REGULATION

PATIENTS LEAD THE WAY

BY EMILY CUKIER-MEISNER, SENIOR WRITER

FDA's draft guidance on Duchenne muscular dystrophy and related dystrophinopathies is the culmination of an extensive effort led by a patient advocacy group that enlisted the support of patients, caregivers, academia and industry.

DMD drug development has been hindered by a lack of defined outcome measures and understanding of surrogate markers or biomarkers that could support approval. To address this, FDA invited Parent Project Muscular Dystrophy (PPMD) and the DMD community to submit a proposed draft guidance that could clarify a clinical development pathway for approval.

FDA spokesperson Kristofer Baumgartner said in a statement to BioCentury that PPMD's submission is the first time in the Center for Drug Evaluation and Research's knowledge that an advocacy group has submitted a proposed draft guidance, and that this type of engagement is an example of how early input from patients and caregivers can contribute to drug development.

PPMD President and CEO Pat Furlong told BioCentury that the group and its collaborators spent years looking for ways to ensure that DMD studies and endpoints would be sensitive to both effective therapies, and benefits that are meaningful to patients and caregivers.

"What we didn't want to have happen is trials that would fail because there weren't sufficiently sensitive measures to understand what was happening, or what was of benefit, or what the patients wanted and needed to see," she said.

PPMD partnered with John Bridges, an associate professor at the Johns Hopkins Bloomberg School of Public Health, to conduct a study that would address one piece of the puzzle: how DMD patients and caregivers perceive benefits and risks. Results from the study were published in 2014 in *Clinical Therapeutics*.

Meanwhile, companies and research institutions in the space were gathering natural history data to help interpret endpoints that may not be consistently sensitive across different stages of the disease.

Both those topics came into play at a December 2013 public-private policy forum, at which PPMD laid out its case to FDA that the state of knowledge was mature enough for a guidance.

She said FDA declined to draft a guidance itself, citing time and resource constraints, but invited the DMD community to submit its own.

To create the guidance, PPMD assembled seven work groups and one steering committee, each of which included patient advocates, industry members and academics. It also enlisted assistance from parties that worked with the AIDS advocacy community, including advisors such as Treatment Action Group Executive Director Mark Harrington.

Each work group researched and wrote one section of the proposal on topics such as benefit and risk considerations, natural history, outcome measures and biomarkers. Furlong said PPMD circulated a draft document among as many other patient groups as it could to capture a broad community perspective.

> "WHAT WE DIDN'T WANT TO HAVE HAPPEN IS TRIALS THAT WOULD FAIL BECAUSE THERE WEREN'T SUFFICIENTLY SENSITIVE MEASURES TO UNDERSTAND WHAT WAS HAPPENING, OR WHAT WAS OF BENEFIT, OR WHAT THE PATIENTS WANTED AND NEEDED TO SEE."
>
> PAT FURLONG, PARENT PROJECT MUSCULAR DYSTROPHY

She said to avoid relying on anecdotal evidence, PPMD included only data that were published or scheduled for publication by its self-imposed submission deadline of June 2014.

That September, FDA created a public docket for interested parties to comment on PPMD's proposed draft, and FDA's resulting draft guidance was published last week.

The recommendations in the agency's and PPMD's drafts are quite similar, apart from the agency continuing to prefer placebo-controlled studies, while PPMD preferred historical controls or placebo-sparing designs.

SENSING THE SPECTRUM

FDA's document emphasized the importance of collecting efficacy data across a broad range of disease stages, and hints at how sponsors might do so given that few endpoints appear sensitive across the full spectrum of disease. It also encourages sponsors to assess multiple efficacy endpoints when feasible, as well as multiple biomarkers to help further science in the field.

The guidance listed several suitable clinical endpoints according to the stage of disease where they were most likely to show meaningful benefit: the North Star Ambulatory Assessment and timed function tests in ambulatory children aged 4-7; myometry in children 5 years or older; and the six-minute walk test (6MWT) in ambulatory children.

But it cautioned that analysis of the 6MWT can be challenging, depending on the proportion of patients who become unable to walk during a trial.

In addition to functional endpoints, the guidance also said respiratory or cardiac endpoints could be used to show effectiveness; however, it did not specify when they might be sensitive.

The guidance is less clear on how sponsors might resolve the quandary of both studying a broad population and finding an endpoint that would be meaningful across it. But it did propose that sponsors select one endpoint as the primary efficacy measure and include multiple additional endpoints to help "characterize the breadth of effects on dystrophin-related pathologies."

"SPONSORS MAY HAVE A WAY FORWARD, EVEN IF A TRIAL FAILS ON THE PRIMARY ENDPOINT BUT SHOWS CONSISTENT EVIDENCE OF EFFECTIVENESS, ON THE BASIS OF SEVERAL ENDPOINTS THAT POINT IN THE SAME DIRECTION."

THOMAS MEIER, SANTHERA

The document encouraged sponsors to propose and develop endpoints sensitive to a wide spectrum of symptoms and disease stages, for example, by combining measures of ambulation and upper body function. Such endpoints could help avoid analysis-confounding "floor" or "ceiling" effects that could occur if a patient can no longer complete the functional measure of an endpoint, or retains that ability consistently throughout the study.

The guidance noted that several clinical endpoints could also serve as the basis for accelerated approval, such as myometry or certain respiratory measures.

Dystrophin was identified as a "potential surrogate endpoint for accelerated approval," though the guidance asked sponsors to consider other biomarkers, such as those measured non-invasively with magnetic resonance imaging or magnetic resonance spectroscopy.

HESITANT OVER HISTORY

Furlong said FDA's guidance did a good job of incorporating patient perspectives from both PPMD's draft and meetings with FDA.

"It reassured me that they learned from the policy forums in which patients talked about what they feel would be useful in terms of their lives, what small change might make a great deal of difference that you wouldn't ordinarily think about," she said.

FDA didn't go as far as the DMD community hoped on the subject of placebo- vs. externally controlled trials.

PPMD's draft said there is "widespread support in the DMD community to move away from placebo-controls," and asked sponsors conducting placebo-controlled trials to consider designs that "limit exposure to placebo."

But FDA's guidance said randomized, placebo-controlled trials are "strongly recommended" to demonstrate efficacy. It did not completely eschew externally controlled trials; however, it said such trials "generally are persuasive only when drug effects are large on objective endpoints that are less susceptible to bias."

Furlong hoped that improved understanding of biomarkers and development of more sensitive efficacy measures would extend the circumstances under which FDA would accept historical controls.

FDA's guidance included one suggestion for speeding drug development beyond the PPMD proposal: certain non-clinical assessments like carcinogenicity, renal or hepatic impairment studies of some dystrophinopathy products could be postponed until after approval, if scientifically justified.

PATHS AHEAD

BioMarin Pharmaceutical Inc. and PTC Therapeutics Inc. used 6MWT as the primary endpoint for registrational studies of their DMD therapies.

PTC CEO Stuart Peltz said FDA's focus on endpoint sensitivity across different disease stages echoed the process that PTC went through in its clinical development program for Translarna ataluren. He said that process included studying the natural history of the disease to characterize the sensitivity of 6MWT as an endpoint.

"Now we have enough natural history data that shows it does change, and there is good correlation between the 6MWT and loss of upper arm function, loss of ambulation and wheelchair use," he said.

Translarna, a small molecule that facilitates complete translation of proteins containing nonsense mutations, has conditional approval in the EU to treat nonsense mutation DMD. PTC plans to complete a rolling NDA submission to FDA this year.

Last month BioMarin completed submission of a rolling NDA for drisapersen, an antisense oligoribonucleotide that induces exon 51 skipping on the dystrophin gene.

Sarepta Therapeutics Inc. used dystrophin-positive muscle fibers as the primary endpoint in its Phase IIb program for eteplirsen and 6MWT as an additional endpoint. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) targeting exon 51.

Sarepta is in the process of submitting a rolling NDA to FDA, which it expects to complete by mid-year. A confirmatory Phase III study of eteplirsen using 6MWT as the primary endpoint is under way.

Santhera Pharmaceuticals Holding AG used a different endpoint, peak expiratory flow, for its Phase III DELOS trial of Catena idebenone, a short-chain benzoquinone, because it is studying more advanced patients who are primarily non-ambulatory.

Peak expiratory flow is a measure of respiratory muscle strength. CEO Thomas Meier said Santhera discussed the endpoint with FDA before beginning the trial, and was glad to see it endorsed in the guidance.

Meier also said he was encouraged that FDA's guidance set down in writing that the agency would consider the totality of evidence when assessing benefits and risks of DMD treatments.

"Sponsors may have a way forward, even if a trial fails on the primary endpoint but shows consistent evidence of effectiveness, on the basis of several endpoints that point in the same direction," he said.

He offered another suggestion for demonstrating efficacy across a broad range of disease stages: prespecified analyses that weigh efficacy measures differently according to patient subgroup.

Last week Santhera said it expects a second pre-NDA meeting with FDA for Catena after the company completes a collaboration with the Cooperative International Neuromuscular Research Group (CINRG) to compare outcomes of the completed DELOS trial of Catena with data from the CINRG Duchenne Natural History Study. Meier said the company will provide an updated timeline for NDA submission after the meeting.

PUSHING THE LIMIT

Furlong said PPMD's next task is to convene a public forum to discuss the FDA guidance and remaining challenges in DMD drug development.

She said the group plans to collect perspectives on benefits and risks from mothers of babies with DMD, and from adult patients over 20 — groups that are typically not included in clinical trials.

Furlong said PPMD also hopes to develop efficient pathways of studying combinations of therapies for DMD, which may be necessary if different treatments address different aspects of the disease.

"If you get a signal in a trial that this is having an effect, when do you have sufficient safety data and efficacy signal to be able to say this patient is free to receive compound Y?" she asked.

COMPANIES AND INSTITUTIONS MENTIONED

BioMarin Pharmaceutical Inc. (NASDAQ:BMRN), Novato, Calif.
Cooperative International Neuromuscular Research Group (CINRG), Washington, D.C.
Johns Hopkins Bloomberg School of Public Health, Baltimore, Md.
Parent Project Muscular Dystrophy (PPMD), Hackensack, N.J.
PTC Therapeutics Inc. (NASDAQ:PTCT), South Plainfield, N.J.
Santhera Pharmaceuticals Holding AG (SIX:SANN), Liestal, Switzerland
Sarepta Therapeutics Inc. (NASDAQ:SRPT), Cambridge, Mass.
Treatment Action Group (TAG), New York, N.Y.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

REFERENCES

Cukier-Meisner, E. "History lesson." *BioCentury* (2014)

FDA. "Duchenne muscular dystrophy and related dystrophinopathies." (2015)

Peay, H.L., et al. "A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy." *Clinical Therapeutics* (2014)