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**RARE DISEASE WORKSHOP SERIES**  
Improving the *Clinical Development Process*

Workshop #2

**Clinical Evaluation of Rare Disease Treatments**

June 14-15, 2011

**Welcome**

Emil D. Kakkis, M.D., Ph.D.

President, Kakkis EveryLife Foundation



# The Rare Disease Workshop Series: Why?

- Rare disease treatment development provides difficult challenges
- The typical approaches to clinical development may not work well
- Can we define better ways of approaching the development of treatment information
- *We can do better than we are doing now*



# Workshop Series Topics

- Workshop #1 Statistical analyses of rare disease studies
- Workshop #2 Clinical evaluation of rare disease treatments
- Workshop #3 Surrogate endpoints & accelerated approval
- Workshop #4 *Perfect* policy solutions: all things for all people



# Workshop #2: Clinical Evaluation of Rare Diseases

Morning Day 1

- Choosing an endpoint

Morning day 1

- Establishing an MID/responder definition

Afternoon day 1

- Developing a PRO for rare diseases

Morning day 2

- Rare disease experiences

Afternoon day 2

- Multi-domain assessment of rare diseases



# Workshop #2 Agenda: Day 1

## Choosing an endpoint

### Day 1 – Morning

8:00 - 8:30 am Registration and Breakfast

#### Clinical evaluation of rare disease: lessons learned in common diseases relevant to rare diseases

8:30 am Welcome

**Emil Kakkis, M.D., Ph.D.**, President, Kakkis EveryLife Foundation

8:40 am Introduction to the major questions and issues for evaluation of disease

**Tom Fleming, Ph.D.**, Prof. of Biostatistics and Statistics, University of Washington

9:00 am Clinical endpoint selection and interpretation

**John Powers, III, M.D.**, Senior Medical Scientist, NIH

9:20 am Selection of meaningful endpoints for patients

Either **Marc Walton, M.D., Ph.D.**, Associate Director, Office of Translational Sciences, OND, CDER, FDA or **Anne Pariser, M.D.**, Associate Director for Rare Diseases, CDER, FDA



# Workshop #2 Agenda: Day 1

## Assessing MID/Responder Definition

### Assessing minimum important difference/responder definition in clinical evaluation of rare diseases

- Strategies for developing and using MID in clinical efficacy evaluation
  - 10:40 am **Gordon Guyatt, M.D.**, Prof. of Clinical Epidemiology and Biostatistics, McMaster University
  - 11:10 am Discussion
  - 11:20 am **John Powers, III, M.D.**, Senior Medical Scientist, NIH
  - 11:50 am Either **Marc Walton, M.D., Ph.D.**, Associate Director, Office of Translational Sciences, OND, CDER, FDA or **Anne Pariser, M.D.**, Associate Director for Rare Diseases, CDER, FDA
- Assessing the responder definition in rare disease situations
  - 12:20 pm **Gerry Cox, M.D., Ph.D.**, Vice President of Clinical Research, Genzyme Corporation
  - 12:40 pm **Kathy Wyrwich, Ph.D.**, Senior Research Scientist, Center for Health Outcomes Research, United BioSource Corporation
  - 1:00 pm Lunch



# Workshop #2 Agenda: Day 1

## Patient Reported Outcomes

### Day 1 – Afternoon

- Exploring patient reported outcomes to support a label claim or to support the results of clinical outcomes
- 2:00 pm     **Emil Kakkis, M.D., Ph.D.**, President, Kakkis EveryLife Foundation — Introduction to PRO interpretation challenges for rare diseases: Aldurazyme response shift case example
- 2:05 pm     **Laurie Burke, R.Ph., MPH**, Associate Director, OND, CDER, and Director, Study Endpoints and Labeling Development, FDA — The latest FDA PRO Guidance translated to rare diseases
- 2:50 pm     **James Witter, M.D., Ph.D.**, Chief Science Officer, PROMIS & Medical Officer, NIAMS,NIH — Customizing a patient reported outcome for rare diseases and utilizing PROMIS tools
- 3:20 pm     **Nancy Kline Leidy, Ph.D.**, Senior Vice President, Scientific Affairs and Senior Research Leader, United BioSource Corporation – PROs



# Workshop #2 Agenda: Day #2

## Rare Disease Experiences

### Day 2 – Morning

8:00 - 8:30 am Breakfast

8:30 am Brief previous day review

**Emil Kakkis, M.D., Ph.D.**, President, Kakkis EveryLife Foundation

- Examples of development of clinical evaluation tools to assess degree of clinical benefit in neurological and rare diseases

8:50 am **Ron Crystal, M.D.**, Prof. of Genetic Medicine, Weill Cornell — Natural history data, development of LINCL clinical scale, interpretation of brain imaging scans

9:20 am **Ali Skrinar, M.A., MPH**, Senior Director, Clinical Research & Regulatory Affairs, Enobia Pharma — Development of rare disease evaluation tools

9:50 am Midmorning Break

10:10 am **P.K. Tandon, Ph.D.**, Senior Vice President, Global Biomedical Data Sciences and Informatics, Genzyme Corporation — Use of registry information to inform on clinical evaluation of rare diseases

10:40 am **Andy Blight, Ph.D.**, Chief Science Officer, Acorda Therapeutics — Successful application of patient reported outcomes



# Workshop #2 Agenda: Day 2

## Multi-domain assessment of rare disease

### Day 2 - Afternoon

- Evaluation of clinical benefit across multiple physiological domains
  - 12:55 pm **Emil Kakkis, M.D., Ph.D.**, President, Kakkis EveryLife Foundation — The necessity for improving the accessibility to multi-domain assessments in rare disease treatment development: A proposal for moving forward
  - 1:25 pm **L.J. Wei, Ph.D.**, Professor of Biostatistics, Harvard School of Public Health — Approaches and challenges to multi-domain analysis and study design
  - 1:45 pm **James Signorovitch, Ph.D.**, Manager, Analysis Group — Evaluation of various statistical approaches for multiple domains using data from three MPS studies



# General suggestions for today

- Let speakers complete their presentations
- Questions at end only for clarification
- Collect questions and prepare your answers for the discussion sessions
- The workshop is a safe zone
- Speak what we think and want based on our own experiences and insights



# Output and actions from the workshop

- All slides to be posted at [www.kakkis.org](http://www.kakkis.org)
- Video recording to be available
- Will consider writing review articles with multiple authors if discussion warrants
- Consider incorporating ideas in the policy workshop #4
- Provide information to key decision makers if relevant to policy decisions



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## Workshop #2 Agenda

# Choosing endpoints: How to do it?

### 9:40 am Discussion:

- What is the **conceptual framework** for understanding the disease as a whole, then selecting the most worthwhile and feasible of these endpoints to be measured in a clinical trial?
- When should a **previously used endpoint** versus an **untested endpoint** be used?
- How do we go about **qualifying a new endpoint** that has not been tested before?

### 10:25 Midmorning Break



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## Workshop #2 Agenda

# MID/Responder Definition: How to do it?

### 1:20 pm Discussion:

How should MID/responder definition be determined in rare disease situations: translation from other diseases or empirical testing in natural history or clinical data?

How should MID/responder definition be analyzed: As a method to interpret clinical meaningfulness of data after obtaining a positive statistical result, or built into the primary analysis?



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# Workshop #2 Agenda: Day 1

## Patient Reported Outcomes

### Adapting existing versus Custom Solutions

- **3:50 pm Discussion**

- For rare diseases, when should developers adopt existing common instruments as their primary strategy for using PROs, and when should they develop new, disease-specific instruments?
- How should a developer meet the guidelines set forth in the FDA PRO Guidance to qualify an endpoint while managing the challenges posed by rare disease drug development, both in adopting an existing instrument and developing one from scratch?
- Can PROs be used to support the clinical meaningfulness of clinical outcomes?



# End of Day #1

- Summary