Energy in Action: Major Outcomes

from the

Externally-led Patient-Focused Drug Development Meeting

on

Mitochondrial Disease

Philip E. Yeske, Ph.D.

Science & Alliance Officer

United Mitochondrial Disease Foundation

Background: UMDF Regulatory Strategy

- Critical to begin a dialogue with FDA early in therapeutic development: **education and guidance**
  - Mitochondrial Disease: FDA Critical Path Innovation Meeting in 2015
- FDA wants to hear the patient perspective on therapeutic development: **patient-focused drug development**
  - Patients who live with a disease have a direct stake in drug review process and are in a unique position to contribute to drug development
  - The **Externally-led Patient-Focused Drug Development Meeting** format provides a forum for the FDA to listen and learn from specific disease communities about burden of the disease and what symptoms future treatments would ideally address
  - Letter of Intent submitted by UMDF to FDA in March 2018- approved!

Patient-Focused Drug Development

Two main goals of the Mitochondrial Disease EL-PFDD meeting:

- Provide broad mitochondrial disease patient perspective to the FDA by presenting testimony, discussing key topics and identifying treatment priorities

- Capture patient-provided data that will help to inform the design of future clinical trials with respect to outcome measures that are meaningful to those affected by mitochondrial disease

Importance of Collaboration

- ✓ Jointly develop program
- ✓ Jointly market meeting
- ✓ Jointly finance meeting
- ✓ Jointly share outcomes

Energy in Action

MITOCHONDRIAL DISEASE EXTERNALLY-LED PATIENT-FOCUSED DRUG DEVELOPMENT MEETING

MARCH 29, 2019 | HYATTSVILLE, MD

UNITED MITOCHONDRIAL DISEASE FOUNDATION®

MDA® Muscular Dystrophy Association

mito ACTION

Agenda: Morning Session

Clinical Overview of Mitochondrial Myopathy in Adults
Michio Hirano, MD, Columbia University, New York, NY

Introduction, Overview of Meeting, and Audience and Remote Demographic Polling for Adults with Mitochondrial Myopathies
James Valentine, JD, MHS, Meeting Moderator

Morning Session: Mitochondrial Myopathy - Adult Patient Perspective on the Burdens of the Disease and Current and Future Approaches to Treatments

Panel #1 – Symptoms and Daily Impacts
- Presentations by 5 Affected Individuals and Caregivers
- Audience and Remote Polling Panel #1
- Moderated Audience Discussion Panel #1

Panel #2 – Current and Future Approaches to Treatments
- Presentations by 5 Affected Individuals and Caregivers
- Audience and Remote Polling Panel #2
- Moderated Audience Discussion Panel #2

Morning Session Closing Remarks
Lucas Kempf, MD, Associate Director, Rare Disease Program, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

Morning Session Key Outcomes

Adult patients with mitochondrial myopathy continuously deal with very difficult issues in their daily lives, the most important of which include:

- Muscle weakness
- Chronic fatigue
- Gastrointestinal problems
- Pain
- Exercise intolerance

Specific activities of daily living that are most important to adult patients with mitochondrial myopathy but which they are unable to do include:

- Moving around independently and safely
- Understandable communication with others
- Walking and standing independently
- Understanding conversation in noisy settings
- Driving

Morning Session Key Outcomes

The most concerning social, emotional or economic consequences for adult patients with mitochondrial myopathy include:

- Social isolation
- Loss of hobbies or activities
- Loss of independence
- Loss of job or inability to get job
- Financial difficulties

The current state of managing adult mitochondrial myopathy is summarized as follows:

- Rest, careful planning of activities, and inactivity
- Diet management and trial-and error treatment with dietary supplements including a “mito cocktail,” which is often personalized and prepared at a compounding pharmacy
- Trial-and-error treatment with prescription medicines including pain medications, anti-depressants or anti-anxiety medications, heart medications and muscle relaxants
- ***Overall, only 17% of participants believe their medications, therapies and lifestyle changes have significantly improved their quality of life***

Morning Session Key Outcomes

New treatments for adult mitochondrial myopathy should focus on the following unmet needs:

- Reduction in chronic fatigue and reduction in muscle weakness are most important
- Reduction in pain, gastrointestinal problems and exercise intolerance are also desired
- Gain in function (e.g., energy, strength, mobility, dexterity, cardiac function, speech) is highly desired
- Slowing / stopping disease progression is very meaningful
- Prolongation of life is important, but not the primary focus

Adults mitochondrial myopathy patients are most likely to use a new medication or participate in a clinical trial based on:

- Lack of serious side effects, which is most important
- Cost
- Burden of administration
- Common side effects

Agenda: Afternoon Session

Clinical Overview: Neurologic Manifestations in Children with Mitochondrial Disease
Amy Goldstein, MD, Children's Hospital of Philadelphia, PA

Audience and Remote Polling – Attendee Demographics for Children with Neurologic Issues
James Valentine, JD, MHS, Facilitator

Panel #3 – Symptoms and Daily Impacts
- Presentations by 5 Parents and Caregivers
- Audience and Remote Polling Panel #3
- Moderated Audience Discussion Panel #3

Panel #4 – Current and Future Approaches to Treatment
- Presentations by 5 Parents and Caregivers
- Audience and Remote Polling Panel #4
- Moderated Audience Discussion Panel #4

Afternoon Session Closing Remarks
Larissa Lapteva, MD, MHS, MBA, Associate Director, Division of Clinical Evaluation, Pharmacology, and Toxicology, Offices of Tissue and Advanced Therapies, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)

Next Steps and Closing Remarks
Philip Yeske, PhD, UMDF Science and Alliance Officer, and Brent Fields, UMDF Trustee Chair

Afternoon Session Key Outcomes

Pediatric patients with neurologic manifestations of mitochondrial disease are highly disabled and progressive and their families continuously deal with very difficult issues in their daily lives, the most important of which include:

- Muscle weakness
- Chronic fatigue
- Gastrointestinal problems
- Speech problems
- Delayed milestones
- Swallowing difficulties
- Learning disability
- Movement disorders
- Seizures
- Exercise intolerance
- Pain

Afternoon Session Key Outcomes

Specific activities of daily living that are most important to pediatric patients with neurologic manifestations but which they are unable to do include:

- Gross motor activities (moving independently, walking, standing, sports)
- Communication
- Fine motor activities
- Going to school or work
- Personal hygiene

The most concerning social, emotional or economic consequences for pediatric patients with neurologic manifestations of mitochondrial disease include:

- Frustration
- Social isolation
- Communication issues
- Loss of independence
- Modified school/work hours
- Lack of hope for the future

Afternoon Session Key Outcomes

The current state of managing pediatric patients with neurologic manifestations of mitochondrial disease is summarized as follows:

- Many types of prescription medications are used to manage a variety of symptoms. Seizure medications, anti-depressants or anti-anxiety medications, pain medications, and muscle relaxants are the most commonly used.
- Diet management and nutritional modifications including the use of a G-tube, J-tube or TPN (Total Parenteral Nutrition), and trial-and error treatment with dietary supplements including a "mito-cocktail" (which is often personalized and prepared at a compounding pharmacy)
- Modifications and accommodations
- Physical therapy
- Occupational therapy
- Speech therapy
- Use of adaptive devices
- Infectious disease management and immunotherapy, including IVIG
- ***Overall, only 23% of participants believe their medications, therapies and lifestyle changes have significantly improved their quality of life***

Afternoon Session Key Outcomes

New treatments for pediatric patients with neurologic manifestations of mitochondrial disease should focus on the following unmet needs:

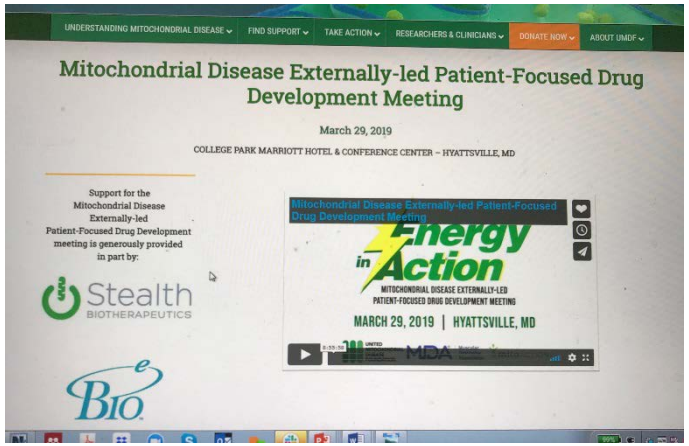
- Reduction in fatigue and muscle weakness are most important
- Improvement in gastrointestinal problems, speech, seizures, pain, movement disorders and swallowing difficulties are also desired
- Gain in function (e.g. energy, strength, mobility, dexterity, cardiac function, speech) or slowing / stopping of disease progression (even without gain in function) are both highly desired
- Prolongation of life is also very important

Caregivers and pediatric patients with neurologic manifestations of mitochondrial disease are most likely to use a new medication or participate in a clinical trial based on:

- Lack of serious side effects, which is most important
- Burden of administration
- Common side effects
- Length of treatment
- Cost and/or travel

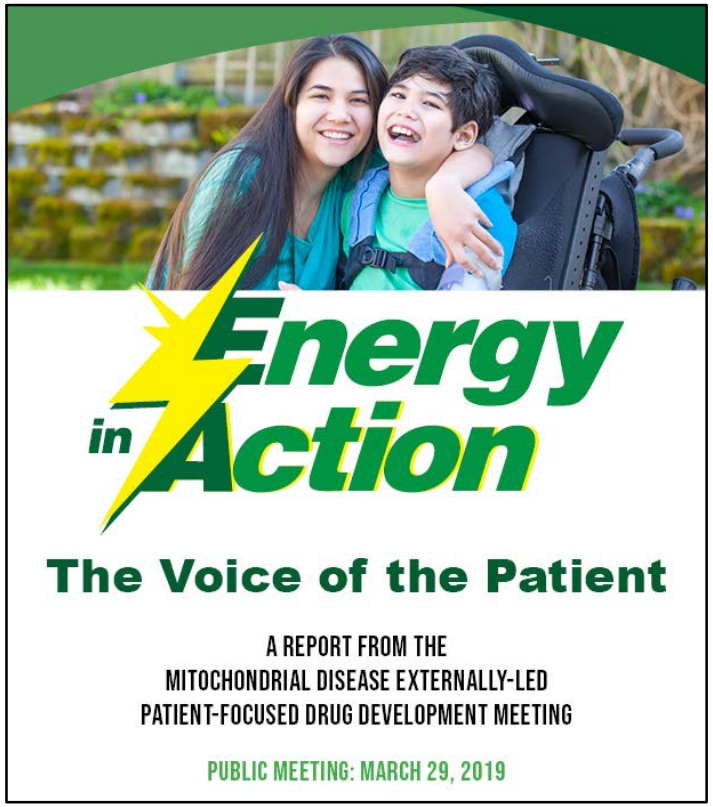
Meeting Reach

- 125 attendees in-person
  - Patients/Caregivers/Families
  - Industry
  - FDA personnel
- 170 unique participants viewed live-stream of meeting
  - Peak viewing at 80 participants
- Over 500 views of 9-hour meeting recording
  - Average per viewing watch time of 45 minutes
  - https://www.umdf.org/pfddmeeting2019/



Post-Meeting Activities

- Online survey
  - 30 day survey exploring meeting topics in greater detail
  - Additional response options, including free text
  - 225 unique responses received from 10 countries!
- Meeting transcript
  - Every word of every speaker captured
- The Voice of the Patient Report
  - Complete meeting summary
  - Drafted pending FDA approval
- FDA Workshop – September 2019
  - Focus on clinical trial readiness



Post-Meeting Activities

- Collected a LOT of data and patient feedback
  - Will help inform future patient perspective studies
  - Prime opportunity to explore utilizing registry tool
- Mitochondrial Disease Community Registry
  - ~2,400 participants
  - Software upgrade will bring roll out new features starting in Q3 2019
  - Paper in preparation summarizing data collected over 5 years

Mitochondrial Disease Community Registry (MDCR): First look at the data, perspectives from patients and families

S. Zilber and P. Yeske

EL-PFDD Panelists – THANK YOU!

Energy in Action



















UNITED MITOCHONDRIAL DISEASE FOUNDATION.

MDA Muscular Dystrophy Association

mito ACTION