Pathway
Development
Consortium

AAV-Gene Therapy for Duchenne Muscular Dystrophy:
Finding a path forward for meaningful clinical endpoints in clinical trials

Introduction

The need for meaningful endpoints for use in clinical trials of potential new therapies for Duchenne muscular dystrophy (Duchenne) was the focus of an inaugural roundtable held virtually on April 6, 2021, by the Pathway Development Consortium.[1] The lack of validated and clinically meaningful endpoints across the disease spectrum has been a key stumbling block in development of gene therapies and other treatments for Duchenne. The primary goal of therapies in development is to stop further loss of function, meaning that endpoints need to be sufficiently sensitive to identify small changes that might indicate potential to retain function. A short-term surrogate endpoint that is reasonably likely to predict clinical benefit would be a major step forward.

There is an opportunity for potential Duchenne treatments to benefit from the type of timely, collaborative approaches used successfully to help overcome other major medical product development challenges for serious diseases with unmet medical need – such as developing vaccines to protect against COVID-19, a cure for hepatitis C, and therapies that transformed HIV/AIDS from a fatal disease to a manageable, chronic one. In addition, FDA has issued regulations at 21 C.F.R. § 312 Subpart E intended to speed the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies, while preserving appropriate standards for safety and effectiveness. The combination of this collaborative approach with the regulatory flexibility addressed in FDA's Subpart E regulations is key to addressing the unmet medical need seen in Duchenne and could also benefit the development of adeno-associated virus (AAV) gene therapies for other serious conditions.

Through collaborative work and partnership between patients, industry, regulators, academia, payers and other stakeholders, the Pathway Development Consortium aims to construct an ideal pathway to ensure that all children born with serious genetic conditions can benefit from effective AAV-gene therapies.[2] The goal of this new public-private partnership is to lay the foundation for addressing challenges and creating opportunities specific to each part of the pathway from diagnosis to managing and even curing the disease. The roundtable was the Consortium's first workstream, intended as a forum to promote scientific and policy interchanges among key Duchenne stakeholders. The event included over 120 attendees.[1]

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[1] *Participants included companies working on AAV-gene therapy for Duchenne (e.g., Audentes Therapeutics, REGENXBIO, Solid Biosciences, Roche, Ultragenyx), government agencies (FDA, NIH), Duchenne patient advocacy groups (CureDuchenne, Muscular Dystrophy Association, Parent Project Muscular Dystrophy), professional organizations (American Society of Gene & Cell Therapy, EveryLife Foundation for Rare Diseases, Genetic Alliance), academia (Stanford, University of California Davis), collaborative science-based organizations (Casimir Trials, Critical Path Institute, Collaborative Trajectory Analysis Project), law firms (FoxKiser, Hyman Phelps & McNamara), and regulatory policy consults (iPolicy Solutions, Prevision Policy), and others.*

Duchenne background

Duchenne is a rare disorder caused by mutations in the dystrophin gene. Estimates of Duchenne prevalence range 0.9 to 16.8 per 100,000 males, with birth prevalence estimates ranging from 1.5 to 28.2 per 100,000 live male births.[3] In 2017, there were estimated to be 16,840 diagnosed cases of Duchenne in the United States.[4] While disease progression in Duchenne is slow, it is always fatal,[5] and often accompanied by cognitive challenges. The unmet medical need in this disease is vast.

AAV-based gene therapy in Duchenne

The AAV-gene therapy field is currently at an early stage, with major efforts underway to unlock its potential for rare diseases including Duchenne. Two AAV-based gene therapies currently have FDA approval: Luxturna® (voretigene neparvovec-rzyl) for a rare inherited retinal disease, and Zolgensma® (onasemnogene abeparvovec-xioi) for spinal muscular atrophy.

To date, few children with Duchenne have been treated with a gene therapy, and most trials have focused on younger, ambulatory patients with early-stage disease. There are currently no trials for older patients, in part due to the greater doses needed, potential immunogenicity, and the likely presence of more muscle fibrosis. Only one adolescent with Duchenne in a wheelchair has been treated with gene therapy. This non-ambulatory patient experienced a decrease in platelet count followed by a reduction in red blood cell count and evidence of complement activation, leading to a clinical hold on the trial.[6] This resulted in a subsequent focus on younger boys with Duchenne, although efforts continue to include older patients with Duchenne in the hope that heart and diaphragm muscle strength can be retained.

Patient and Caregiver Preferences

Parent Project Muscular Dystrophy (PPMD) has been surveying patients and caregivers since 2013 to elicit preferences. Working in collaboration with all stakeholders, including regulators, biopharma companies, clinicians and social scientists, this group sought to determine how much risk is acceptable in return for how much potential benefit. PPMD research has shown that participants prioritized benefits to muscle function above all other factors in trial decision-making.[7] Concerns about participation limiting later use of gene transfer and gene editing were also important to patients, as were the chance for improved lung and heart function. Risk of death fell near the middle. Participants cared least about muscle biopsies and potential for randomization to placebo. The study found similar priorities between patients and caregivers.

Caregivers were found to be willing to take on risk and uncertainty in exchange for stopping or even slowing progression of disease with a non-curative therapy. Caregivers chose improvements in quality of life (slowing disease progression) over added years of lifespan. A follow-on study found that caregivers and patients had similar preferences overall. Overall, the highest tolerance for mortality risk was seen in the late stages of disease, when patients were losing the ability to feed themselves. PPMD continues to survey patients and caregivers and hopes to have more data on patient and caregiver preferences this year.

Need for equitable access for patients of all ages and socioeconomic status

In addition to the unmet medical needs of young Duchenne patients, there is also an urgent need for treatment options for older boys, whose participation in earlier trials helped build today's knowledge base in this indication. The potential for efficacy in these older patients is less certain. The fact that patients may be limited to participating in only one gene therapy trial makes the decision to participate in any future

trials a complex and strategic calculus for families. Open label studies might be a promising option for including these older patients in future trials.

There is also a need to establish a more equitable way of enrolling patients to expand access to individuals from all socioeconomic strata.

Regulatory elements

Since 2017, FDA has approved two AAV-gene therapy products, neither of which targets Duchenne.[8] The Agency has issued multiple guidance documents, including topics such as safety, potency, and purity of retroviral vector-based gene therapy and the specifications for long-term follow-up observations. In addition, in 2018, FDA issued a final guidance entitled, Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry.

FDA has indicated that regulatory flexibility is appropriate in serious diseases, including life-threatening diseases such as Duchenne. Substantial evidence of effectiveness and a finding that a drug is safe for its intended use are necessary for FDA approval. Clinical investigations supporting effectiveness should be of appropriate design and of high quality (i.e., adequate and well-controlled). The clinical endpoints studied are a critical aspect of quality. Clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit) can be used as the basis for traditional approval. Accelerated approval can be based on a demonstrated effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit but where there are not sufficient data to show that it is a validated surrogate endpoint. Effects on intermediate clinical endpoints can also be a basis for accelerated approval. For drugs granted accelerated approval, FDA requires post-approval trials to verify the predicted clinical benefit.

2019 FDA draft guidance on demonstrating substantial evidence of effectiveness notes that although randomized superiority trials with a placebo- or active-control design generally provide the strongest evidence of effectiveness, there are cases where not using a placebo control, superiority design, or randomization may be acceptable.[9] The draft guidance notes that, "In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need)."

Therefore, appropriate clinical trial designs must be clarified that can support the finding of substantial evidence, while allowing broad access to provide informative prescribing information for clinician and patient decision making. It is also key to identify meaningful endpoints that can support either traditional or accelerated approval for products being studied for Duchenne across all functional statuses.

Duchenne clinical trial design

A key need in rare disease is to maximize the opportunity for trial participants to receive therapy. The gold standard of clinical trial design – a randomized controlled trial (RCT) – is typically not practical for rare diseases. In addition, it may be unethical or infeasible to have a placebo, or other concurrent control (e.g., active agent, lower dose of investigational agent) arm in a serious and rare disease clinical trial. Information from natural history studies or from earlier RCTs may be used as an external control as part of an adequate and well-controlled clinical investigation in situations where placebo is not optimal or feasible, such as during a Duchenne study.

Design approaches can include the use of crossover designs, weighted assignment, platform trials, or Bayesian modeling. More specifically, adaptive clinical trial designs and enrichment strategies can be helpful. For example, adaptive trials allow trials to adjust to information that was not available when the trial began. They can provide advantages related to statistical efficiency, ethical considerations, improved understanding of drug effects, and may be more acceptable to patients. Enrichment strategies can focus trial enrollment on those most likely to show benefit with exposure to an investigational agent. However, it is key to consider not only how a clinical trial design will address the need for demonstrating substantial evidence of effectiveness, but also the determination that a drug is safe for its intended uses. In addition, the use of narrow inclusion criteria, which can be the case when using an enrichment strategy, should be considered when evaluating the impact to trial access for patients and the resulting information that will inform labeling and prescribing. In addition, genetic heterogeneity and its impact on disease progression are important factors to consider.

Trial designs should consider approaches that allow trials to enroll a broadly inclusive patient population to gather safety and efficacy data, with a planned analysis of efficacy endpoints in certain prespecified subgroups. It may be helpful to work with immunologists to develop inclusion criteria to mitigate the risk of a genetic response; at present, there is an incomplete understanding of what levels of AAV-neutralizing antibodies might pose a safety risk and/or interfere with efficacy, the role of seroprevalence or conversion and the potential to re-dose. This knowledge gap poses a tremendous emotional burden on families as they weigh the benefits/risks of trial enrollment and when patients are excluded from trials.

Design considerations for programs that intend to pursue accelerated approval must also be addressed. It might be appropriate to develop a model to determine safety, gene expression and proper dose in one population (e.g., those with more advanced disease), while concurrently confirming clinical benefits in a younger, ambulatory population.

Pathway forward: Endpoints to assess clinical benefit
While Duchenne trials to date have focused on ambulatory endpoints, future assessments of Duchenne progression should reflect the diversity of functioning of Duchenne patients and segment trial participants by function rather than age. This could help reduce noise in trial data, improving the chances of detecting a therapeutic effect when one exists.

There is a need for clinically meaningful measures of disease progression and therapeutic effectiveness that reflect patient and caregiver priorities across the disease spectrum. For example, from Duchenne patients' perspectives, the ability to exercise – as measured by the six-minute walk test (6MWT) and North Star Ambulatory Assessment (NSAA), and other timed function tests – is not the most important outcome. Functional independence is a key goal for these individuals and their families, including ease of movement, upper limb function, hand dexterity, self-feeding, computer access, and independent positioning of the body. In addition, the 6MWT and NSAA can be affected by steroid treatment and by maturation, and there is potential for motivational biases among patients and caregivers. These biases may extend to clinical evaluators and investigators who know that a patient needs a certain score to be eligible to enter a trial.

In addition, meaningful clinical endpoints may differ based on stage of disease or functional status of the Duchenne patients. Therefore, endpoints that reflect the spectrum of disease progression need to be identified to allow measures of benefit at different points of disease burden. Consideration should be given not only to endpoints that directly measure clinical benefit, but also those that can be the basis of

accelerated approval (i.e., reasonably likely to predict clinical benefit) and those endpoints that would be the basis of confirmatory trials used to verify and describe clinical benefit. Furthermore, using endpoints that correlate to disease progression and burden, rather than generally to age, will be more informative and accurate due to the heterogeneity of the Duchenne population.

Biomarkers and surrogate endpoints
Biomarkers and surrogate endpoints may be helpful tools for Duchenne gene therapy development. The FDA guidance on dystrophinopathies notes that, "Even if it cannot be concluded that a given biomarker can serve as a surrogate endpoint, positive findings based on a biomarker may help support the mechanism of action of a drug, help identify the appropriate patient population to study or treat, or support the validity of findings on other endpoints."[10]

AAV-gene therapy products in development for Duchenne utilize miniaturized versions of the dystrophin gene referred to as microdystrophins. Currently, uncertainty remains about what level of microdystrophin expression could be viewed as "reasonably likely to predict a clinical benefit" for purposes of accelerated approval. The production of truncated dystrophin was used as a surrogate endpoint for the accelerated approval of eteplirsen, golodirsen, viltolarsen, and casimersen.[11] It is key to apply the learnings from the use of truncated dystrophin for specific mutations under accelerated approval to the use of microdystrophin in Duchenne. If it is possible to prove a functional benefit for truncated dystrophin or microdystrophin expression in a narrow population, this surrogate might then also be useful in a broader population that includes older patients. Another interesting potential surrogate endpoint for Duchenne or stratification tool is fat fraction in skeletal muscle, measured by quantitative MRI imaging.[12] This is a predictive measure of age at loss of ambulation.

Digital health technology
Wearable sensors have potential to capture more sensitively many physical changes related to the disease, enabling nuances to be detected that might indicate disease stabilization and benefit in response to therapy. Greater use of sensors could enable trials to be faster, less burdensome for families, more reflective of disease progression and patient benefit, and more inclusive of non-ambulatory patients. Advantages of wearables and biosensors include the fact that they are objective, scalable, responsive to endurance and fatigue, allow for decreased clinical visits, and are less subject to motivational biases than clinical-based tests, while having the potential to provide real-world, clinically meaningful data at a high level of precision (granular data on activity, mobility, movement).

Wearable technologies and other digital advances might enable the rates of patient stabilization or decompensation to be quantified, allowing any changes, including compensatory changes, to be tracked over time. Research is underway to examine the potential of granular movement changes and ease of movement to evaluate whether a patient is declining, stable, or improving.

While there has been great progress in the development of wearable devices to measure real-world functioning, endurance, and disease stabilization and improvement in Duchenne, there is not yet sufficient evidence to allow these measures to be used as primary endpoints in evaluation of therapeutics. Other factors need to be considered when evaluating the appropriateness and meaningfulness of data from wearables, such as changes in stride length, which may indicate disease progression and may not be captured if only measuring distance rather than steps taken. In addition, the impact of seasonality (e.g., less activity in winter vs. summer) and sensitivities around using wearables must be understood. However, there are approaches being developed to address these and other potential issues with wearables. In 2019, the EMA qualified stride velocity 95th centile as a secondary

endpoint in Duchenne as measured by a valid and suitable wearable device.[13]

Pulmonary function

Duchenne care standards and management are already based on pulmonary function and spirometry. This points to the potential of pulmonary endpoints, particularly forced vital capacity (FVC), as potential surrogate endpoints for skeletal muscle function.[14]

Pulmonary function – which is prognostic for time to mechanical cough assistance, time to non-invasive mechanical ventilation, and risk of death – may be a more objective measure than the 6MWT or NSAA. Ongoing studies indicate that pulmonary function in Duchenne patients declines over time, so improvement or stabilization compared with what is seen in natural history of the disease could indicate a meaningful therapeutic response, potentially delaying time to mechanical ventilation. Lung function is especially significant in Duchenne patients, for whom progression to a 1-liter FVC is associated with a four-fold increased risk of death.

However, it will be important to identify what change (either in stabilization or improvement) could be considered clinically meaningful for traditional approval or could be used as the basis for accelerated approval.

Performance of upper limb

The performance of upper limb (PUL) metric has several advantages, including the fact that it is disease-specific, has no maturational effects, has been shown to be responsive to treatment in a one-year trial, and bridges the transition from late ambulatory to non-ambulatory states.[15]

Casimir assessment

The Casimir assessment, a promising patient reported outcome (PRO)- and video-based assessment, is in development in collaboration with patient, family, subject matter expert, and regulator input.[16] This assessment aims to identify changes in disease progression among ambulatory boys with Duchenne,[17] to provide a granular picture of disease progression and the impact of therapies. The assessment focuses on quality and ease of movement. As additional natural history and clinical trial data are collected, this assessment is expected to have increased utility as a trial endpoint. As this is a video-based assessment tool, it allows for independent physical therapists to score the videos to provide a more consistent, robust, and quantitative analysis.

Hercules model

The Hercules model of Duchenne disease[18] uses defined milestones in Duchenne progression in both ambulatory and non-ambulatory patients, such as loss of the ability to stand from the floor or walk 10 meters, loss of hand-to-mouth function, and loss of distal hand function (with or without steroids). This model may be useful for registries and phase 4 studies.

Other Duchenne scales

Other approaches include the disease-specific Duchenne Lifespan Mobility Scale (DMD-LMS), and a second Duchenne-specific scale in development by Prof. Chad Heatwole of the University of Rochester.[19] Patients younger than 8 years typically require parent proxy assessments, while in adolescents, it is useful to obtain both patient and parent proxy assessments.

Conclusion

This inaugural meeting of the Pathway Development Consortium provided a substantive departure point

for future progress. There is a need to consider innovative and more dynamic approaches to Duchenne trial design, with the goal of detecting early signals of efficacy rather than waiting until participants reach a 12-, 18- or 24-month endpoint. Continued work on identifying meaningful clinical endpoints, and surrogate endpoints for accelerated approval, is needed.

Attendees expressed a need for FDA to think innovatively around how it can promote therapeutic development for rare diseases. As access to approved therapeutics is the goal, the need for evidence of therapeutic benefit will be essential for ensuring payer reimbursement and patient access going forward. FDA expressed its commitment to working collaboratively with stakeholders and to using existing tools to support therapeutic development for rare diseases, including Duchenne. This might involve approaches such as the application of Bayesian designs, promising biomarkers, patient-focused endpoints, and trial designs that enroll a larger group of patients, with the prespecified efficacy analysis on a specific subpopulation, and the collection of safety data from the full enrolled population.

Continuous involvement of all key stakeholders from the earliest stages is essential. Also key to successful implementation is shared learning across development programs. In addition to valuable factual exchanges, the day's discussions highlighted the shared stakeholder passion and commitment to rapidly bring benefit to all Duchenne patients – from the youngest to the oldest.

This summary was drafted by co-founding members REGENXBIO and Solid Biosciences. The opinions expressed in the summary do not necessarily reflect the opinions of the attendees of the workshop.

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