“GREAT” Clinical Trial Endpoints in IBD: A Perspective of the Former FDA DGIEP Deputy Director (2010-2016)

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Partnership is the Key

“Coming together is a beginning; keeping together is progress; working together is success.”

Henry Ford

http://www.brainyquote.com/quotes/authors/h/henry_ford.html
Guidance for Industry on Ulcerative Colitis Trial Endpoints

Docket ID: FDA-2016-D-2319
Agency: Food and Drug Administration (FDA)
Parent Agency: Department of Health and Human Services (HHS)
Points for Discussion

1. Background of *i-IBD* and GREAT Conferences for the FDA  Ulcerative Colitis Guidance

2. Specific Guidance Comments and Issues Related to:
   1. Mucosal Healing
   2. Clinical response definition
   3. Extrapolation and Pediatric Issues
Strategic Goals

• FDA works hard to maintain public trust and further our global leadership role in fostering innovation by staying engaged in a variety of formal harmonization efforts with our international regulatory partners.

• The ultimate goals of these efforts being international harmonization/regulatory convergence, but also to minimize regulatory uncertainty for industry, while protecting and maximizing public health and safety.
International IBD (i-IBD) Working Group: 2012-2016

- Consists of regulatory scientists from:
  - U.S. Food and Drug Administration (FDA)
  - European Medicines Agency (EMA)
  - Health Canada
  - Pharmaceuticals and Medical Devices Agency of Japan (PMDA)

- **Goal:** To facilitate global harmonization on regulatory issues affecting drug development in Pediatric Ulcerative Colitis (UC) and Crohn’s Disease:
  1. Extrapolation
  2. Trial design
  3. Disease outcome assessments
  4. Efficacy endpoints
  5. Pharmacokinetic considerations
Alternate Endpoints and Clinical Outcome Assessments in Pediatric Ulcerative Colitis Registration Trials

• Conclusion:
  • Pediatric-specific endpoints were used, but outcome measures and definition of clinical response were not consistent in pediatric UC trials. Consensus on the definition of successful treatment outcome (clinical response and/or remission) and collaboration in the development of well-defined and reliable measures of signs and symptoms for use in conjunction with endoscopic parameters of mucosal healing will facilitate pediatric drug development.


Sun, Haihao; Lee, Jessica J.; Papadopoulos, Elektra; Lee, Catherine S.; Nelson, Robert M.; Sachs, Hari C.; Rodriguez, William J.; Mulberg, Andrew E.
Exposure as a Surrogate of Efficacy: Exposure Matching

Extrapolation

Partial

Single efficacy study

PK/PD, exposure/response, uncontrolled efficacy study

Full

PK/safety study

APPENDIX A²¹

Pediatric Study Decision Tree

Reasonable to assume (pediatrics vs adults)
✓ similar disease progression?
✓ similar response to intervention?

NO → YES TO BOTH

- Conduct PK studies
- Conduct safety/efficacy trials

Is there a PD measurement**
that can be used to predict efficacy?

NO → YES

- Conduct PK/PD studies to get C-R for PD measurement
- Conduct PK studies to achieve target concentrations based on C-R

YES

Reasonable to assume similar concentration-response (C-R)
in pediatrics and adults?

NO 

- Conduct PK studies to achieve levels similar to adults
- Conduct safety trials

YES
Pediatric Extrapolation Decision Tree

Is it reasonable to assume that children, when compared to adults, have a similar: (a) disease progression? (b) response to intervention?

- Yes to both
- Is it reasonable to assume a similar exposure-response (ER) in children when compared to adults?
  - Yes
  - Conduct PK studies to achieve drug levels similar to adults, then safety trials at the correct dose
  - “Full Extrapolation”
  - “Partial Extrapolation”

- No
- Is there a PD measurement that can predict efficacy in children?
  - No
  - Conduct PK studies to establish dose, then pediatric efficacy and safety trials
  - “No Extrapolation”
  - Yes
  - Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentrations based on ER, then safety trials at the correct dose
Steps towards Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis --- a Global Scientific Discussion
Part 1: Efficacy Endpoints and Disease Outcome Assessments

Steps towards Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis --- Global Scientific Discussion
Part 2: Data Extrapolation, Trial Design, and Pharmacokinetics

Well-Defined and Reliable Clinical Outcome Assessments for Pediatric Crohn's Disease: A Critical Need for Drug Development.
Ulcerative Colitis: Extrapolation

**Issue:** Although disease progression and response to intervention are sufficiently similar between pediatric and adult UC, the similarity of the exposure-response (E-R) relationship has not been adequately established to allow full extrapolation of efficacy from adult data.

**IBD perspective:**
- Until there is adequate evidence to support a sufficiently similar E-R relationship between adult and pediatric UC, *partial extrapolation* of efficacy from adequate and well-controlled adult trials is acceptable.
- In the absence of a validated PD marker, a clinical endpoint can be used to establish the E-R relationship.
Ulcerative Colitis: Trial Design

- For mild pediatric UC and during the maintenance phase of moderate to severe pediatric UC, the sponsors could consider:
  - placebo-controlled trial with an early escape option
  - 3-arm trial (product, placebo, active comparator) or a randomized withdrawal design
- Initiating pediatric trials at completion of adult efficacy trials but prior to marketing approval in adults will allow earlier labeling for children and facilitate recruitment without extensive off-label use.
Ulcerative Colitis: Disease outcome assessments

• **Issue:** No widely accepted disease outcome assessments are available (3 different indices used in approval of 2 pediatric UC products)

• **IBD perspective:**
  - Signs and symptoms represent one component of disease activity in pediatric UC
  - Endoscopic assessment equally important to include in clinical outcome assessment at this time
    - Blinded central reading of endoscopies recommended.
    - Ideally, the same outcome assessment(s) would be validated for use in both pediatric and adult patients to facilitate extrapolation of efficacy data from adults.
Ulcerative Colitis: Efficacy endpoints

**Issue:** For product labeling and correct use of the drug, well-defined, reliable, and clinically relevant endpoints that measure tangible benefits (how patients *feel, function, and survive*) are essential

**IBD perspective:**
- At this time, the primary endpoint should include both clinical and endoscopic findings.
- Timing of endpoint assessment(s) should be guided by the product’s mechanism of action and durability of its effect.
- Noninvasive biomarkers need further investigation to justify their use as clinically meaningful surrogate endpoints.
- Sponsors are encouraged to collect biomarkers prospectively.
Ulcerative Colitis: Pharmacokinetic considerations

• **Issue:** A PK study that achieves target concentrations similar to adults does not reliably result in appropriate dose(s) for children.

• *IBD perspective:*
  • PK study alone may be inadequate if there is a lack of understanding of the E-R relationship in children.
  • In the setting of partial extrapolation, PK/PD studies are needed to establish an E-R relationship that can link to the adult trial data.
  • A dose finding study that explores a range of doses (or weight-based dosing) should be conducted early in drug development.
  • Once a proper pediatric dose is determined, a safety trial may be conducted.
Concept of the GREAT Conference

- The purpose of this workshop is to provide a forum to consider issues related to endpoints that can support drug development in the following disease areas:
  - Pediatric and adult inflammatory bowel diseases.
  - Other GREAT conferences have focused on assessment of efficacy in Crohn’s disease trials in children and adults, including the use of patient-reported outcome (PRO) measures, endoscopic evaluation, and the role of registries and patient participation in inflammatory bowel disease drug development programs.
  - Parenteral Nutrition Associated Liver Disease
  - Eosinophilic Esophagitis
Concept of Collaboration

- The Food and Drug Administration (FDA) Center for Drug Evaluation and Research, in co-sponsorship with the American College of Gastroenterology, the American Gastroenterological Association, the Crohn's and Colitis Foundation of America, Inc., the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and the Pediatric IBD Foundation, is announcing a 2-day public workshop entitled “Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT II).”

- Partners and stakeholders planning the workshop also include patients and representatives from the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health.
Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT) Workshop

September 19, 20, 21 and 24, 2012
8:00 am to 5:00 pm (each day)

Holiday Inn
10000 Baltimore Avenue
College Park, Maryland
• ___ is interested in finding medicines that treat ulcerative colitis. Because of the challenges with development in this area, we suggest that the FDA continue to engage with the scientific community before the guidance is finalized. Continued discussions such as the Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT)

• Workshops provide the FDA the opportunity to discuss themes from the guidance with individuals from the research community, industry, and other patient and provider groups.
Key Issues Remaining

- Endpoint Measures
  - Signs/Symptoms and Endoscopy/Histology
    - Co-Primary Endpoints or Composite Endpoint
      - Mayo Score without PGA
  - Definitions of Clinical Remission and Disease Severity
    - Mild/Moderate vs. Moderate/Severe Paradigm
- Induction/Maintenance Paradigm
Co-Primary Endpoints or Composite Endpoint

<table>
<thead>
<tr>
<th>Scale</th>
<th>Instrument</th>
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| Signs and symptoms            | Well-defined and reliable Patient-Reported Outcome (PRO) Instrument:  
                                 | • Clear and easily interpretable  
                                 | • e.g., number of bloody stools (not quantity of blood in stools)  
                                 | • e.g., Bristol stool scale in conjunction for evaluation of diarrhea  
                                 | • Qualitative research  
                                 | • Confirm relevant signs/symptoms with pts/caregivers  
                                 | • Understanding of the instrument by pts |
| Endoscopic and histologic     | Well-defined and reliable Clinician-Reported Outcome (ClinRO) Instrument requires agreement by clinicians on:  
                                 | • Definitions of scale components,  
                                 | • Procedures necessary when performing the rating  
                                 | • Specific criteria to guide their judgments in selecting a response |
Mayo Score

- **SF:**
  - Stool frequency
    - 0 = Normal number of stools for this patient
    - 1 = 1-2 stools more than normal
    - 2 = 3-4 stools more than normal
    - 3 = 5 or more stools more than normal

- **RB:**
  - Rectal bleeding
    - 0 = No blood seen
    - 1 = Streaks of blood with stool less than half the time
    - 2 = Obvious blood with stool most of the time
    - 3 = Blood alone passed

- **PGA:**
  - Physician's global assessment
    - 0 = Normal
    - 1 = Mild disease
    - 2 = Moderate disease
    - 3 = Severe disease

- **Endoscopy:**
  - Findings of endoscopy
    - 0 = Normal or inactive disease
    - 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
    - 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
    - 3 = Severe disease (spontaneous bleeding, ulceration)
Timing of Assessments of Clinical Response and Clinical Remission

- What is the **clinical treatment goal** for the patient?
  - **Design the trials** with this goal in mind
    - *Labeling* that reflects the trial design
- Traditional design:
  - **Clinical Remission - Early (4-12 wks)**
    - *Induction Trial*
  - **Clinical Remission - Late (6-12 mo’s)**
    - *Maintenance Trial*
  - Re-randomization of clinical responders and clinical remitters

"**Induction of Clinical Remission**"  
"**Maintenance of Clinical Remission**"
IBD Trial Design Features

- **Sustained Remission (Durability)**
  - No re-randomization allows assessment of natural history of clinical remission
  - Assesses proportion of patients who respond or remit over time
    - Duration of induction at specified time point, e.g., 8 or 52 weeks
    - Concern of immunogenicity related to prolonged exposure
    - Drug exposure continues without assessing need to stop

- **Maintenance of Remission**
  - Requires re-randomization after induction of remission at defined time point
  - Cannot address potential of variability in time to induction of remission
  - Is design too strict to accommodate drugs with different mechanism of action and ability to induce remission?
    - Concern of immunogenicity related to intermittent exposure
    - Stopping drug exposure in one arm allows assessment of need for continued treatment
Importance of Phase 2 Data

1) Opportunity to determine when will have substantial portion of patients in Clinical Remission

2) Opportunity to determine the proportion of patients that will be slower to achieve Clinical Remission
   ▪ Time frame for achieving Clinical Remission in this group
   ▪ Subgroups:
     ➢ “endoscopic remitters” with residual symptoms vs.
     ➢ “partial responders” across all the assessments (including endoscopy)

3) Discuss role of mucosal histology