Duchenne Platform Trial Stakeholder Meeting

September 9, 2019
Sheraton Silver Spring
Silver Spring, Maryland

Sponsored by:

Table of Contents

1 Agenda

7:30 am **Registration and Continental Breakfast**
Cypress Ballroom

8:30-9 am **Welcome and Introduction**

Abby Bronson, MBA, Parent Project Muscular Dystrophy
Ed Connor, MD, MBE, Institute for Advanced Clinical Trials for Children
Jane Larkindale, DPhil, Critical Path Institute

9-9:30 am **Opening Remarks**

Janet Woodcock, MD, U.S. Food and Drug Administration
Billy Dunn, MD, U.S. Food and Drug Administration

9:30-10 am **The DPT Protocol in Practice**

Scott Berry, PhD, Berry Consultants

10-10:30 am **Overview of the DPT Proposed Protocol**

Deborah Ascheim, MD, d2a ltd.

10:30-10:45 am Q & A

10:45-11 am BREAK

11 am-Noon **Panel Discussion 1: Protocol Objectives and Eligibility**

Moderators: Abby Bronson, Scott Berry

Panelists:
Joanne Donovan, MD, PhD, Catabasis Pharmaceuticals
Michael Panzara, MD, MPH, Wave Life Sciences
Oscar H. Mayer, MD, Children's Hospital of Philadelphia
Paula Clemens, MD, University of Pittsburgh
Gretchen Egner, Parent/Advocate

Noon-12:45 pm LUNCH

12:45-1:45 pm Panel Discussion 2: Endpoints and Schedule of Events

Moderators: Deborah Ascheim, Jane Larkindale

Panelists:
Craig McDonald, MD, University of California, Davis
Tina Duong, MPT, Stanford University
Linda Cripe, MD, Nationwide Children's Hospital
Jodi Wolff, PhD, Santhera
Roxana Dreghici, MD, Roche
Beth Bumgarner, Parent/Advocate

1:45-2:45 pm Panel Discussion 3: Operations and Governance

Moderators: Jane Larkindale, Deborah Ascheim

Panelists:
Laura Lee Johnson, PhD, U.S. Food and Drug Administration
Marianne Chase, BA, Massachusetts General Hospital
Russell Butterfield, MD, PhD, University of Utah
Karla Kramer, Parent/Advocate

2:45-3 pm BREAK

3-4 pm Q&A - Parent Commentary and Advocacy Perspective

Moderator: Pat Furlong, Parent Project Muscular Dystrophy

4–4:15 pm Key Take-Aways from Panel Discussions and Next Steps

Deborah Ascheim

4:15–4:30 pm Closing Remarks

Abby Bronson
Ed Connor
Jane Larkindale

2 Introduction

The Duchenne Platform Trial (DPT) Stakeholder Meeting included parents of patients and representatives from advocacy organizations, industry, academia, medical professionals and therapists and the Food and Drug Administration (FDA). The goals of this meeting were to 1) discuss the draft Duchenne muscular dystrophy (DMD) master protocol and the rationale for the DPT with key stakeholders, 2) obtain feedback, build consensus and seek active community engagement and 3) delineate next steps and timelines for the master protocol and the DPT.

There was overarching agreement from all stakeholders regarding the purpose of the DPT: namely, *to optimize the efficiency of DMD clinical trials and to accelerate the clinical development of promising new therapies.*

In her opening keynote address, Dr. Janet Woodcock (Director, Center for Drug Evaluation & Research, FDA) emphasized that "the goal isn't to test just one intervention or one dose, it's really to progressively improve disease outcomes over time. That is patient-centered drug development. We will know what to do and what will give the best outcomes and multiple things can be tested." She also noted that "the [other] advantage here is the ability to study multiple arms and generate natural history data as you go; you can also look at biomarker data and look at all sorts of functional outcome data; learn; and make iterations to the trial."

Successful platform trials are ongoing in oncology indications, Alzheimer's disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), Crohn's disease and most recently in Ebola. While these trials are complex, they represent an important innovation in drug development and FDA has provided leadership and guidance in the development of a platform trial for DMD.

In his opening remarks, Dr. Billy Dunn (Director, Division of Neurology Products, CDER, FDA), said, "While we know these trials are challenging, the allure to do it is high. The ability to create a dynamic living trial that moves along with care and research is a tremendous opportunity. Yes, we [FDA] are ready to work on these trials in Duchenne. These trials are the future and we are happy you [the Duchenne community] are on the cutting edge."

During the meeting, stakeholders discussed key elements of the master protocol design and implementation in a panel format, with input, questions and comments from attendees. A summary of the meeting topics related to potential action items for the draft DPT master protocol is included below.

3 Summary of Key Meeting Topics Related to the Protocol

3.1 Protocol Objectives and Eligibility

Age and functional limitations of DMD patients at various stages of the disease were major discussion points, since these factors limit some boys' eligibility to enter clinical trials. Some stakeholders were interested in including patients < 5 years of age to collect important natural history data and to allow them to be randomized once they are eligible. For this younger patient population, discussion centered on the endpoints that could be measured and patients' ability to follow directions and complete assessments.

Different stages of pulmonary decline occur as DMD progresses, with clinically meaningful decline occurring in later stages, so functional status and other relevant clinical inflection points will need to be considered in finalizing the pulmonary function criteria. One suggestion was to change the exclusion criteria for forced vital capacity (FVC) to < 30% predicted instead of < 35% predicted to allow for broader inclusion of patients.

There was discussion about clarification that a sponsor can add inclusion/exclusion criteria to its appendix protocol in case of specific safety concerns. It also was suggested that criteria be updated to include a waiting period (e.g., 6 months or 1 year) for patients who choose to withdraw from the study. The current protocol does not allow these patients to re-enroll.

3.2 Endpoints and Schedule of Events

Participants suggested that endpoints should include the lowest number of assessments possible to minimize burden to patients, but also to provide the best markers of change in disease severity in a broad population. Implications for eventual insurance-coverage decisions also need to be considered when finalizing the endpoints for the DPT. Assessment procedures and training will be standardized across study sites to optimize consistency in measurements and quality of the data. This standardization should include information about thresholds and "inflection points" (e.g., scoliosis, contractures, noninvasive ventilation) that can affect the ability to collect some endpoint data. There was generalized agreement that data detailing clinical thresholds and inflection points should be collected at baseline and over time.

Concerns were raised about the reliability and relevance of pulmonary function tests (PFTs) in patients < 6 years of age. Some stakeholders recommended starting the PFTs at 5 years of age. Other stakeholders recommended using timed function tests (TFTs) for 5- to 6-year-old patients

to determine the point at which patients in this age group can follow instructions and provide reliable data, at which time PFTs would be initiated.

Dr. Scott Berry's presentation discussed a proposed concept of using primary endpoints that measure "disease slowing," measured with different instruments depending on the stage of disease. For example, lower extremity physical function tests could be used for younger/ambulatory patients, upper extremity physical function tests could be used for older/non-ambulatory patients and PFTs used for latest-stage patients. This framework could be introduced in the statistical analysis section of the protocol.

During this session, participants commented on endpoints to consider, including:

- **TFTs, including 10-m walk/run, 4-stair climb test and supine to stand.** Some stakeholders said they believe these TFTs are clinically meaningful and will show rate of progression.

- **6-minute walk test (6MWT).** Participants had a robust discussion of the pros and cons of the 6MWT. Some stakeholders said they think the 6MWT is clinically meaningful and more responsive than other timed tests, while many others had significant reservations about the test. It was noted that several current and former trials have used the 6MWT and thus it provides historical context for interpretation – and that (since it was included) payers may require 6MWT as qualification for certain treatment. It also was suggested that given that sponsors have used the 6MWT in the past, they may prefer its inclusion in the master trial. On the other hand, patients' mood/motivation and subjectivity issues were noted by many stakeholders as factors that render the 6MWT less valuable as an endpoint in clinical trials. Over time, use of the 6MWT has decreased in frequency in DMD trials. In general, motivationally dependent tests have not been preferred by regulators, although this may differ in the US and EU. Lastly, if 6MWT is added to the battery of tests, it was suggested that this be put later in the testing order, so that it does not interfere with the collection of other physical functioning data.

- **Cardiac magnetic resonance imaging (MRI) and echocardiography (echo).** Some stakeholders said they believe cardiac MRI offers more information on how an investigational product affects the heart, but concerns were raised about the use of MRI in younger patients. Stakeholders generally recommended using echo for safety endpoints only.

- **Strength testing.** Adding grip strength was suggested by several stakeholders as an additional measure of upper extremity functioning.

- **Pulmonary function testing (PFT).** Stakeholders generally agreed that the following should be measured:
    - Forced Vital Capacity (FVC), because this includes both inspiration and expiration.
    - Forced Expiratory Volume in 1 second (FEV1), although this measure does not add more information than FVC except in the youngest patients, who may not be able to perform FVC correctly.
    - Inspiratory Flow Reserve (IFR), which may be useful for older patients.

The discussion regarding endpoints also included consideration of endpoints that could be removed from the current draft of the master trial protocol:

- **Brooke Upper Extremity Scale.** Stakeholders commented that this measurement appears redundant, since the information is collected in the entry item for the Performance of Upper Limb test (PUL 2.0), which is included in the protocol.

- Among **PFTs,** stakeholders generally agreed that maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are variable in this population and thus are not useful endpoints in this trial.

3.3 Operations and Governance

The organization of governance for the master protocol is a critical element and while committee names and structure may be modified, the group discussed main concepts for governance. The recommended Steering Committee for the DPT will include DMD scientific/clinical experts as well as parents and advocates. Among other activities that will evolve over time, the Steering Committee will manage protocol amendments, determine which protocols and therapies are included in the DPT and create a publications/communications subcommittee. During the meeting, it was suggested that a Therapy Evaluation Subcommittee be included to make scientific recommendations to the Steering Committee. It also was anticipated that a representative from the sponsor of an Appendix would chair an Appendix Committee that reports to the Steering Committee.

The Data Monitoring Committee and Safety Monitoring Committee for the DPT will include independent clinicians, scientific experts, biostatisticians and ethics experts.

In addition to the plans presented, participants suggested that review by the TREAT-NMD Advisory Committee for Therapeutics be considered for proposed DPT protocols to provide

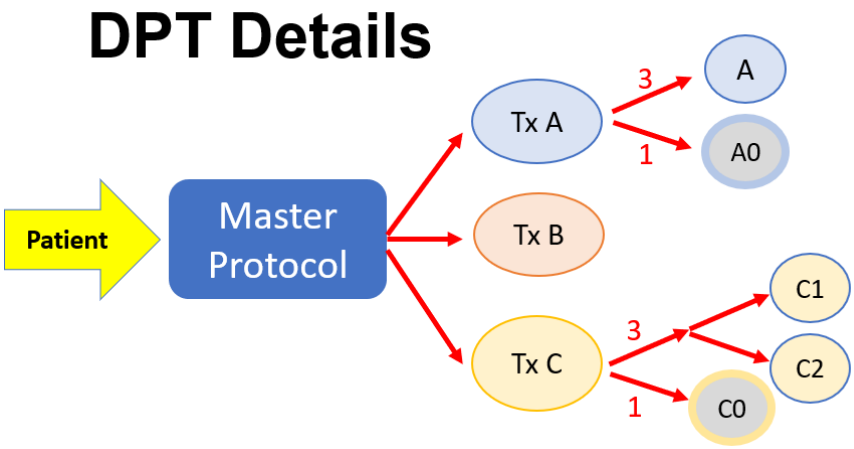
independent, unbiased scientific advice to the steering committee, leveraging an existing entity. It also was noted during the meeting that the plan is to use common centralized committees (e.g., Adjudication Committees, core labs) whenever feasible. Standardized and common core case report forms (CRFs) will be used and are expected to be helpful to the study sites in maximizing their efficiency. They also will standardize data for submission to FDA.

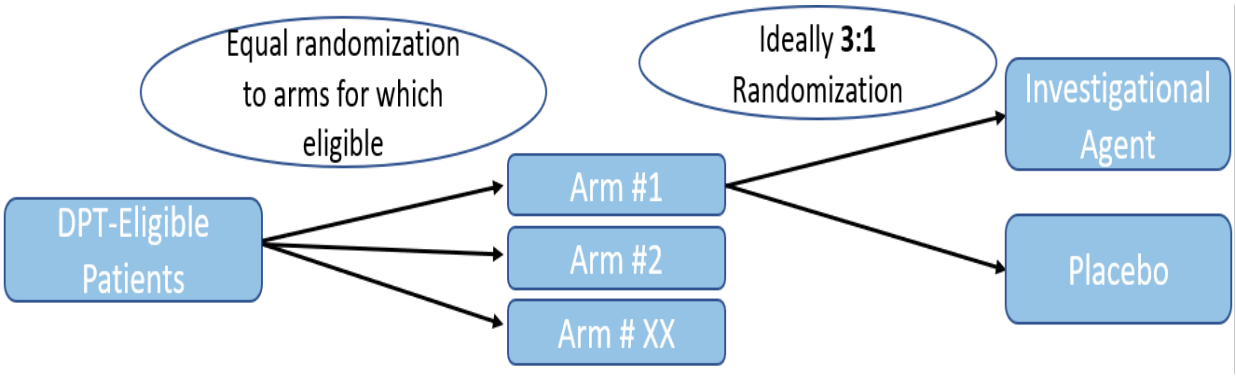
3.4 Additional Items to Consider for the DPT Protocol

Industry representatives were interested in the global approach and adaptability of the DPT outside of the United States. If this infrastructure were made global, it seemed this would be more appealing to sponsors. Sponsors were concerned with the economics of using the DPT for their trials and all agreed that it should provide cost savings or at least be cost neutral. Sponsors also were interested in incorporating a paired registry to aid in enrollment efforts.

The concept of a platform protocol will need considerable and ongoing education for all stakeholders. I-ACT for Children and other collaborators will need to optimize the processes for educating patients, parents and the study sites about the DPT.

With that in mind, it was suggested that the protocol be updated with one or both of the below figures that were included in slide presentations at the meeting. These could be incorporated into Section 4: Study Design:




Equal randomization to arms for which eligible
Ideally 3:1 Randomization
DPT-Eligible Patients
Arm #1
Arm #2
Arm # XX
Investigational Agent
Placebo