



Memorandum

Date: November 18, 2015

Subject: Critical Path Innovation Meeting Regarding Drug Development for Mitochondrial Diseases

Date of meeting: October 19, 2015

Requestor: Mitochondrial Disease Clinical Trials Working Group

Note: Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants.

ATTENDEES

The attendees are listed at the end of this document.

1. BACKGROUND

Dr. Falk requested the CPIM on behalf of the Mitochondrial Disease Clinical Trials Working Group (referred to as MDCTWG in this document), a consortium formed from the North American Mitochondrial Disease Consortium (NAMDC) and the United Mitochondrial Disease Foundation (UMDF) advocacy group.

2. DISCUSSION

The meeting began with the MDCTWG presenting an overview of the diversity of mitochondrial diseases, the state of current patient data repositories, the need to be patient-centered, and thoughts about potential designs of clinical trials. FDA asked for thoughts on the use of placebo as a control for clinical trials in mitochondrial diseases. Dr. Thompson, the discussant who presented about clinical trial designs, stated that he favored a placebo control. FDA expressed that in general a placebo control provides the best opportunity to discern treatment effects and is ethically justified in most situations, as all patients would continue to receive standard of care. FDA encouraged the use of randomization and a placebo control from the earliest stages of clinical development. This could help avoid the perception by patients that a drug in development has been proven to be efficacious based on early open-label data, as such perceptions make placebo controlled trials more difficult to enroll during later stages of clinical development.

FDA noted that it has experience with clinical development programs for numerous inborn errors of metabolism, and a hallmark of these diseases is their heterogeneity. For many of these diseases, lack of knowledge of natural history (the course of the disease in the absence of effective therapies) is a

challenge for drug development. FDA stated that the progress described by the MDCTWG in obtaining natural history data, especially in a longitudinal manner, is encouraging.

FDA stated that the lack of approved therapies for mitochondrial diseases means there is no precedent for drug development and no established endpoints. FDA may apply flexibility in the development and review of therapies to treat rare diseases (due to the limitations imposed by the restricted availability of patients with such conditions), however, approval of these therapies must be based on demonstration of “substantial evidence of effectiveness” from adequate and well-controlled investigations, a regulatory standard applied to all drug applications. Because approval relies on adequate and well-controlled investigation, they require a control to allow discrimination of patient outcomes caused by the study drug from outcomes caused by other factors, such as a disease. The use of an external control from natural history data can be problematic and should generally be reserved for situations when the course of untreated disease is uniform and outcomes can be predicted reliably. Using a historical control is most likely to be persuasive when the study endpoint is objective, when the outcome on treatment is markedly different from that of the non-treated group. Use of a baseline control (patients’ baseline characteristics serving as their own control) poses real challenges, but may be appropriate in selected situations.

Standard approval relies on demonstration of efficacy in terms of a clinically meaningful benefit, such as how a patient feels or functions or the effect on survival. The second pathway is “accelerated approval”, in which surrogate endpoints are reasonably likely to predict clinical benefit or an early clinical outcome measure are used for initial approval. In the case of an accelerated approval based on such an endpoint, FDA would have to understand the relationship of the change in the endpoint to clinically meaningful outcomes. At the time of approval under an accelerated pathway, a confirmatory trial measuring clinically relevant endpoints is expected to be ongoing. Psychometric data collected from patients is likely to be important. In addition, it will be important to conduct a trial to test the direct clinical impact of the treatment.

FDA stated that because of the likelihood that trials in rare diseases such as mitochondrial diseases will be global, it is especially important to design and maintain controls over the quality of the conduct of these trials.

MDCTWG asked whether patients for clinical studies should be defined genetically, biochemically, or phenotypically. FDA responded that a disease may have to be defined in terms of more than one of these categories, and that may depend on the endpoint(s) selected to demonstrate efficacy. Several approaches to dealing with the heterogeneity of mitochondrial diseases were discussed, including the use of a composite primary endpoint or an individualized primary endpoint. The primary and secondary endpoints of a clinical trial will depend on the individual disease, or subtype of disease under study. FDA is flexible in trial design, but it would be important to justify what would constitute a clinically meaningful change for any given endpoint. Research on outcomes can be initiated early in a drug development program. FDA stated that we are available to discuss endpoints and other aspects of trial design in the context of a proposed drug at a pre-IND meeting. Given the complexity of clinical trials in rare diseases, FDA encourages sponsors to seek advice early in the development program. FDA emphasized that in a rare disease clinical program every datapoint is important and trial quality and good data management are essential for success.

MDCTWG stated that supplement use is widespread in patients with mitochondrial disease and asked what FDA standards exist for supplements as contrasted to drugs. FDA stated that the standards are different because the claims are different. Drugs are approved based on a claim of efficacy in the cure, treatment, or prevention of a disease. A supplement could be approved as a drug, but this would depend on the claims being made, and each component of the supplement would have to conform to drug quality standards and be proven to contribute to efficacy. MDCTWG stated that some mitochondrial disease patients are on numerous supplements. FDA stated that while discontinuing the use of supplement use during the conduct of a clinical trial may be ideal in order to limit confounding, there is no requirement to do so. However, allowable supplement use should be standardized before and during the clinical trial (e.g., patients should be on a stable dose of allowable supplements for a prespecified period prior to trial enrollment, and changes to supplements should not be made during the treatment phase of the clinical trial). In addition, stratifying randomization based on baseline supplement use may help to ensure the treatment arms are similar for comparison.

MDCTWG stated that some biomarkers of mitochondrial disease vary with the phenotype of disease, and can even have daily variation. They may be labile biochemically. Some appear to be specific to mitochondrial disease and some nonspecific. FDA stated that it might be useful to screen multiple biomarkers for their association with different phenotypes of disease to determine the usefulness of those biomarkers in a clinical trial. This research can be initiated in natural history studies.

FDA stated that we are available to discuss the issues presented at this meeting, in the context of a proposed drug program, at a pre-IND meeting. FDA stated that we could consider another CPIM, focusing on some of the issues presented at this meeting, such as the development of a clinical outcome assessment (e.g., PRO, ObsRO). In addition, FDA has a biomarker qualification program in which FDA evaluates candidate biomarkers for their suitability for use in multiple different drug development programs (website for additional information <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm>)

Appendix: Attendees

FDA

Center for Drug Evaluation and Research

Office of Translational Sciences (OTS) Immediate Office

Shashi Amur, Ph.D., Biomarker Qualification Program Scientific Coordinator

ShaAvhrée Buckman-Garner, M.D., Ph.D., F.A.A.P., Director

James Kaiser, M.D., CPIM Scientific Lead

Susan McCune, M.D., Deputy Director

Ameeta Parekh, Ph.D., Senior Advisor for Scientific Collaborations

Sarmistha Sanyal, Ph.D., ORISE Fellow

Alicia Stuart, Project Manager

OTS Office of Clinical Pharmacology

Michael Pacanowski, Pharm.D., M.P.H., Supervisory Pharmacologist,

Vikram Sinha, Ph.D., Director, Division of Pharmacometrics

Office of New Drugs (OND) Immediate Office

Jonathan Goldsmith, M.D., FA.C.P., Associate Director, Rare Diseases Program

OND Division of Gastroenterology and Inborn Errors Products

Dragos Roman, M.D., Ph.D., Acting Deputy Director,
Laurie Muldowney, M.D., Acting Clinical Team Leader
Dina Zand, M.D., Medical Officer

Center for Food Safety and Applied Nutrition

Office of Nutrition, Labeling, and Dietary Supplements (ONLDS)

Shawne Suggs-Anderson, MMSc, R.D., Consumer Safety Officer, Infant Formula and Medical Foods Staff
Carrie Assar, Pharm.D., M.S., Acting Director, Infant Formula and Medical Foods Staff

ONLDS Division of Dietary Supplement Programs

Robert Durkin, Esq., M.S., R.Ph. Acting Director
Cara Welch, Ph.D., Acting Deputy Director

REQUESTER

Requester Discussants

Mitochondrial Disease Clinical Trials Working Group (MDCTWG)

Kathryn Camp, M.S., R.D., Office of Dietary Supplements (ODS), National Institutes of Health (NIH)
Marni Falk, M.D., Children's Hospital of Philadelphia, University of Pennsylvania
Richard Haas, M.B., B.Chir., M.R.C.P, University of California San Diego
Michio Hirano, M.D., Columbia University, North American Mitochondrial Disease Consortium (NAMDC)
Danuta Krotoski, Ph.D., National Institute of Child Health and Human Development, NIH
Frank Sasinowski, J.D., M.P.H., M.S., National Organization for Rare Disorders
J.L.P. (Seamus) Thompson, Ph.D., Columbia University, NAMDC
Philip Yeske, Ph.D., The United Mitochondrial Disease Foundation (UMDF)

Representative Academic Researchers in Mitochondrial Disease Therapeutics

Carlos Moraes, Ph.D., University of Miami
Peter Stacpoole, Ph.D., University of Florida

Representative Pharmaceutical Companies in Active Mitochondrial Disease Clinical Trials

Matthew B. Klein, M.D., Edison, Pharmaceuticals, Inc.
William Lang, M.D., Raptor Pharmaceuticals, Inc.
Colin Meyer, M.D., Reata Pharmaceuticals, Inc.
Nicholas Coppard, Ph.D., Santhera Pharmaceuticals Holding Ltd.
John C. Campbell, Stealth BioTherapeutics

Family and Advocacy Group Representatives

Charles Mohan, UMDF CEO
Richard Leach, J.D., Parent
Elizabeth Kennerly, Patient

Web-Only Participants

Mitochondrial Disease Community Clinicians, Researchers, Pharma, Patients, and Advocates