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RARE DISEASE WORKSHOP SERIES
Improving the Clinical Development Process

Welcome to Workshop #3:
Use of Surrogate Endpoints in Rare Disease Treatment Development
November 8-9, 2011
Sofitel Hotel Washington, D.C. Lafayette Square

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President
EveryLife Foundation for
Rare Diseases



The EveryLife Foundation For Rare Diseases

- Formed to focus on improving the development of treatments of rare diseases in February 2009
- Conducting workshops and participating in conferences to help promote scientifically sound change
- Advocating for improvements and support for FDA
- Great successes in rare disease treatments do exist
- We hope to make the process better and more efficient to translate more science into medicine
- ***181 Foundation Partners***



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



Regulations and Guidances For Biomarkers in drug development

- Accelerated Approval Established 1992
 - Surrogate endpoints may be used in pivotal trials for articles used to treat serious or life threatening diseases with unmet medical need
 - *“Reasonably likely to predict clinical benefit”*
 - Included in amendment to the law in FDAMA
- Guidances for Industry
 - Qualification process for drug dev. tools (DDT)
 - E16 Biomarkers for development



Accelerated Approval in Rare and Ultra-rare diseases

- Challenges in qualifying a surrogate to be “reasonably likely to predict clinical benefit”
- Lack of prior clinical or any treatment data
- Lack of prior clinical studies or natural history
- Yet science and medicine may be solid and clear

Key question:

How do we practically qualify surrogates for use in ultra-rare diseases with little prior clinical experience?



Matthew Evangelista Child with MPS VII

- Disease treated in mice in 1993
- No humans ever treated
- How will we approach the ultra-rare diseases?



Using Biomarkers as Surrogate Endpoints in Clinical Development

AGENDA

Day 1 Morning

8:00 am	<i>Welcome and Opening Remarks</i>	Emil Kakkis, M.D., Ph.D.
8:10 am	<i>Surrogate markers in clinical development</i>	Thomas Fleming, Ph.D
8:40 am	<i>Biomarkers as Surrogates: Appraising Persuasiveness</i>	Marc K. Walton, M.D., Ph.D.
9:10 am	<i>The history and challenges of surrogate endpoints</i>	Emil Kakkis, M.D., Ph.D.
9:30 am	Discussion	
9:40 am	<i>Surrogate markers for urea cycle disorders</i>	Mendel Tuchman M.D.
9:55 am	<i>The development of Phe for PKU</i>	Emil Kakkis, M.D., Ph.D.
10:10 am	Discussion	
10:20 am	Midmorning break	
10:40 am	<i>Urinary Oxalate in Primary Hyperoxaluria</i>	Pontus Larsson, M.Sc
10:55 am	<i>GL-3: a urinary biomarker in Fabry disease?</i>	Pol Boudes, M.D.
11:10 am	<i>Urinary glucose tetrasaccharide for Pompe disease</i>	Sarah Young, PhD, FACMG
11:25 am	<i>Urinary GAG as a biomarker in MPS disorders</i>	Emil Kakkis, M.D., Ph.D.
11:40 pm	Discussion	
11:50 am	Lunch	



Using Biomarkers as Surrogate Endpoints in Clinical Development

Agenda Day 1 – Afternoon

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| 12:50 pm <i>Electrical impedance myography as a biomarker</i> | Seward B. Rutkove, M.D. |
| 1:05 pm <i>Advanced neuroimaging methods for urea cycle dis.</i> | Andrea Gropman, M.D. |
| 1:20 pm <i>X-linked Adrenoleukodystrophy</i> | Kathleen M. Zackowski, Ph.D., O.T.R. |
| 1:35 pm <i>Radiographic Endpoint for Hypophosphatasia</i> | Alison Skrinar, Ph.D. |
| 1:50 pm Discussion | |
| 2:00 pm <i>Chitotriosidase assay, surrogate endpoint in Gaucher</i> | Mariëtte van der Velden, MSc |
| 2:15 pm <i>The use of pathology surrogate markers in Fabry</i> | Beth L. Thurberg, M.D., Ph.D. |
| 2:30 pm Discussion | |
| 2:40 pm Afternoon break | |
| 3:00 pm <i>Spinal Fluid Substrate Markers in MPS I</i> | Agnes Chen, M. D. |
| 3:15 pm <i>Is CSF GM2 a Surrogate Marker for the GM2 Ganglio.?</i> | Shripad S. Bhagwat, Ph.D. |
| 3:30 pm <i>A prospective natural history study of MPSIIIA</i> | Patrick Haslett, M.D. |
| 3:45 pm <i>CSF substrate markers as predictors of CNS outcome</i> | Emil Kakkis, M.D., Ph.D. |
| 4:00 pm Discussion | |
| 4:10 pm <i>Opportunities and Challenges for Muscle Dystrophin</i> | John Babiak, Ph.D. |
| 4:25 pm <i>Semi-quantitative immunohistochemistry of dystrophin</i> | Diane Frank, Ph.D., |
| 4:40 pm Discussion | |
| 4:50 pm <i>Wrap-up of Day 1</i> | |
| 5:00 pm End of Day 1 | |