapeutic drugs
    - ↓Radiologic joint space narrowing and erosions with DMARDS for RA
    - ↓Radiologically diagnosed fractures with therapeutics for osteoporosis
  - Performance (e.g. sensitivity, specificity) in trials of diagnostic drugs

Considerations for Drug Approval: Imaging vs. Therapeutic drugs

Similar regulatory process

- Evidence standards for safety and efficacy
- Risk-benefit considerations
- Marketing application
- Review procedures

Unique efficacy consideration for imaging drugs

Ability to provide clinically useful information (no clinical outcome measures necessary)

Efficacy of Optical Imaging Drugs: Unique Considerations?

Clinical value: Self-evident e.g.

- Increased conspicuity of poorly visualized structure in procedures associated with surgical complications. E.g. dye for visualization of ureters in laparoscopic procedures.
  - Historical control vs. parallel arm control
  - Primary Endpoint: objective measure of meaningful improvement in visualization
  - Secondary Endpoint: exclude an increase (define margin) in complication relative to historical experience or relative to parallel control

Efficacy of Optical Imaging Drugs: Unique Considerations?

Clinical value: Self-evident e.g.

- Debulking widely infiltrative tumors
  - Intra-patient control vs. parallel arm control
  - Primary endpoints: superiority in tumor resection (tumor mass weight, residual tumor on imaging)
  - Secondary endpoints: non-inferiority (defined margin) for loss of organ function/disability, survival, superiority in patient reported outcomes