Advancing the Development of Therapeutics Through Rare Disease Patient Community Engagement

December 14, 2023 | 12:00 - 5:00 p.m. ET
Welcome & Introduction

Marianne Hamilton Lopez, PhD, MPA
Senior Research Director, Duke-Margolis Center for Health Policy
Agenda

- Opening Fireside Chat
- FDA Overview of Drug Review Process
  - Presentation
- Engaging Patients and Other Experts in Trial Design and Related Aspects of Drug Development
  - Presentation
  - Moderated Discussion and Audience Q&A
- Case Studies: Engaging Patients and Other Experts Throughout the Drug Development Process
  - Presentations
  - Moderated Discussion and Audience Q&A
- Where We’re at and Where We’re Going
  - Moderated Discussion and Audience Q&A
Statement of Independence

• The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

• For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.
Virtual Meeting Reminders

• Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.

• This meeting is being recorded, and the recording and slide deck will be posted on the Duke-Margolis event page in the weeks following the meeting.
Opening Fireside Chat

Marianne Hamilton Lopez, Duke-Margolis Center for Health Policy

Peter Stein, U.S. Food and Drug Administration

Nicole Verdun, U.S. Food and Drug Administration
FDA Overview of Drug Review Process

Robyn Bent & Teresa Buracchio

U.S. Food and Drug Administration
Patient-Focused Drug Development

Robyn Bent, RN, MS
CDER Patient Focused Drug Development
Office of the Center Director
Center for Drug Evaluation and Research (CDER)
PFDD Meetings and Patient Listening Sessions

Questions:

1. How might the information from Patient Focused Drug Development (PFDD) meetings and Patient Listening Sessions be used by medical product developers?

2. How does FDA use the information from PFDD meetings and Patient Listening Sessions during discussions with sponsors?

3. How does FDA use the information from PFDD meetings and Patient Listening Sessions as part of the marketing review process?

4. If a PFDD meeting or Listening Session is held early in the drug development process, and a marketing application is received by FDA some time later, how can we be sure that reviewers, including new reviewers, are aware of the previously held meeting?
# Condition-Specific Meeting Reports and Other Information Related to Patients' Experience

<table>
<thead>
<tr>
<th>Disease or Condition (alphabetical)</th>
<th>Type of Meeting</th>
<th>Resource(s)</th>
<th>Meeting Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td>EL-PFDD Meeting</td>
<td><a href="#">Meeting Report</a></td>
<td>January 21, 2021</td>
</tr>
<tr>
<td></td>
<td><em>Host: Acromegaly Community, Inc.</em></td>
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</tr>
<tr>
<td>Acute Porphyrias</td>
<td>EL-PFDD Meeting</td>
<td><a href="#">Meeting Report</a></td>
<td>March 1, 2017</td>
</tr>
<tr>
<td></td>
<td><em>Host: American Porphyria Foundation</em></td>
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<td></td>
</tr>
<tr>
<td>Adrenomyeloneuropathy (AMN)</td>
<td>Patient Listening Session</td>
<td><a href="#">Patient Listening Session Summary</a></td>
<td>May 7, 2021</td>
</tr>
<tr>
<td>Adult Dermatomyositis</td>
<td>Patient Listening Session</td>
<td><a href="#">Patient Listening Session Summary</a></td>
<td>April 26, 2022</td>
</tr>
<tr>
<td>Adult Polyglucosan Body Disease (APBD)</td>
<td>Patient Listening Session</td>
<td><a href="#">Patient Listening Session Summary</a></td>
<td>October 28, 2021</td>
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<tr>
<td>Alopecia Areata</td>
<td>FDA-led PFDD Meeting</td>
<td><a href="#">Agenda</a>, <a href="#">Slides</a>, <a href="#">Recordings</a></td>
<td>September 11, 2017</td>
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<tr>
<td></td>
<td></td>
<td><a href="#">Transcript</a>, <a href="#">Summary Report</a></td>
<td></td>
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</tbody>
</table>
Resources

Externally-Led Patient Focused Drug Development Meetings:
• https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings

Office of Patient Affairs- Patient Listening Sessions
• https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-sessions

Condition-Specific Meeting Reports and Other Information Related to Patients' Experience
• https://www.fda.gov/industry/prescription-drug-user-fee-amendments/condition-specific-meeting-reports-and-other-information-related-patients-experience
FDA Overview of Drug Review Process

Teresa Buracchio, MD
Director, Office of Neuroscience
Center for Drug Evaluation and Research
Disclosure

• This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred
• The materials presented are available in the public domain
Incorporating Stakeholder Perspectives into the Drug Review Process

• Patient Listening Sessions
• Patient-focused drug development meetings
• Engagement with stakeholders
  o Scientific meetings
  o Working Groups
  o Public-Private Partnerships
  o Research Roundtables
Drug Development

- Discovery/Nonclinical studies
- Early-Stage Development
- Late-Stage Development
- Post-Approval

Stakeholder engagement

IND: Investigation New Drug Application
NDA: New Drug Application
BLA: Biologics License Application
Multi-disciplinary review team

- Core Review Team
  - Clinical reviewers
  - Nonclinical reviewers (pharmacology/toxicology)
  - Clinical pharmacologists
  - Product quality reviewers (manufacturing)
  - Statistical reviewer

- Others:
  - Clinical outcomes assessments, pharmacovigilance/epidemiology, controlled substances staff, pediatric and maternal health, and more
- Identification of lead compound
- Small batches of product manufactured
- Initial studies in animals to assess toxicity and inform dosing

- Meets with sponsors, if needed, to discuss data to support an IND submission and initial clinical studies
- Interact with stakeholders

- Initial engagement with sponsor and FDA to facilitate understanding of the condition and drug development needs (e.g., natural history studies and development of outcome assessments, patient outreach)
• Submits IND
• Conducts initial studies to assess safety, tolerability, drug metabolism, and preliminary signals for efficacy

• Review of IND to ensure studies do not place human subjects at risk
• Review of submissions to IND (e.g., protocols, safety reports)
• Meets with sponsor to provide advice on development issues

• Continues engagement on drug development needs (e.g., endpoints)
• Provide patient’s perspective on benefit and risk (e.g., “clinically meaningful” benefit, acceptance of uncertainty, and tolerance of risk)
• Design and conduct of studies to demonstrate safety and efficacy
• Other activities to support development (manufacturing, nonclinical studies, pharmacology studies, etc.)

• Meetings with FDA to reach agreement on study design and endpoints for registration trials and discuss ability of data to support an application
• Review of protocols, statistical analysis plans, safety reports

• Provide input to FDA and sponsor on elements of trial designs (e.g., study endpoints, feasibility and burden of assessments)
Considerations for Clinical Trial Design

- Characteristics of the disease that may be amenable to treatment
- Anticipated effects of the treatment
- Size of disease population
- Rate of disease progression
- Heterogeneity of the disease
- Feasibility/Patient Burden
Innovation

• Goal to increase trial efficiency and maximize contributions of patients
• External controls
• Seamless trial designs
• Platform trials
• Decentralized trials
• Novel endpoints
Selection of endpoints

• Clinically meaningful vs. surrogate endpoints
• Characteristics of optimal endpoints
  o Can be reliably measured
  o Anticipated to be responsive to treatment
  o Able to demonstrate change during the duration of the trial
NDA/BLA Submission and Review

• Application includes human and animal data and analyses of that data and manufacturing information
• Initial filing decision based on adequacy of the data to support review
• Review takes into consideration input from stakeholders during the drug development process
• For approval, must meet requirements for “substantial evidence of effectiveness” and safety for its intended use; benefit-risk assessment supports use in intended population
• Traditional vs accelerated approval
• Advisory committee may be convened to advise on challenging issues
What is **benefit-risk assessment** in drug review?

**Evaluation** of the demonstrated benefits and risks of a medical product, and

Making a **judgment** as to whether the expected benefits outweigh the potential risks associated with its expected use

**Assessment** takes into account therapeutic context (e.g., seriousness of disease, available therapies, tolerance of risk, feasibility of additional studies)
Ongoing surveillance of safety and submission of periodic safety updates
Performs any post-marketing requirements (PMRs) (e.g., safety studies, registries, risk evaluation and mitigation strategies)
Potential for ongoing development in new indications or populations

Ongoing surveillance of safety (review of safety updates, published literature, MedWatch reports)
Advises sponsor on ongoing development activities (e.g., new indications or populations)

Continued engagement and input on ongoing post-marketing activities
Voluntary reporting of adverse events
Relevant Guidances


Engaging Patients and Other Experts in Trial Design and Related Aspects of Drug Development

Michelle Campbell
U.S. Food and Drug Administration
Engaging Patients and Other Experts in Trial Design and Related Aspects of Drug Development

Michelle Campbell, PhD
Office of Neuroscience
Center for Drug Evaluation and Research
Considerations for Clinical Trial Design

• What do We Know About the Population
  – Prevalence of disease
  – Disease progression
  – Heterogeneity
Considerations for Clinical Trial Design

• What do We Need for an Optimal Trial Design
  – Patient/Caregiver Lived Experience
  – Selection of Relevant Endpoints
    • Anticipated effects of treatment
    • Characteristics of disease that may be amendable to treatment
  – Any safety concerns with treatment
  – Feasibility to enroll population and minimize patient burden
  – Statistical analyses plan that can sufficiently evaluate trial data
Moderated Discussion and Audience Q&A

**Moderator:** Michelle Campbell, U.S. Food and Drug Administration

**Panelists:**
- Danielle Boyce, Tufts University School of Medicine
- Emma D’Agostino, Cystic Fibrosis Foundation
- Thomas Miller, Bayer
- Joe Horrigan, AMO Pharma
- Kelley Kidwell, University of Michigan School of Public Health
- Rebecca Chiu, U.S. Food and Drug Administration
Rare Disease Clinical Trial Needs

- Decrease number on placebo
- Allow all to receive active treatment at some point
- Allow continuation of treatment if response
- Dose-find and dose-confirm in the same trial
- Deal with heterogeneity of disease
- Use external data
- Robust conclusions with small numbers
  - Move beyond standard frequentist norms
snSMART Design: 3 active treatments

- Comparative effectiveness study
- No placebo = increased recruitment
- Goal: Estimate the first stage treatment effect of A, B, C using data from stages 1 and 2
- Outcome: binary (response rate) or continuous (score)
snSMART Design: Dose Find & Confirm

Fang, F, Hochstedler, KA, Tamura, RN, Braun, TM, Kidwell, KM. Bayesian methods to compare dose levels with placebo in a small n, sequential, multiple assignment, randomized trial. *Statistics in Medicine*. 2021; 40: 963–977

Fang, F, Tamura, RN, Braun, TM, Kidwell, KM. (2022) Comparing Dose Levels to Placebo using a Continuous Outcome in a Small n, Sequential, Multiple Assignment, Randomized trial (snSMART), *Statistics in Biopharmaceutical Research*,
Break

We will reconvene at 2:20 p.m. ET for the next session.
Case Studies: Engaging Patients and Other Experts Throughout the Drug Development Process
Case Studies: Engaging Patients and Other Experts Throughout the Drug Development Process

**Moderator:** Gerrit Hamre, Duke-Margolis Center for Health Policy

**Speakers:**
- Monica Morell, U.S. Food and Drug Administration
- Jen Farmer, Friedreich’s Ataxia Research Alliance
- John Sleasman, Duke University
- Connie Lee, Alliance to Cure Cavernous Malformation
- Lili Garrard, U.S. Food and Drug Administration
- Tejashri Purohit-Sheth, U.S. Food and Drug Administration
Success in Rare Disease Drug Development – Friedreich’s Ataxia

Duke Margolis – FDA Meeting, Dec 14, 2023

Jen Farmer, CEO, Friedreich’s Ataxia Research Alliance (FARA)
Disclosures

This is FARA’s version of events:
The Path of the First Treatment Approval for Friedreich’s Ataxia

FARA receives sponsorships from Reata for some of our programs.
None of this funding is linked to FA-COMS.

FARA does not have any financial interest or investment in the early discovery data that led to the development of compounds targeting the Nrf2 pathway.

FARA does not have any financial interest or investment in Reata Pharmaceuticals or commercialization of Skyclarys.
The Path to the First Approval for Friedreich’s Ataxia

2009
Nrf2 target first reported by research group in France

2013
California research group links Nrf2 to pathophysiology in FA Mice
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Reata: a company seeking out Reata: a company with a drug targeting the pathway
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Reata: a company with a drug targeting the pathway

2014
Reata responds with a compound they believe is a clinical candidate
Reata and FARA meet

Both attend a clinical development planning meeting at CHOP
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FARA
seeks out Reata: a company with a drug targeting the pathway

2015
First clinical trial launched
Moxie Part 1 Clinical Trial

CONTRIBUTIONS TO THE PART 1 STUDY

- Consulting on Trial Design
- Site Selection
- Recruitment!
- Interpretation of Results
- Planning Part 2 Study
MOXie Part 1 Clinical T

• Phase 2 Study: Two parts 2a and 2b
  • Double-blind
  • Randomized
  • Placebo-controlled
  • Dose-ranging
  • Multi-center
  • International trial
• 69 total patients randomized 3:1 to omav or placebo across 7 dose levels
• 12 week treatment duration

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First clinical trial launched

2017
Second clinical trial launched
Moxie Part 2
Pivotal Study

CONTRIBUTIONS
TO THE PART 2
STUDY

Trial Design: Data from FA-COMS (NH Study) informed power analysis
Regulatory alignment on outcome endpoint mFARS
Recruitment!
Investigator Meetings
Interpretation of Results
Moxie Part 2 Pivotal Study

• International, double-blind, placebo-controlled, randomized, registrational trial

• Largest global interventional study in patients with FA

• Enrolled a representative cohort with FA (16-40yrs)

• Participants randomized 1:1 to receive 150 mg omav or placebo for 48 weeks

• Primary endpoint: change from baseline in mFARS at Week 48

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2020
Multiple meetings with FDA

FARA
Friedreich’s Ataxia Research Alliance
Engagement in the Regulatory Process

CONTRIBUTIONS IN THE REGULATORY PROCESS

- Participation in sponsor-led FDA Meetings
- Communicating Patient Voice: Ex-Led PFDD Meeting & Report Petition
- FA-COMS awareness
- C-Path & FA-ICD Data availability
- Publication of Results and Interpretation of Data
Regulatory Guidance for Establishing Substantial Evidence for Efficacy

- FDAMA (115) recognizes 2 pathways allowing regulatory flexibility, requiring only one adequate and well-controlled trial
  - Seriousness of disease, particularly with unmet medical need
  - Size of the patient population
- Extremely low p-values that are “statistically very persuasive” are difficult in FA
  - Limited # of participants
  - Slow rate of progression (over four decades)

Single Trial Regulatory Pathways

Challenging to Meet in Rare Diseases Like FA

Omaveloxolone Regulatory Path

Other Adequate and Well-Controlled Clinical Trial with Statistically Very Persuasive, Compelling Results

One Adequate and Well-Controlled Clinical Trial Plus Confirmatory Evidence
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Second clinical trial launched

2020
Multiple meetings with FDA

2021
coordinates a petition to Reata and the FDA 74,000+ signatures!
Petition to Reata and FDA with overwhelming community support

74,070 individuals have signed on to the FA Community Response letter requesting Reata Pharmaceuticals submit a New Drug Application (NDA) on an urgent basis and FDA consider approval of an NDA for omaveloxolone in FA based on the existing evidence from clinical trials.

- North America: 38,539 • 52%
- Europe: 17,922 • 24%
- South & Central America: 12,348 • 17%
- Australia & New Zealand: 2,618 • 4%
- Africa: 1,492 • 2%
- Asia: 852 • 1%
- Middle East: 252 • <1%

*177 signers did not indicate a country
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Multiple meetings with FDA

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Coordinates a petition to Reata and the FDA 74,000+ signatures!

2022
Reata initiates rolling submission of NDA for omaveloxolone
Meeting Regulatory Guidance for Establishing Substantial Evidence for Efficacy

**Primary Evidence**

**MOXIe Part 2**
- 2.4 point improvement in mFARS (vs placebo) after 48 weeks of treatment ($p=0.14$)

**Confirmatory Evidence**

**Mechanism of Action**
- Nrf2 suppressed in FA.
- Omav induces Nrf2 targets with dose-dependent response associated with mFARS improvements.

**Delayed Start Analysis**
- Separation observed at Week 28 of MOXIe Part 2 maintained through Extension Week 144

**Propensity-Matched Analysis**
- Progression in mFARS slowed by 55% after 3 years with omav vs untreated patients in FA-COMS

**Safety**
- Well-tolerated, with few discontinuations or SAEs
- Fewer cardiovascular AEs
- No new safety findings in the MOXIe Extension Study

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Friedrich's Ataxia Research Alliance
The Path to the First Approval for Friedreich’s Ataxia

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First clinical trial launched

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Second clinical trial launched

2020
Multiple meetings with FDA

2021
FDA approves first-ever treatment for Friedreich’s ataxia: Skyclarys™

2022
Reata initiates rolling submission of NDA for omaveloxolone

2023
FARAP Associated Research

74,000+ signatures!
SKYCLARYSTM First and Only FDA Approved Therapy Indicated for Patients with Friedreich’s Ataxia

**Overview of Prescribing Information**

<table>
<thead>
<tr>
<th>Indication Statement</th>
<th>SKYCLARYS is indicated for the treatment of Friedreich’s ataxia in adults and adolescents aged 16 years and older</th>
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</thead>
<tbody>
<tr>
<td>Contraindications</td>
<td>None</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>None</td>
</tr>
<tr>
<td>Risk Evaluation and Mitigation Strategy</td>
<td>None</td>
</tr>
<tr>
<td>Dosing and Administration</td>
<td>Obtain ALT, AST, bilirubin, BNP, and lipid parameters prior to initiating SKYCLARYS and during treatment. Recommended dosage of SKYCLARYS is 150 mg (3 capsules) taken orally once daily.</td>
</tr>
</tbody>
</table>
| Warnings and Precautions | Elevation of Aminotransferases  
  Elevation of B-type Natriuretic Peptide (BNP)  
  Lipid Abnormalities |
| Adverse Reactions     | Elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain |

No contraindications or restrictions based on pes cavus, ambulatory, or cardiovascular status

No upper age limit or mFARS score restriction
Key Takeaways

Reliable, High-Quality Data

Essential datasets included:
- Mechanistic data
- Established, trusted Natural History study
- BLINDED open-label extension study

Published data:
- Transparency – from Reata & site investigators
- Led to scientific consensus

Collaboration

Both Reata and the FDA committed to:
- Multiple meetings
- Working together to apply regulatory flexibility
- Determination of the data sets necessary for valid confirmatory evidence
- Focused on quality data AND meeting regulatory standards

Communication

Consistent, open dialogue:
- Scientific community
  - Communicated clinical significance of the data
- FA community
  - Stayed informed & involved
  - Communicated the meaningfulness of the trial results and depth of need
- Regulators
  - Heard the community
  - Applied regulatory flexibility
Thank you to FDA, Reata, and the FA Community!
First use of Cultured Thymus Tissue Implantation (CTTI) in the Treatment of Congenital Athymia

December 14, 2023

John W. Sleasman, M.D.
Dr. Glenn A. Kiser and Eltha Muriel Kiser Professor of Pediatrics
Chief, Division of Allergy and Immunology
Duke University School of Medicine

Disclosures: Duke University receives royalties for the development of RETHYMIC (allogeneic processed thymus tissue-agdc). Dr. Sleasman receives grant support from Sumitomo Pharma, America, Inc.
Pathogenesis of Thymus Aplasia

Syndromic Features

- Dysmorphic Facies
- Hypoparathyroid
- Thymus aplasia
- Conotruncal Heart Defects

3rd & 4th Pharyngeal Pouches

Cellular Disruption
neural crest cells
TEC/stomal

Affected genes/syndromes

- TBX1 (22q11.2 deletion)
- CHD7 (CHARGE)
- FOXN1 ("nude-SCID")
- PAX1 (otofaciocervical)
- Diabetic Embryopathy

4th week of Fetal Development
### Timeline for the development of CTTI

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>1996</td>
<td>Improved thymus tissue culture methods developed</td>
</tr>
<tr>
<td>1997</td>
<td>First report of CTT treatment of infant with congenital athymia</td>
</tr>
<tr>
<td>1999</td>
<td>Report for first 5 infants with congenital athymia treated with CTT at DUMC</td>
</tr>
<tr>
<td>2007</td>
<td>Results reported for 44 infants with congenital athymia treated with CTT between 1993 and 2006 at DUMC</td>
</tr>
<tr>
<td>2014</td>
<td>Results reported for 59 infants with congenital athymia treated with CTT between 1993 and 2010 at DUMC</td>
</tr>
<tr>
<td>2018</td>
<td>SCID newborn screening implemented in all 50 states, Puerto Rico, Navajo Nation, and District of Columbia</td>
</tr>
<tr>
<td>2021</td>
<td>CTT approved as RETHYMIC® (allogeneic processed thymus tissue-agdc) by the US Food and Drug Administration for immune reconstitution in pediatric patients with congenital athymia (based on 1997 to 2020 results from 105 infants treated at DUMC)</td>
</tr>
</tbody>
</table>
Clinical outcomes of congenital athymia

Bone marrow

Absent Thymus

No thymic output
No T cell Immunity
Severe Infections

Aberrant T cell activation and differentiation

Autoreactive T cells

Autoimmunity
>40% of infants
Pre-therapy and post-therapy outcomes

Pre-CTTI Diagnosis

- CHD7 12 (11.4%)
- 22q11.1 del 38 (36.2%)
- FoxN1 3 (3.2%)
- TBX1 1 ((1%)
- TBX2 1 (1%)
- IDM 39 (41%)
- Unk 9 (8.6%)

Kaplan-Meier Estimate of Survival

CTT Clinical Trial Population (EAS; N = 95)

Censored

Natural History Population (N = 49)
Management Timeline for Congenital Athymia

Regular Pathogen Screening
- HSV, HHV6, CMV, EBV, Adeno
- Respiratory viral panels

Infection Prophylaxis
- TMP/SMZ 3x/week
- Weekly Azithromycin
- Daily Fluconazole
- SCIG/IVIG
- RSV prophylaxis (palivizumab)
Allogeneic processed thymus tissue-agdc (CTT)

Donors
- Unrelated infants ≤ 9 months undergoing heart surgery.
- Donor consent to use child’s thymus tissue, pathogen, immune screening.
- Tissue typing not required

Tissue processing
- Thymus tissue cultured for 12–21 days ex vivo
- Manufacturing process removes most donor T cells
- Thymus epithelial cells and tissue structure are preserved
- Sterility, endotoxin, and mycoplasma tested prior to release
- Dosing calculated surface area of slices/BSA recipient
Surgical Implantation of Cultured Thymic Tissue (CTT)

Drug product dish containing up to 4 CTT slices, each on a separate filter membrane, on up to 2 sponges
CTTI Implantation Reconstitutes Naïve T cells with Evidence of Functional Thymic Tissues

Reconstitution of Naïve T cells post CTTI

Biopsy of thymus tissue follow CTTI

b Markert et al, Postnatal thymus transplantation with immunosuppression as treatment for DiGeorge syndrome, Blood 104(8):2574-2581, 2004
Current treatment sites for Congenital Athymia

Duke University, Durham, NC
Great Ormond Street Hospital for Children, London, UK

U.S. Cost of RETHYMIC®
>$2.7 million
Sources for this presentation


ALLIANCE TO CURE
CAVERNOUS MALFORMATION

Working with Industry

Connie Lee PsyD
What is a Cavernous Malformation?

A **cavernous malformation** is a blood vessel abnormality characterized by large, adjacent capillaries with little or no intervening brain.

- These capillary malformations can occur anywhere in the central nervous system.
- The blood flow through these vessels is slow and can leak into the surrounding brain or spinal cord tissue, causing seizures, hemorrhage, and functional neurological deficits.
- There are sporadic and autosomal dominant familial forms of the disease.
- Only treatment is brain surgery, which is not always possible.
Working with Industry - 2 examples

- Identified and targeted BioAxone for our disease.
- Introduced company to animal model researchers for pre-clinical testing.
- Consulted on patient journey and trial design.
- Organized FDA CPIM meeting to discuss clinical endpoints and surrogates.
- Now in Phase 1 (Neurelis)

- CEO presented his research as a graduate student at our Scientific Meetings.
- Joined CAB.
- Participated in Type B and Type C FDA meetings as voice of the patient.
- Organized FDA Patient Listening Session to expand understanding of disease impact.
- Assisted with Ph 2 trial site development, CRO & staff education, recruiting, and development of PRO.
- Ph 2 enrollment completed ahead of schedule.
Where PAGs may add value

PAGs can have a role to play in pre-clinical research.

1. Advising on animal model choices and experiment design
2. Connecting industry with labs.

PAGs can partner in regulatory meetings

1. Regulatory - sharing the patient voice at sponsored-requested meetings.
2. Well-timed patient-requested meetings.
3. Some mentorship is required, but worth the investment.

PAGs can be full team members in rare disease clinical research:

1. Trial design, including endpoint identification
2. CAB recruitment
3. Site selection & introductions
4. Patient education & recruitment, including addressing diversity of participants
5. PROM development

Cautions

1. Not all diseases have PAG with scientific expertise, connections, etc.
2. Even mature PAGs vary in their strengths.
3. Working with a PAG without a service agreement is not in either party’s best interest.
Break

We will reconvene at 4:00 p.m. ET for the next panel discussion.
Where We’re at and Where We’re Going
Moderated Discussion and Audience Q&A: Where We’re at and Where We’re Going

**Moderator:** Victoria Gemme, Duke-Margolis Center for Health Policy

**Panelists:**
- Karin Hoelzer, National Organization for Rare Disorders
- Collin Hovinga, Critical Path Institute
- Jennifer Panagoulias, Foundation for Angelman Syndrome Therapeutics
- Saira Sultan, Haystack Project
- Bobby Wiseman, Patient Advocate
- Kerry Jo Lee, U.S. Food and Drug Administration
Closing Remarks

Marianne Hamilton Lopez, PhD, MPA

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