Rare Disease Clinical Trials
An Opportunity for Differentiated Services

Michael Murphy, M.D., Ph.D.
Chief Medical and Scientific Officer

Leslie Wetherell
Executive Director, Rare Disease Franchise
Redefining the Method
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POLL #1
Rare Disease Clinical Trials: An Opportunity for Differentiated Services

Redefining the Method
What Are They?

- Acromegaly
- Amyotrophic Lateral Sclerosis
- behavioral variant, Frontotemporal Dementia, Granulin mutation
- Bullous pemphigoid
- Cystic fibrosis
- Duchenne muscular dystrophy
- Down Syndrome
- Fabry disease
- Gaucher disease
- Growth hormone insensitivity syndrome (Laron Syndrome)
- Hemophagocytic lymphohistiocytosis
- Idiopathic pulmonary fibrosis
- Idiopathic thrombocytopenic purpura
- Juvenile idiopathic arthritis
- Lambert Eaton myasthenic syndrome
- Mucopolysaccharidosis I (Hurler syndrome)
- Mucopolysaccharidosis II (Hunter syndrome)
- Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)
- Niemann–Pick type C
- Pulmonary arterial hypertension (PAH)
- Sickle cell disease
- Hemophilia B
- Thrombotic microangiopathy: Thrombotic thrombocytopenic purpura (TTP)
- Von Willebrand disease
- Velocardiofacial syndrome, psychosis

What is an orphan indication?

- US = Fewer than 200,000
- Europe = 1/2000
- “Ultra” adds an additional dimension
- Genotypic- phenotypic variation
- Frequently multiple organ systems affected
- Coordinated multidisciplinary care
- Frequent transition points in clinical care
- Collectively, 7,000 diseases affecting 300 million people worldwide
... With an Opportunity to Apply Innovation

- Permissive science, innovative technology
- Novel and repurposed products
- Evolving regulatory climate
- Innovative, efficient study designs
- Diverse Measures
- Unique operational solutions
- Participatory research models
- Globalization in clinical research

http://www.21stcentech.com/genomics-key-defeating-orphan-diseases/
Creative Designs for Interventional Studies

Minimizing sample
- Adaptive randomization
- Longer trials, more events/patient
- Risk stratification
- Continuous and composite measures,
- “relaxed alpha’s”
- Bayesian frameworks

Maximizing treatment
- Imbalanced randomization
- Crossovers and permutations
- Factorial
- “n-of-one”
- Randomized placebo
- Stepped wedge and variations
- Randomized withdrawal

See Cornu et al, 2013; Gagne et al 2014
... With a Portfolio of Observational Options

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...That Can Answer Diverse Questions

To inform protocol design?
As a complement to a submission strategy?
To shape formulary & reimbursement decisions?

With many objectives
• Natural history of disease
• Burden of illness
• Treatment Pathways
• Disease Management
• Post-Marketing Usage (on & off label)
• Comparative effectiveness
... Noting Every Orphan is Uniquely Different

Behavioral Variant, Frontotemporal Dementia, Granulin Mutation
“medical monitor as an internal CMO”

Gaucher Disease
“design and operations are always linked”

Pulmonary Arterial Hypertension (PAH)
“everyone wants the same patients”

Thrombotic Microangiopathy: Thrombotic Thrombocytopenic Purpura (TTP)
“sometimes there is rare, and then there’s really rare”

Hemophagocytic Lymphohistiocytosis
“multinational studies, multilingual complex informed consents”
Defining The Box, Then Stepping Out Of It

- The conundrum of placebo?
- The contribution of historical data?
- Most sensitive and specific measures in a multi-organ disease state?
- Innovative designs?
- Hybrid monitoring strategies?
- Is a “one and done” registration strategy tenable?
Evidentiary Standards - Orphan Drug Approvals

**Conventional**: at least two adequate and well-controlled trials, each meeting primary endpoint, by pre-specified primary analysis, \( P \leq 0.050 \)

**Administrative**: two different methods, either affecting number of studies (e.g., single study) or type of evidence (subpart H).

**Case-by-case**

“...19, or just over two-thirds, of the 27 non-cancer orphan drugs approved between July 1, 2010, and June 30, 2014, were-based on some exercise of flexibility by FDA...”
A Strategy for “One-and-Done” Programs?

“Accelerated”-“Fast Track”-“Breakthrough”

“[t]here is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease.” (Guidance for Industry - Rare (b) (6) (b) (6)(b) (6)Diseases: Common Issues in Drug Development, August 2015).

“fewer, smaller, or shorter” clinical trials than is typical for a traditional approval…” (FDASIA Section 901(a)(1)(C))

“trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval.” (FDA Guidance for Industry: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment, June 2015)

Explore

• Given that primary outcome is significant; secondary measures are supportive and GCP compliance assured

Is this true?

• “Informative” study already exists?
• Registry with case-controlled matching contributes to evidence of efficacy to support approval [e.g. Illustrated by Cole et al, 2011 for Gaucher Disease]? 
• Prior clinical data & Post-marketing commitment to registry will support safety labelling?
But What if One Isn’t Enough?

Issues:
• Proposed surrogate endpoint ≠ a clinical endpoint
• No surprise-> population too heterogeneous to find differences
• Possibly predictable-> therapies dangerous in combinations
• Patient population drifted -> risk and response different
• “The Will Rogers Effect”

Conclusions:
• Not TA specific--Divergent results across all indications
• Not MOA specific--Across classes of investigational products
• Limited data -- > limited utility of benefit : risk assessment
... In the Case of Uncertainty— “Go Registry”?

Characterized

- Representative populations, representative providers
- Examination of “Interaction” effects
- Heterogeneous patient groups and disease trajectories

Objectives

- To inform safety
- To inform value
- To inform future trials
- To support registration?

Antonini, Graham, and Murphy, Worldwide Clinical Trials
Leslie Wetherell

Executive Director, Rare Disease Franchise
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Redefining the Art
POLL #3
Patient Focused Engagement

- Patients and families provide insight into the “illness” vs. the “disease”
- Patients can help define robust patient engagement strategy
- Fitting patients’ life into trials doesn’t work as well as fitting trial into patients’ lives
- Patient voice should be routinely solicited to ensure outcomes that matter most to patients are met
- Not all risks are equally accepted and not all benefits are equally valued
Patient Voice Throughout the Life of Trials and Beyond

- Preclinical
- Phase I - 3
- Filing
- Launch
- Post-Launch
Outreach, Support and Engagement Tactics

- Social Media
- Advocacy
- Local support groups
- Blogs/Forums
- Study Website
- Paid search ads

Raising Awareness
Fueling Interactions
Engaging Community
Patients Like Me

Social Media
Advocacy
Local support groups
Blogs/Forums
Study Website
Paid search ads
Specialized Study Teams

- Require experienced team and quick learners
- Thorough indication training required by medical monitor
- Distribution of sites and countries require far global reach
- Understanding of KOL and specialist referral sites
- Team must be dynamic and highly engaged on recruitment, retention and quality
- Understanding patient pathway of treatment and close follow up with site for study inclusion
Site Engagement

- Rare diseases may be treated by key opinion leaders with limited GCP
- CRAs must be able to engage at deeper level of understanding
- Need increased attention to detail support sites through activation
- Increased remote interaction with site
- Sporadic on-site activity
- CRAs to follow up on patient retention with study staff
- Ability to flex approach as needed
Quality Planning and Discipline

**Medical Input**
- MM review eligibility
- Prompt safety reporting and closure of reported events
- Automate lab alerts as they relate to endpoints or values of interest

**Data Quality**
- CRA on site for first patient dosing day if possible
- Real time remote data review
- Timely listing review
- Set criterion for increased on site monitoring

**Follow Through**
- KPIs/KQIs relevant to site
- Identify trends across sites or data fields
- Retrain teams as needed
- Increase monitoring as required
- Proactively avoid patient replacement
Final Thoughts

**Engagement**
Integration that transcends a transactional relationship

**Creativity**
“One eye on heaven, with both feet on the ground”

**Commitment**
“A sword in one hand, a pharmacopeia in the other”
Questions?

Contact:
Lynn Ledwith
Senior Vice President, Global Strategic Marketing & Commercial Operations
lynnledwith@worldwide.com
Thank You!

Contact:
Lynn Ledwith
Senior Vice President, Global Strategic Marketing & Commercial Operations
lynnledwith@worldwide.com