It is with a tremendous feelings of optimism and gratitude that I submit these comments to the Advisory Committee in preparation for this landmark product review – a sense of optimism about what lays ahead for the Duchenne muscular dystrophy (Duchenne) community as the first products ever designed specifically for our patient community are reviewed and a deep sense of gratitude for the extraordinary efforts of so many that have gotten us to this critical point that few of us only dared dream of not long ago.

More than 30 years ago, I was forcibly enlisted in the army against Duchenne when my two sons, Christopher and Patrick, were diagnosed with this dreadful disease. My two sons and our entire family fought hard. But as the disease process marched on and the therapy landscape remained barren, my sons could not fight against time. Duchenne always wins. Even today, while many patients are making remarkable progress in this battle thanks to advances in research and improvements in diagnosis and clinical care, Duchenne has a perfect record of lives claimed.

Twenty years ago, in 1995, my family lost our son Christopher. Just a few months later, Patrick too was gone, claimed by Duchenne.

From the time of my sons’ diagnoses – a lengthy and torturous process – until their deaths, I devoured the medical literature and traveled the nation to speak with researchers and clinicians who might, just might, have a remedy. At this time, however, the Duchenne research landscape was nearly barren aside from some amazing and deeply committed minds – people like Lou Kunkel and Eric Hoffman who led the team that discovered the dystrophin gene that causes Duchenne in 1986.

More than 20 years ago and shortly before I lost Christopher and Patrick, I joined together with other parents to form Parent Project Muscular Dystrophy. While many families would form charities to advance research and care for their own child, PPMD was not about saving my sons, rather it was about saving everyone’s sons. My son Christopher said “if you won’t help all of us, who will?”
The mission of PPMD is simple – to end Duchenne muscular dystrophy. We will achieve this goal through a number of high-impact activities ranging from supporting research at all levels to ensuring that all Duchenne care is of the highest quality possible to developing necessary evidence and tools to drive the development of treatments, a topic I will speak more about shortly.

For our families, including my own, this journey has been a lengthy and challenging one marked by multiple setbacks and, for too many families, the loss of loved ones. It has been a journey with periods of optimism dashed by the hard realities of the complexities associated with therapy discovery, development, and clinical testing. While none of these challenges were easy, I believe they have tested our community and have ultimately made us stronger.

Today, we are potentially moving toward the beginning of a new chapter in the book of Duchenne, a chapter in which patients will hopefully have access to a range of disease-modifying treatments that will slow the progression of the disease. We know that with any new therapy there is a possibility of risk, but as I will share in a moment, our community feels strongly that patients deserve options, information, and the tools to make informed choices as this is a disease that includes daily tradeoffs even in the absence of disease modifying therapies. We know that the early stage of this new future will be limited to a subset of the patient community. But we are hopeful that, just as we have seen in other fields, these first-generation-wins will provide a foundation to encourage others to enter or stay in the Duchenne arena and to create a smoother, more predictable and shorter pathway to other therapies.

An Overview of Duchenne

Before I share a little more about living with Duchenne from the perspective of a patient or family caregiver, I will first provide a brief overview of the disease.

First described by pioneering French neurologist Guillaume Benjamin Amand Duchenne about 150 years ago, Duchenne is one of nine distinct degenerative muscle disorders known broadly as muscular dystrophy. It is a genetic condition caused by the absence of the protein called dystrophin, a structural muscle protein that is essential for muscle integrity and stability. The production of dystrophin is disrupted by a variety of genetic mutations within the largest gene in the human body – the dystrophin gene which includes 79 exons. Duplications, deletions, frame-shifts within the gene can all result in Duchenne. As an X-linked recessive disorder, Duchenne primarily affects males though a small number of females are also affected. Within the last decade, our scientific and clinical community has grown to have a much deeper understanding of the intricate genotype-phenotype correlations associated with Duchenne sub-populations, or those with similar genetic mutations.

The first clinical signs of muscle weakness are often observed during the toddler years, although most parents can trace their first concerns back to as early as within the first 6-12 months of their child’s life. For my sons, I noticed that both had poor muscle tone, walked later than average and had other developmental challenges. Young boys during the elementary school age
will frequently experience difficulty walking – frequent falls, an awkward gait, the inability to keep up with peers – as ambulation declines to the point where most become non-ambulatory during their pre-teen years.

All skeletal muscle and all systems are compromised by the absence of dystrophin. This leads to a myriad of problems across multiple systems to include a chronic inflammatory response to all muscles with downstream complications to the respiratory and circulatory system. The loss of muscle and bone weakness inherent in Duchenne bring about challenges such as significant risk of fractures accompanied by loss of function, bone deformity, and scoliosis. By the early teens, arm function is significantly decreased, activities of daily living such as self-feeding and personal care become impossible. Most teenagers with Duchenne develop left sided heart failure and diminished pulmonary function. In adolescence young men with Duchenne typically require ventilation, first at night and in later stages of the disease, around the clock. Death is caused by cardiac or pulmonary failure.

When I and others who have experienced Duchenne directly speak of the disease, we often speak of the many “little deaths” associated with the disease. By little deaths, we mean the setbacks that, while not always glaringly apparent, are significant in that they lead to further decline. While regulators measure in gains; we measure in losses. We have the gradual decline in mobility that results in a total loss of ambulation. Once a boy reaches the non-ambulatory stage, his physical descent impacts every financial, employment, housing, and day-to-day household decision made by his immediate family. Delaying this stage or slowing further progression, as you will hear soon, is thus vitally important to the patient and the caregiver.

A mother of a 13-year-old son paints the most vivid picture of this reality:

“You cannot get back what this disease takes from boys every day. The loss of a step in a timed test indicates something much more than loss of function. It is death itself and it is coming for these boys at an insidious pace.”

Beyond the advancements in research and discovery that have gotten us to where we are today, perhaps the other most rewarding development over the past 15 or so years has been the extension of life for the average patient with Duchenne as well as improvements in quality of life. When my sons were first diagnosed, it was a rare patient with Duchenne who lived past his late teens. Today, however, we have patients living into their late 20s, early 30s, and beyond.

Living with Duchenne – Understanding Patient and Caregiver Preferences

Now, I want to focus on what all of this means when you are a person or a family member of a person living with Duchenne.

You will note that I used the verb living. I did not say impacted or affected by, suffering from, or dying from Duchenne though technically each of those verbs is accurate too. Each and every day, thousands of young men and their families are, as noted above, ‘living’ with this disease.
and living longer, more productive lives. But these patients and families are also making a series of decisions and trade-offs. Some of these are relatively modest, but many are complicated and can bring about serious and lasting consequences. These decisions and trade-offs are made by each family individually, taking into consideration the unique circumstances that surround that family, their child’s specific genetic mutation and rate of disease progression, and any past experiences with offered clinical interventions. It is this decision-making by our patients or primary caregivers that lies at the heart of your decision today.

As noted earlier, no one has ever defeated Duchenne. Many, including my sons, have battled valiantly and a growing number are living longer. But Duchenne is 100% fatal. If approved, the candidate therapy before the panel today will provide a subset of our population with the means of maintaining muscle function for a longer period of time. It will not stop the disease. It will not reverse it and it will not cure it. But it would, for the first, time, offer us a disease-modifying therapy.

In real words and not clinical or academic speak, this means that candidates for the drug could stay on their feet for longer periods of time, which translates into overall health benefits for a longer period of time. It means people with Duchenne could potentially use their arms and legs and keep pace with their siblings and their peers. It means that their hearts and lungs will be stronger, delaying the need for ventilation. In short, it means the ability to live fuller and longer lives.

Of course, for every positive there is a negative, for every pro there is a con, and for every benefit there is a risk. For the past several years, PPMD has focused extensive energy and resources to better understand what our Duchenne community thinks about this most important issue. We recognized that the FDA needs scientific evidence upon which it can make decisions and that even the most impassioned pleas could not carry the day without more objective patient input.

The Process of ‘Quantifying the Tears’

Each and every family has their own personal story about Duchenne. Each and every family is able to relate a story of loss, the ‘little deaths’ experienced as their loved one loses function. But we recognize that regulatory agencies make decisions based on rigorous data and to that end, we, the patient community believed it would be critical to the FDA’s decision making process if we were able to provide data related to caregiver and patient preferences.

In order to accurately measure opinions or preferences we used scientifically validated approaches to ensure that whatever we did we did correctly. We partnered with researchers at the Johns Hopkins University School of Public Health. These partners helped us develop an appropriate instrument that we used to survey nearly 120 Duchenne parents, the first-ever quantitative survey of Duchenne community preferences on potential benefits and corresponding risks of candidate therapies. Specifically, we used the best-worst scaling (BWS) method that measured respondents’ views on six relevant and understandable benefit or risk
scenarios such stopping or slowing progression of muscle weakness, longer lifespan, nausea, and risks of bleeding. In addition, we collected the narrative stories of our families and found that the stories provided qualitative data in support of the quantitative data collected.

The primary study objective was to explore how parents/guardians of individuals with Duchenne prioritize risk and benefit in the context of new therapies.

Specific Aims:

- Describe risk tolerance, health-related QoL, and numeracy
- Explore treatment preferences, risk tolerance, and benefit priorities
- Explore Duchenne-related worries
- Evaluate the effect of child’s disorder progression on treatment preferences and worries

Treatment preferences and Duchenne-related worries of parents or guardians were studied in a cross-sectional design using BWS. The survey includes hypothetical treatment attributes (such as weakness progression) and levels (such as stops progression of weakness; slows progression of weakness; no change to progression of weakness). Attributes and levels were selected through rounds of consultation with parents of children with Duchenne, healthcare providers experienced in treating Duchenne, and representatives of biotech and pharmaceutical companies. Worry attributes were developed through collaboration with parent informants and reviewers.

In the survey, participants were provided with sets of simulated treatment scenarios and asked to choose the best and worst of each treatment scenario; later, participants were provided with sets of Duchenne-related concerns and asked to choose the one they worried about the most in the past seven days and the one they worried about the least. Thus, participants evaluated and compared their preferences towards the attribute levels and selected the pair of attribute levels that they perceive to be furthest apart.

What We Learned

Overall, we have found that parent participants prioritized protection of muscle function over any other attribute, including longer lifespan, each of two serious risks, nausea, and more information about the drug’s risk and benefits.

Participants’ most significant worries were related to the child’s illness progression and care. The study suggests a parent population that is highly concerned about Duchenne’s effect on their child’s strength, and is willing to accept risk and uncertainty for a treatment that would slow or stop muscle weakness.
We found that by and large, parents are willing to accept significant but finite levels of risk, particularly when associated with treatments able to slow progression of muscle weakness. In fact, by a large margin, stopping and slowing progression of muscle weakness ranked significantly higher than the next highest benefits of 5 or 2 year gains in the lifespan (see diagram above). On the risk side, respondents were most concerned about potential increased risks for heart arrhythmia followed by potential increase risk for stroke and resulting lifelong disability. Overall, however, the preference for a treatment to stop progression offset either negative score.

Perhaps most interesting is that the data shows that parents value stopping or slowing muscle progression more highly than lengthening life. As someone intimately familiar with this disease, I can tell you that this makes sense in that greater muscle function means a greater quality of life. It means the ability to run and jump for longer, the ability to feed and care for oneself, the ability to visit and play with friends, the ability to “fit in” with peers at school, the ability to remain more independent. In shorter, it means more time truly living with Duchenne.

In response to requests from FDA, PPMD has been working to expand this work further to capture a larger segment of the Duchenne community population.

Most recently, we partnered with an industry collaborator to understand patient preferences regarding a specific pulmonary candidate therapy. Through this work, involving more than 130 patients and caregivers, we found again that patients are willing to accept risks and burdens to achieve pulmonary benefits, notably improvement in cough strength. In this case, respondents
chose to accept a strong benefit with an accompanying high risk more than two-thirds of the time, and the majority of respondents assigned low perceived burdens to three side-effects of taking medication, sustaining blood draws, and diarrhea.

**Accepting Risk and Uncertainty**

As you will hear at the Advisory Committee Meeting in a couple of weeks, no candidate therapy is completely without risk or uncertainty. But if I can implore you to do one thing, to take one action, it is to heed the voice of the Duchenne patient and caregiver on benefit/risk preferences.

Through PPMD’s *Share Your Story* project, we have gathered feedback from more than 160 patients and close family members of patients with Duchenne. Here is a little bit of what they are saying:

> “Because DMD shortens the lifespan of those afflicted, I would encourage the FDA to consider being more aggressive with the approval of certain drugs where the benefits include quality of life and lifespan. Some families welcome the risks that may come with treatments, feeling that doing something is better than just waiting for their child to deteriorate and die.”

> “We hear each tick of the clock very loudly in our heads, worried that science will take too long to develop a treatment that will slow/eliminate the progression. Our bigger worry is that science will develop it and the FDA will take too long to approve it.”

> “Simply put, we don’t have years to wait….Without the medications, these boys have no future.”

I urge you to listen to parents like this father writing about his 6-year-old son Miles who stands to benefit from the candidate therapy:

> “Miles doesn’t yet know that in many ways, life is (maybe?) better now than it will ever be for him again. I dread the day that brutal reality sinks in to his consciousness, just the recognition of inevitable, brutal, crushing decline and loss of abilities feels unbearable. I would do almost anything to prevent or postpone that moment of terrible recognition. But, I know that without help it’s coming, maybe in a year or two. Each day that passes will see him lose more of his capability, mobility, stamina.”
I urge you to listen to a mother of a preteen who is no longer ambulatory:

“I know that we are now in the second of what is described as the three phases of Duchenne. I know that permanent seating brings on a host of health complications, like contractures and scoliosis and weight gain and increased heart rate and decreased pulmonary functions. He is 12 years old. He should be running and growing and instead he is changing seating positions and using the standing function on his power chair. He is lifted onto the toilet and unable to get into his best friend’s house because they have steps. He is sitting on the railroad tracks and the train is coming full speed ahead....These first (generation) drugs may not be perfect and our means to demonstrate their effectiveness may be incomplete, but these first drugs give every indication of effectiveness and they should be given the green light while we work on improvements.”

And I urge you to listen to a mother of 9-year-old Elijah:

“I know that without a viable therapy, I will slowly lose my son to this devastating disease. As the disease progresses, he will no longer be able to complete basic daily skills, much less do his favorite activities. Helping his mother make cookies will become a distant memory. If there is a treatment out there that can help children with this diagnosis, slow the course, and give them a chance to live longer, fuller lives it needs to be approved and utilized....As a parent, I am willing to accept risks that could come with these treatments.”

Labeling and Shared Decision Making

In December 2013, PPMD held a policy forum. During that meeting, the community expressed a need for broad labeling. We understand the need to study individuals most sensitive to change, the subset most likely to demonstrate both safety and efficacy, given the primary outcomes used in current clinical trials. Today, for families, this means an ambulatory population, a young man able to walk between 300 and 450 meters in 6 minutes (6mwt) and one who is older than 7 years and given the track record of Duchenne, likely younger than 12 years of age. Boys younger than 7 and all of those non-ambulatory are unable to participate, are left waiting and waiting for days like this one, where a recommendation for approval lies in the balance. They have waited through development and clinical trial and need and deserve access to approved therapies. They have no time to wait for additional studies. They have waited long enough. Broad labeling is essential for this significant unmet need.

As members of our patient community work together with clinical providers to make empowered and informed health care choices, it will be critical that the labeling of all products that enter the marketplace include clear and transparent information about the safety and tolerability of the product, so that the community will be able to make a personal benefit/risk determination with their provider.
Closing

For far too many families, my own included, the milestones before us today have been too long in coming. We had too many sons lose their ability to walk. We have had too many grandsons or nephews never have the ability to hit a baseball, to shoot a basket, to score a touchdown. We have seen too many brothers have their hopes and dreams dashed as they faced one little death after another. And we have lost too many boys to the enemy that is Duchenne.

The candidate therapy before us today is not a perfect cure-all. It will not improve or save every life touched by Duchenne and it will not eradicate overnight the many challenges of our community. But based upon what has been shared about the clinical study results, approval of this product should provide meaningful benefit for a segment of our community by slowing progression of the disease and enabling affected patients to live higher-quality lives.

From a patient and parent perspective, given the preference data already mentioned, this candidate – and any agent with a similar profile – deserves a favorable recommendation and, ultimately, FDA approval.

If the candidate compound is favorably recommended, the future for the Duchenne community will look different, not only for the patients and families, but for all involved, researchers, advocates, developers and regulators. Through the flexibility, perseverance, and resourcefulness of using all the tools available, the Duchenne community will be a beacon of hope for all other rare diseases.

So many people have worked so hard to get us to this point, including the hundreds of Duchenne families who have shared their perspectives on benefit and risk to provide you and the FDA with the evidence you need to make an informed decision. Please heed this information, listen to the pleas of our patients and families.

In addition to meaningful benefits to patients, an approval will give the entire community hope that we are, indeed, entering a new dawn in our quest to end Duchenne – an era in which therapies for other mutations as well as second-generation therapies are developed and subsequently approved, a time when Duchenne is a manageable condition like so many others.

Ultimately, I hope and pray for the day when Duchenne is no more, where an effective, safe, and accessible therapy exists to make the disease go away or make it largely non-existent, where no parents are given the dreadful diagnosis and told there is nothing more they could do.

Christopher and Patrick have been gone a long time, but not a single day goes by that I don’t think of them, what their lives could have been like had they never been diagnosed with Duchenne, and how different all of our lives would be.

Many are familiar with the phrase “standing on the shoulders of giants,” often attributed to Sir Isaac Newton, that recognizes the scientific discoveries of yesterday are responsible for the
breakthroughs realized today. The Duchenne community is standing on the shoulders of many giants – every single patient who has bravely borne this diagnosis, including the many who have gone before us. Please honor these contributions as you review the experiences of our patient community and the data being evaluated today. **We urge you to approve eteplirsen.**