Pathway Development Consortium

Advancing AAV Gene Therapy for Duchenne Muscular Dystrophy

A Pathway Development Consortium White Paper*

I. Executive Summary

Duchenne Muscular Dystrophy (Duchenne) is a serious, rare genetic disease, affecting primarily boys, that is characterized by progressive muscular degeneration. Although there are some treatment options available, predominantly for small subsets of the patient population, Duchenne is a disease with unmet medical need and patients and their families require other treatment options.

Gene therapy based on adeno-associated virus (AAV)-mediated delivery of shortened, yet functional genes (microdystrophin genes) has emerged as a promising method, since genes encoding the full-sized dystrophin protein are too large to be accommodated into AAV vectors.

The Pathway Development Consortium (PDC) was launched in 2021 with the aim of working collaboratively across a broad group of stakeholders, including the FDA, to construct a pathway to ensure that all born with serious genetic conditions can access effective and efficiently developed AAV gene therapies. The PDC decided to focus its initial activities on Duchenne.

This white paper seeks to provide an overview of the current regulatory landscape for therapeutic development for Duchenne patients. This includes summarizing FDA's regulatory programs and guidances that are relevant for the development of products for Duchenne and reviewing highlights from FDA decisions relating to approval of products for this disease. In addition, this white paper aims to conceptualize how the accelerated approval pathway could be used to help advance AAV gene therapy development for Duchenne patients.

II. INTRODUCTION

A. Duchenne Muscular Dystrophy and Related Therapies

Duchenne is a recessive, X-linked neuromuscular disorder caused by mutations in the dystrophin gene that result in near complete absence (typically less than 3% of normal levels)[1] of the dystrophin protein, a protein critical in stabilizing muscle cells. Duchenne is characterized by progressive muscular degeneration, and primarily manifests in patients as progressive muscle weakness impairing walking and other motor functions, such as breathing, and cardiac function[2] with the most common cause of death being cardio-respiratory failure.[3] Additionally, Duchenne patients have a high rate of cognitive and learning disabilities as well as neurobehavioral disorders.[4] Although there is much heterogeneity in symptom progression in the Duchenne population, muscle weakness typically begins between ages 3 to

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5 years, with loss of ambulation usually occurring by 12 years of age. Duchenne predominantly affects males and most patients do not live beyond 30 years of age. Duchenne is estimated to occur in approximately 16 live male births per 100,000 in the US.[5] Rarely, females are also affected by Duchenne, with around 8% of female carriers having muscle weakness to some extent.[6]

There are five FDA-approved treatments for Duchenne: deflazacort, eteplirsen, golodirsen, viltolarsen, and casimersen. Deflazacort is a glucocorticoid that was granted traditional approval, while the rest are exon-skipping drug products that were granted accelerated approval based on a mean increase in truncated dystrophin production in skeletal muscle using a western blot assay and in the range of 0.3% to 5.4%. These four latter therapies are only indicated for treatment of a small fraction of Duchenne patients, based on the specific genetic subtype studied, and, because they were granted accelerated approval, the sponsors are required to undertake additional studies to verify and describe their clinical benefit.

For the purposes of regulatory review by the U.S. Food and Drug Administration (FDA), Duchenne is considered a serious disease with unmet medical need. Currently, there are many types of medical products under development for Duchenne. One direct way of treating this disease would be to restore the expression of dystrophin. Gene therapy based on AAV-mediated delivery of microdystrophin genes has emerged as a promising method, since genes encoding the full-sized dystrophin protein are too large to fit inside AAV vectors.[7] Microdystrophin genes are designed to be small enough to fit into an AAV vector, and yet retain the functionality of the normal sized dystrophin. AAV vectors are able to transduce cells that are not actively dividing, and are understood to be non-integrating, non-pathogenic and less immunogenic than gene therapies that utilize other delivery mechanisms. Trials underway are studying the safety and efficacy of systemically administering AAV vectors to deliver different forms of microdystrophins to restore function of muscle and other organs throughout the body.[8]

B. Pathway Development Consortium

A key component of facilitating therapeutic development for any disease is collaboration between stakeholders, but this is even more important for serious diseases with unmet medical need. The PDC was launched in 2021, spearheaded by two biotechnology companies, and through collaboration between a broad group of stakeholders, including the FDA. The group seeks to construct a pathway to ensure that all those born with serious genetic conditions can access effective and efficiently developed AAV gene therapies.[9] The PDC believes that the key to accelerating progress to address areas with unmet medical needs is working together to share learnings and apply them collectively to advance therapeutic development. This approach seeks to reduce redundancy and inefficiency and ensure that collaboration leads to enhanced medical product development.

On April 6, 2021, the PDC held its inaugural roundtable, focused on defining clinically meaningful clinical trial endpoints for the range of functional status seen in Duchenne patients.[10] This event aimed to promote scientific and policy interchanges among a broad range of Duchenne stakeholders, such as companies working on AAV-gene therapy for Duchenne, government agencies, Duchenne patient advocacy groups, professional organizations, academia, and other science-based collaborative organizations in Duchenne.

Building on that initial roundtable, the PDC is issuing this white paper to:

(1) Provide an overview of the current regulatory landscape for therapeutic development for Duchenne patients. This includes summarizing FDA's regulatory programs and guidances that are relevant for the development of products for Duchenne and reviewing highlights from FDA decisions relating to approval of products for this disease.

(2) Conceptualize how the accelerated approval pathway could be used to help advance AAV gene therapy development for Duchenne patients.

III. OVERVIEW OF FDA REGULATORY LANDSCAPE FOR DUCHENNE THERAPEUTIC DEVELOPMENT

As stated in the FDA regulations in 21 CFR part 312, Subpart E,[11] the Agency has committed to facilitating and expediting 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 Subpart E regulations specifically recognize that patients and physicians "are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses," than they would for less serious diseases.

A. Summary of Relevant FDA Programs and Guidances

1. FDA Guidance on Expedited Programs for Serious Conditions – Drugs and Biologics

In May 2014, FDA issued final guidance on available programs to expedite the development of drugs and biologics for serious conditions.[12] In addition to other programs, this guidance discusses the use of the accelerated approval pathway for products for "a serious or life-threatening disease or condition" based on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity, mortality or other clinical benefit.[13] This accelerated pathway has been used for four of the five products currently approved by FDA for Duchenne. Further details are included in Appendix 1 (a).

2. FDA Guidance on Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

In February 2019, FDA issued final guidance on section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act, which addressed criteria for classification of regenerative medicine advanced therapies (RMAT).[14] In this guidance, FDA notes that human gene therapies may meet the RMAT definition and that RMATs may be eligible for accelerated approval based on agreed surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit, or data from a meaningful number of sites. This guidance also provides for sponsors of RMATs that receive accelerated approval to potentially fulfill the post-approval requirements from clinical evidence obtained from sources other than the traditional confirmatory clinical trials. Additional details are provided in Appendix 1 (b).

3. FDA Draft Guidance on Human Gene Therapy for Neurodegenerative Diseases

In January 2021, FDA issued draft guidance to assist sponsors developing human gene therapy products for neurodegenerative diseases.[15] This draft guidance discusses clinical trial endpoints that could be used in trials intended to demonstrate effectiveness. It notes that "because many neurodegenerative diseases are rare and complex, with limited understanding of their pathogenesis, identification and characterization of a surrogate or intermediate endpoint is often challenging. Therefore, an effect on a clinically meaningful endpoint generally would be used to support a marketing application under the traditional approval pathway." However, the guidance also notes that the accelerated approval pathway could be appropriate when a suitable surrogate endpoint has been identified. More details are given in Appendix 1 (c).

4. FDA Guidance on Duchenne Muscular Dystrophy and Related Dystrophinopathies

In February 2018, FDA issued final guidance on the development of drugs for the treatment of Duchenne and related dystrophinopathies.[16] The guidance notes that "FDA has no defined set of required or recommended clinical outcome measures for studies in dystrophinopathies" and suggests that existing or novel outcome measures that can measure clinically meaningful effects in patients may be appropriate. The guidance further encourages the use of "endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages," including endpoints that can assess function across different stages of the disease (e.g., for both ambulatory and non-ambulatory patients). The guidance discusses the use of clinical outcome assessments, including patient- or observer-reported outcomes to assess the abilities and experiences of patients across a spectrum of disease stages and severities, and performance-based outcome assessments. The document also considers clinical outcome assessments by age and/or disease stage and discusses the use of endpoints that can demonstrate an effect on respiratory and/or cardiac function. Additional details are provided in Appendix 1 (d).

B. Highlights of FDA's Approvals of Products for Duchenne

1. Traditional approval

a) Deflazacort

Deflazacort is a corticosteroid indicated for the treatment of Duchenne in patients 2 years of age and older. It received traditional approval for patients 5 years and older in February 2017[17] and a supplement was approved in June 2019 to expand the indication to patients 2 years and older.[18] Efficacy was demonstrated by a single multicenter, randomized, double blind, placebo-controlled, 52-week study comparing two doses of deflazacort, an active comparator (prednisone 0.75 mg/kg/day), and placebo. The primary efficacy endpoint was average change in muscle strength from baseline to week 12 compared with placebo. A second study provided supportive evidence of the results of the first study. A more comprehensive summary of the two clinical trials used to demonstrate substantial evidence of effectiveness is included in Appendix 2.

The medical review[19] said the following about the primary efficacy endpoint of the first study:

"Note that the primary endpoint effects…with a maximum change from baseline strength of 0.26 for deflazacort and -0.1 for placebo, are statistically significant but represent very small changes on the eleven-point strength scale. Over the course of only 12 weeks, such a small change would likely not be clinically meaningful for a patient. The muscle strength continues to improve beyond 12 weeks in the deflazacort group, as seen in the secondary endpoint 52-week analysis…becoming more clinically meaningful."

2. Accelerated approvals (listed in order of approval)

a) Eteplirsen

Eteplirsen, an exon-skipping phosphorodiamidate morpholino oligomer (PMO) therapy targeting exon 51, received accelerated approval in September 2016, based on the surrogate endpoint of an increase in truncated dystrophin production in skeletal muscle. In a study of 13 patients (only 12 with evaluable results), the mean increase of dystrophin level after 48 weeks was 0.3%[20] using a western blot assay.[21] Eteplirsen is indicated for those with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping (about 13% of DMD patients). The applicant submitted data from three studies (one of which was an open-label extension of another) to FDA in support of the application. A summary of these studies is included in Appendix 3.

The accelerated approval of eteplirsen was discussed in detail in the summary review included in the approval package.[21] Dr. Janet Woodcock, at the time Director of the Center for Drug Evaluation and Research, ultimately determined that the data met the standard for accelerated approval. There was a subsequent appeal within the Agency related to this approval and Dr. Robert Califf, then FDA Commissioner, made the determination to defer to Dr. Woodcock's judgment and to approve eteplirsen under accelerated approval. The detailed discussions included in the package are included in Appendix 3.

b) Golodirsen

Golodirsen, an exon-skipping PMO therapy targeting exon 53, received accelerated approval in December 2019. This was based on the same surrogate endpoint used for the accelerated approval of eteplirsen, an increase in truncated dystrophin production in skeletal muscle.[22] Golodirsen is indicated for those with a confirmed mutation of the dystrophin gene amenable to exon 53 skipping (about 8% of Duchenne patients). Golodirsen was evaluated in a single two-part phase 1/2 efficacy study and a summary of these two parts is included in Appendix 4.

Golodirsen initially received a complete response letter (CRL), which was overturned on appeal. The CRL was issued by Dr. Ellis Unger, Director of the Office of Drug Evaluation I, based on infections in the eteplirsen program, renal toxicity findings from nonclinical studies, and experience with other antisense oligonucleotides (ASOs). Dr. Unger wrote that the small mean change in dystrophin level of 0.92% as measured by western blot after 48-59 weeks of treatment, an unverified measure of benefit, did not outweigh the risks, which were not apparent at the time of the approval of eteplirsen.[23] The applicant submitted a Formal Dispute Resolution Request and ultimately Dr. Peter Stein, Director of the Office of New Drugs, overturned the CRL. Further details on the issues related to the golodirsen approval are provided in Appendix 4.

c) Viltolarsen

Viltolarsen is an ASO indicated for the treatment of Duchenne in patients who have a confirmed mutation of the dystrophin gene that is amenable to exon 53 skipping (about 8% of Duchenne patients, and the same population for which golodirsen is indicated). Viltolarsen received accelerated approval in August 2020 based on the same surrogate endpoint as eteplirsen and golodirsen, an increase in truncated dystrophin production in skeletal muscle (mean increase of dystrophin level of 5.3% (80 mg/kg) and 5.4% (40 mg/kg) by Week 25 as measured by western blot analysis). The effect of viltolarsen on dystrophin production was evaluated in one study in which the primary endpoint was the change from baseline to week 25 in dystrophin protein levels as measured by western blot analysis.

The Summary Review noted that the submitted study results "rigorously established that viltolarsen is able to produce statistically significant increases in truncated dystrophin at dosages of 40 mg/kg and 80 mg/kg administered once weekly."[24] The Summary Review also stated that "the positive and highly statistically persuasive results, with support across both dose levels and secondary endpoints, make reliance on a single efficacy study appropriate to support approval… The seriousness of the indication along with the unmet medical need make the risk for renal toxicity acceptable, and manageable through labeling and enhanced pharmacovigilance." A more comprehensive summary of the clinical data relied upon for the approval is included in Appendix 5.

d) Casimersen

Casimersen is an ASO indicated for the treatment of Duchenne in patients who have a confirmed mutation of the dystrophin gene that is amenable to exon 45 skipping (about 8% of Duchenne patients). Casimersen received accelerated approval in February 2021 based on the same surrogate endpoint as the prior exon-skipping products: an increase in truncated dystrophin production in skeletal muscle (mean increase of dystrophin level of 0.81% as measured by western blot at Week 48).[25] The effect of casimersen on dystrophin production was evaluated in one double-blind, placebo-controlled, multicenter clinical study. From this, FDA determined that patients who received casimersen showed a significantly greater increase in dystrophin protein levels from baseline to Week 48 of treatment compared to those who received placebo. FDA's Summary Review of casimersen[25] noted that "…the statistically significant increase in de novo (truncated) dystrophin protein…supports accelerated approval of casimersen for the treatment of [Duchenne] in patients with a genetic mutation amenable to exon 45 skipping. Study 4045-301 is ongoing, and the clinical outcomes from the study will serve to assess the clinical benefits of the observed increases in dystrophin." A more comprehensive summary of the clinical data relied upon for approval is included in Appendix 6.

IV. ACCELERATED APPROVAL PATHWAY FOR AAV GENE THERAPY DEVELOPMENT FOR DUCHENNE PATIENTS

As noted previously, Duchenne is a serious, rare disease with unmet medical need. Given the challenges faced by all stakeholders interested in designing and conducting clinical trials, it is important to work collaboratively to facilitate and expedite the development of therapeutic options, including leveraging available regulatory flexibility. This includes the potential use of accelerated approval and other programs, when relevant criteria are met, such as fast track, breakthrough therapy, RMAT, and priority review. This collaboration will involve sponsors and other stakeholders in sharing learnings, helping

foster the development of each company's product, while also moving the entire development space for Duchenne forward.

The PDC seeks to work collaboratively to identify approaches that could enable the use of the accelerated approval pathway. Critical to any development program is the need for endpoints that can be the basis for approval. As noted in FDA's draft guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,[26] "the 'substantial evidence' of effectiveness standard in the statute…refers to both the quality and the quantity of the evidence. It clearly provides that all clinical investigations supporting effectiveness should be of appropriate design and of high quality…The clinical endpoints studied are a critical aspect of evidence quality…The Agency accepts 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) as the basis for traditional approval. In contrast to 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."

It is unclear how FDA's conclusion that truncated dystrophin at low levels is a surrogate endpoint reasonably likely to predict clinical benefit will translate to AAV gene therapy, which is currently focused on the production of microdystrophin. Finally, no intermediate clinical endpoints for accelerated approval have been identified for use in Duchenne drug development.

The PDC seeks to continue the work initiated at its initial Duchenne Roundtable in April 2021[10] The consortium aims to facilitate the identification and rationale for Duchenne endpoints to support approval in various subgroups of patients with differing Duchenne disease burdens. It is important to ensure therapeutic development for the entire spectrum of Duchenne patients (e.g., inclusive enrollment, approaches to extrapolate data to other populations not part of the primary analysis). The use of the accelerated approval pathway is an important tool for providing access to treatments for Duchenne, especially those designated as RMAT. Therefore, PDC efforts will focus on endpoints that could be the basis for accelerated approval. These could include both surrogate and intermediate clinical endpoints. However, the PDC plans to focus initially on applying lessons learned from the use of truncated dystrophin expression as a surrogate endpoint, to support the use of microdystrophin as a surrogate endpoint for accelerated approval of AAV gene therapies for Duchenne. Another key aspect of an accelerated approval is the need for confirmatory studies to verify clinical benefit.

Finally, in addition to demonstrating efficacy, sponsors seeking product approval also require data to meet the same statutory standards for safety. The safety standard for approvals requires "having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling."[27] This safety standard "implies a risk/benefit judgment" in which "the effect shown must be such as to outweigh the risks of the treatment under the conditions of use."[28] FDA has further explained that "the goal of safety evaluation during drug development is to characterize the drug's safety profile in a reasonable number of patients over a reasonable duration of time, consistent with the intended use of the drug."[29] For rare diseases, however, "reasonable" requires "consideration of feasibility challenges posed by the limited number of patients with the disease."[29] The legal safety standard remains unchanged and is evaluated by "what is a

feasible and sufficient safety assessment is a matter of scientific and regulatory judgment based on the particular challenges posed by each drug and disease, including patients' tolerance for risk in the setting of unmet medical need."[29] Therefore, when evaluating how the accelerated approval pathway can be used for AAV gene therapies, the PDC will consider approaches to ensure adequate safety data is available for risk/benefit determinations.

I. Appendix 1 –Summary of Relevant FDA Programs and Guidances

A. FDA Guidance on Expedited Programs for Serious Conditions – Drugs and Biologics

FDA issued final guidance on available programs to expedite the development of drugs and biologics for serious conditions in May 2014.[12] This discusses the accelerated approval pathway, used for four of the five products currently approved by FDA for Duchenne. The accelerated approval provisions included in the FDA Safety and Innovation Act (FDASIA), amending section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), provide that FDA may grant accelerated approval to:

> "…a product for a serious or life-threatening disease or condition…upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

This 2014 guidance notes that, "the accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. For drugs granted accelerated approval, post-marketing confirmatory trials have been required to verify and describe the anticipated effect on irreversible morbidity and mortality (IMM) or other clinical benefit."[13]

B. FDA Guidance on Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

In February 2019, FDA issued final guidance on section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act, which addressed regenerative medicine therapies.[14] Under section 506(g) of the FD&C Act, a regenerative medicine therapy can be designated as a regenerative advanced therapy if it meets certain criteria. FDA refers to such designation as "regenerative medicine advanced therapy" (RMAT) designation. In this 2019 guidance, the Agency notes that "based on FDA's interpretation of section 506(g), human gene therapies…may meet the definition of a regenerative medicine therapy." The guidance also clarifies specific provisions related to accelerated approval for those products with an RMAT designation, noting that "RMATs may be eligible for accelerated approval based on:

- Previously agreed-upon surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit, or
- Reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate."

Section 506(g)(7) of the FD&C Act also provides that sponsors of products that have been granted RMAT designation and which receive accelerated approval may be able to fulfill the post-approval requirements from clinical evidence obtained from sources other than the traditional confirmatory clinical trials, including:

- "The submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence such as electronic health records;
- The collection of larger confirmatory data sets as agreed upon during product development; or
- Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy."

C. FDA Draft Guidance on Human Gene Therapy for Neurodegenerative Diseases

FDA draft Guidance on Human Gene Therapy for Neurodegenerative Diseases, issued in January 2021,[15] states that the agency "encourages sponsors to explore a wide range of endpoints to assess preliminary safety, activity and effectiveness of a GT [gene therapy] product in early-phase trials. Clinical endpoints should enable assessment of potential clinical benefit; biomarkers and potential surrogate endpoints may indicate activity of the GT product. Such endpoint assessments may help guide further clinical development. For example, changes in the amount of transgene product expressed in the targeted tissue may provide early evidence of GT product activity and thus inform subsequent dose selection."

This guidance also notes that "patient experience data may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development, and to submit such data in the marketing application."

D. FDA Guidance on Duchenne Muscular Dystrophy and Related Dystrophinopathies

In February 2018, FDA issued final guidance on the development of drugs for the treatment of Duchenne and related dystrophinopathies.[16] The guidance notes that "FDA has no defined set of required or recommended clinical outcome measures for studies in dystrophinopathies" and suggests that existing or novel outcome measures that can measure clinically meaningful effects in patients may be appropriate. The guidance further encourages the use of "endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages," including endpoints that can assess function across different stages of the disease (e.g., for both ambulatory and non-ambulatory patients).

The guidance discusses the use of clinical outcome assessments:

- Patient-reported outcomes (PROs) or observer-reported outcomes that "assess the abilities and experiences of patients across a spectrum of disease stages and severities. PROs can be useful to assess the clinical meaningfulness of an objective finding of relatively small magnitude and to contribute to assessments of benefit and risk." The guidance encourages the use of PRO instruments that include a limited number of items assessing the most important aspects of the outcome of interest.
- Performance-based outcome assessments that demonstrate the patient's ability to perform an activity. This might include time to event for decline or loss of an ability, or for young children in whom abilities are still developing, time to event in the positive sense (i.e., the time to reach a certain developmental milestone). The guidance notes the potential impact of bias on functional endpoints, where patient effort and/or coaching can impact outcomes and encourages blinding and other measures to minimize any such influence.

In addition, the guidance provides considerations for clinical outcome assessments by age and/or stage of the disease:

- For children up to age 4, developmental scales (e.g., the Griffiths Scale of Mental Development or Bayley Scales of Infant and Toddler Development, Third Edition).
- For ambulatory children aged 3 and older, the NSAA or an age-appropriate modified NSAA "can provide a useful measure of gross motor function," as can timed function tests such as time to climb four stairs or time to walk/run 10 meters, among others.
- In children 5 years and older, myometry may be an appropriate endpoint for treatments that increase or preserve muscle strength. The guidance notes that measures of muscle strength could potentially be appropriate as intermediate clinical endpoints to support accelerated approval.
- In children as young as 5, the 6-minute walk test (6MWT) or shorter versions can measure both strength and endurance, though these tests do have specific challenges including natural performance improvement in very young patients and natural worsening performance in older patients.
- In older, non-ambulatory patients, a number of outcome measures are available that primarily measure upper extremity function.

The guidance also discusses the use of endpoints that can demonstrate an effect on respiratory and/or cardiac function:

- Respiratory outcomes included in the guidance are nocturnal desaturation, aspiration pneumonia, and progression to mechanically assisted ventilation. Measures mentioned in the guidance include forced vital capacity, maximal inspiratory pressure, and maximal expiratory pressure. The guidance notes that such measures could also be considered as intermediate clinical endpoints to support accelerated approval.
- Improved exercise capacity could be considered an appropriate endpoint. However, the guidance notes that, "One obvious disadvantage of an approach demonstrating improvement in exercise capacity is that the effects of skeletal muscle function and cardiac muscle function might not be easily distinguished."

II. Appendix 2 – Summary of Deflazacort Data

The Medical Review for deflazacort provided a detailed overview of the clinical trials used to demonstrate substantial evidence of effectiveness.[19] A summary follows below:

- Study NM-001 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, 52-week study comparing two doses of deflazacort (0.9, 1.2 mg/Kg/day), an active comparator (prednisone 0.75 mg/Kg/day), and placebo. The primary efficacy endpoint was average change in muscle strength from baseline to Week 12 compared with placebo. Following the initial 12-week segment of the study, placebo patients were randomly assigned to one of the three active treatment groups for the remaining 40 weeks of the study. Those already in an active treatment group continued in that study arm for the remaining 40 weeks. This study showed that mean strength increased slightly in both deflazacort groups (~2-3%) compared to a small decrease in strength in the placebo group (<1%) over the 12-week placebo arm of the study. The findings at Week 12 in both deflazacort groups were statistically significant. In addition, for both deflazacort doses, the mean muscle strength continued to trend upwards to study completion at 52 weeks, with an approximate improvement of 5% in mean strength compared to baseline.

  To assess the primary efficacy endpoint, patients were asked to perform specific movements in various positions (sitting, prone, side-lying, and supine) at each visit. Each test was graded using an 11-point scale (from 10-normal strength to 0-no movement). The following strength tests were assessed, and modalities listed in parentheses were used only with patients who could not perform movements against gravity.

  Sitting
  - Shoulder abduction
  - Elbow flexion
  - Wrist flexion
  - Wrist extension
  - Thumb abduction
  - Hip flexion
  - Knee extension
  - Ankle dorsiflexion
  - Ankle eversion
  - Ankle inversion

  Prone
  - Neck extension
  - Shoulder external rotation
  - Knee flexion
  - Ankle plantar flexion
  - Hip extension

  Lying on Side
  - Hip abduction
  - (Hip flexion)
  - (Hip extension)
  - (Knee flexion)
  - (Knee extension)
  - (Ankle dorsiflexion)

- (Ankle plantar flexion)
- (Neck extension)

Supine
- Elbow extension
- Neck flexion
- (Shoulder abduction)
- (Hip abduction)

(Repeat Lying on Side)
- (Neck flexion)

(Repeat Sitting)
- (External shoulder rotation)
- (Elbow extension)

Although multiple secondary endpoints were included in the study, the only secondary endpoint that was statistically controlled for Type I error was the least squares (LS) mean change from baseline in average muscle strength scores from Week 12 to Week 52 in the intention-to-treat (ITT) population. Therefore, the review noted that other secondary endpoints are considered as exploratory, and any positive results can only be viewed as nominally significant:

- Change in myometric measurements (these measurements recorded muscle force in Newtons for shoulder abduction, elbow flexion/extension, and knee flexion/extension)
- Change in timed functional tests (standing from a lying position, climbing 4 stairs, running or walking for 30 feet, and propelling a wheelchair for 30 feet)
- Change in pulmonary function tests (forced vital capacity and maximum voluntary ventilation)
- Muscle metabolic markers (aspartate aminotransferase [AST], creatine kinase [CK] and lactate dehydrogenase [LDH])
- Physician global assessment using an analog scale (number line) where 0 cm = “no symptoms” and 10 cm = “as bad as it could be.”

- Study NM-002 was a randomized, double-blind, placebo-controlled, 104-week clinical trial that also examined average muscle strength. Although this study had a negative finding for the primary endpoint at Year 2, the loss of most placebo patients from the study at Year 2 made the primary endpoint result unclear; positive results at Year 1 combined with the results of the secondary endpoint analyses provided confirmatory evidence to support the results of study NM-001.

  The primary endpoint was defined as the change in muscle strength from baseline to 2 years or loss of ambulation using a 0 to 5 point verbal rating scale, assessed manually, and converted to a Medical Research Council (MRC) index score. The MRC score, assessed at 6 months and at 1, 2, and 3 years, was expressed as a percentage of “normal strength” for the sum of 4 strength measurements (right triceps, right deltoid, right quadriceps, and right iliopsoas). Therefore,

unlike study NM-001, this study only included ambulatory patients for the primary endpoint calculation, as patients who lost ambulation during the study were dropped.

Secondary efficacy endpoints were assessed at 6 months and at 1, 2, and 3 years. The secondary endpoints were only presented descriptively as part of the review as the submitted protocol did not contain information on the statistical analysis methods and the key secondary efficacy endpoints were not prespecified. They included:

- Change from baseline in muscle function (walking, climbing stairs, standing up from a chair with no armrests, standing from sitting on floor [Gower's Maneuver], putting on a shirt without buttons)
- Change from baseline in muscle strength using the Hammersmith myometer
- Time to loss of ambulation
- Age at time of loss of ambulation
- Condition as assessed by the patient's parent (improved, worsened, or stable)
- Cooperation as assessed by the patient's parent (good, sufficient, or nil)
- Physical therapy regularity (regular, sporadic, or none) as reported by patient's parent

III. Appendix 3 – Summary of Eteplirsen Data

The applicant submitted the following study results to FDA in support of the eteplirsen application:

- *Study 1* (NCT01396239, aka 201) was a single-center (US), double blind, placebo-controlled, parallel-dose study in which 12 patients were randomized to receive weekly infusions of eteplirsen (30 mg/kg, n=4); eteplirsen (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was change in the number (%) of dystrophin positive fibers from baseline compared to 12 weeks as measured in the muscle biopsy tissue on immunohistochemistry (IHC); a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed.

- *Study 2* (NCT01540409, aka 202) was a multicenter (US), open-label, multiple-dose extension study in which the 4 patients from Study 1 originally randomized to placebo were re-randomized 1:1 to eteplirsen at either 30 or 50 mg/kg/week resulting in 6 patients on each dose. All investigators and patients remained blinded to dose. Patients in Study 2 were compared to an external historical control group (FDA noted many concerns with these historical controls). The primary clinical efficacy outcome measure was the change from baseline in 6MWT at week 240. There was no significant difference in this measure between patients treated with eteplirsen and those treated with placebo. In a study of 13 patients (only 12 with evaluable results), the mean increase of dystrophin level after 48 weeks was 0.3%[19] using a western blot assay.[21] The western blot quantification measure showed a mean dystrophin value of 0.93% of normal after 3 to 3.5 years of treatment, though the values were virtually the same for the lower and higher dose groups.

- *Study 3* (NCT02255552 aka PROMOVI, study 4658-301) was a Phase 3 open-label, multi-center (37 sites in US), study that ultimately enrolled 109 male Duchenne patients aged 7-16. The primary endpoint was change in 6MWT from baseline to week 96. At the time of submission, this study was ongoing, and FDA requested western blot analyses of biopsy samples to gain additional information on the viability of Becker-type dystrophin production as a surrogate endpoint. The mean dystrophin quantification via western blot was between 0.22% and 0.32% of normal. No clinical data were submitted from this study.

- A confirmatory trial was required by the FDA to verify clinical benefit. The approval letter described a post-marketing requirement of a 2-year randomized, double blind, controlled trial in the approved dose and a significantly higher dose. The letter states, "The primary endpoint will be the North Star Ambulatory Assessment."

Internal FDA discussion on the eteplirsen approval

The accelerated approval of eteplirsen was discussed in the summary review section of the approval package.[21] The memoranda included in this package contain extensive discussions of relevant endpoints in Duchenne. Dr. Ellis Unger, Director of the Office of Drug Evaluation I, disagreeing with the ultimate decision to approve, wrote in his memo that "there is no debate about the appropriateness of dystrophin as a surrogate endpoint for Duchenne muscular dystrophy." The review team, as well, was willing to assume that whatever shortened, Becker-type dystrophin the drug produces would function as well as in the Becker form of the disease, which has milder symptoms than Duchenne. However, the minimum level of Becker-type dystrophin that is reasonably likely to predict clinical benefit is unknown;

the review division had proposed 10% of normal dystrophin levels as a minimum level to confer measurable benefit, which was greater than the production shown in these trials. There was also internal disagreement about whether dystrophin production was clearly demonstrated in two trials or just one; Dr. Unger's memo described various difficulties in interpretability that rendered one study not adequate and well controlled in his judgment.

The first study and its open-label extension collected physical performance data, but the review division concluded that no patient clearly deviated from natural history. Additionally, for the 4 patients whose 6MWT performance was best preserved, 2 had the highest levels of dystrophin detected and 2 had levels close to zero. As discussed later, the concerns noted by the review division reflect an ongoing challenge for Duchenne trials: the heterogeneity of the disease, combined with its relatively long time to progression (as compared to some other rare diseases), makes functional endpoints difficult to assess as compared to natural history controls.

Dr. Unger also disagreed that the study met the primary endpoint of a meaningful benefit based on the 6MWT. His memo noted the study was externally controlled, the statistical test was based on a non-randomized comparison, and the patients did not demonstrate a substantial treatment effect on walking velocity that clearly differentiated their course from natural history, among other issues. FDA had agreed to this design prior to the study but expressed concern that the 6MWT endpoint was not a "hard" endpoint and was subject to influence by multiple factors, and thus the treatment effect would have to be dramatic, especially given the external control. Additionally, other measures, including rise time, timed 10-meter run, and the NSAA showed steady decline that did not substantially differ from the decline in the external control group. Dr. Unger's memo noted that, "The NSAA is thought to be a comprehensive outcome measure, well reflecting the functional abilities of DMD patients." However, despite patient-reported claims of improvement with eteplirsen, the study found no patients with consistent improvement in physical performance as assessed by formal testing, including the 6MWT, NSAA, or 10-meter run.

Dr. Janet Woodcock, at the time Director of the Center for Drug Evaluation and Research, ultimately determined that the data met the standard for accelerated approval. She disagreed that the first study and its open-label extension was rendered entirely inadequate by the issues cited above. She asserted that the data clearly showed that the drug increases dystrophin production in some patients, albeit at a low level. Her memo noted that although dystrophin content above 10% is usually associated with a Becker muscular dystrophy phenotype, a proportional inverse relationship between disease severity and protein expression has not generally been demonstrated within that phenotype. She wrote that the evidence suggests that protein quality plays a key role in determining phenotype and there is no evidence of a threshold value.

She also evaluated the NSAA in children who could still walk and who had a dystrophin result at Week 180 and found a positive inverse correlation between dystrophin and rate of decline in NSAA score (though this methodology was disputed by others). She concluded that low-level increases in dystrophin production are reasonably likely to predict clinical benefit. These disagreements were internally appealed. Eventually, Dr. Robert Califf, then FDA Commissioner, made the determination that he had no special knowledge that would justify questioning the judgement of the most senior drug regulator in the agency and chose to defer to Dr. Woodcock's judgment and to approve eteplirsen under accelerated approval.

IV. Appendix 4 – Summary of Golodirsen Data

Golodirsen was evaluated in a single two-part Phase 1/2 study (NCT02310906)

- Study 1, Part 1 was a global multi-site (US, France, Italy, UK) double blind, placebo-controlled, dose-titration study in 12 male patients aged 6-15 with a confirmed DMD gene mutation amenable to exon 53 skipping designed to assess 4 dose levels.
- Study 1, Part 2 was a 168-week, open-label study assessing efficacy and safety at a dose of 30 mg/kg/week in 25 patients (the 12 patients enrolled in Part 1, plus 13 additional treatment-naïve patients with Duchenne amenable to exon 53 skipping).
- Following accelerated approval, the FDA is requiring that a placebo-controlled, post-marketing confirmatory trial be completed, titled ESSENCE, which was ongoing at the time of approval. This trial is expected to conclude by 2024.[22] The approval letter described a post-marketing requirement of a randomized, double-blind, placebo-controlled, 96-week multicenter study comparing both golodirsen and casimersen with placebo with an open-label extension to 144 weeks. The approval letter states ,"The primary endpoint will be the 6-minute walk test."

Data in the application showed a mean increase in truncated dystrophin quantification by western blot from 0.1% of normal at baseline to 1.02% after 48-59 weeks of treatment, which was a highly statistically significant change. The 6WMT and forced vital capacity (FVC) test, with at least 144 weeks of follow-up, showed a decrease from baseline, but this was deemed to be uninterpretable due to the lack of a control group and the fact that the study was underpowered to detect a relationship between these endpoints. Additionally, the progression did not appear to differ significantly from natural history.

Internal FDA discussion on the golodirsen approval

Following the CRL issued by Dr. Ellis Unger for golodirsen, the applicant submitted a Formal Dispute Resolution Request and ultimately Dr. Peter Stein, Director of the Office of New Drugs, overturned the CRL.[30]

Dr. Stein posited that the risks could be monitored and addressed with updated labeling and other measures. He added that the increase in dystrophin levels was similar to that seen with eteplirsen, which had received accelerated approval on the basis that such increase was reasonably likely to predict clinical benefit. Without new evidence to suggest otherwise, he argued that the similar dystrophin levels warranted accelerated approval of golodirsen as well.

Dr. Stein's memo further explored the proposed surrogate endpoint, noting that animal models have also demonstrated that even low levels of dystrophin provide a survival benefit as well as functional improvements. Additionally, patients can generally be categorized by severity of disease progression based on ranges of dystrophin production, with those with less than 3% having the most severe course. Acknowledging that it is unknown whether natural dystrophin levels and dystrophin produced via ASO treatment can be treated as comparable, there is evidence that truncated dystrophin can be functional. His memo further reasoned that even modest improvements in hand or leg muscle strength, or diaphragmatic strength that led to improvements in hand coordination, grip strength, ambulation, respiratory function, or other similar improvements, would be meaningful and are reasonably likely based on evidence of effects of low levels of dystrophin compared to complete absence of the protein.

V. Appendix 5 – Summary of Viltolarsen Data

The Summary Review for viltolarsen[24] provided a detailed description and overview of the biomarker and safety data from one study in the application (Study NS-065/NCNP-01-201) which assessed dosages of either 40 or 80 mg/kg/week in 16 ambulatory Duchenne patients 4 to <10 years of age (mean age of 7 years) on stable doses of corticosteroids with no evidence of symptomatic cardiomyopathy, as well as additional safety data that were provided from an ongoing long-term extension study (202) in these patients. That information is summarized below:

- The effect of viltolarsen on dystrophin production was evaluated in one study, Study NS-065/NCNP-01-201, which was conducted in Duchenne patients with a confirmed mutation of the dystrophin gene that is amenable to exon 53 skipping. Patients who received 80 mg/kg once weekly had mean dystrophin levels that increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5, mean change 5.3% p=0.01, median 3.8%) of normal (assessed by western blot) by Week 25. Patients who received 40 mg/kg once weekly demonstrated an increase in relative dystrophin levels from 0.3% of normal at baseline to 5.7% (mean change 5.4%, p=0.001; median 4.6%) by Week 25. The primary endpoint was the change from baseline to week 25 in dystrophin protein levels (in biceps muscle biopsy samples) determined by western blot analysis.

- Additionally, assessments of the multiple functional outcomes related to muscle strength, mobility, and functional exercise capacity were collected as secondary endpoints and measured at 25 weeks compared to a matched natural history control group from the Cooperative International Neuromuscular Research Group (CINRG) network natural history database. According to FDA's Summary Review: "the applicant's analysis did not show any clinically meaningful difference in clinical function at the end of 24 weeks of treatment with viltolarsen 40 and 80 mg/kg/week, compared to natural history."

- Following approval, the FDA is requiring the completion of a study to verify the clinical benefit. The study is a Phase 3, randomized, double blind, placebo-controlled, multi-center study to assess the efficacy and safety of viltolarsen in ambulant boys with Duchenne over 48 weeks. The primary endpoint will be the Time to Stand test, and it is expected that the trial will conclude by 2024. Additionally, FDA issued postmarketing requirements (PMRs) for assessments of QT prolongation and immunogenicity.

FDA's Summary Review of viltolarsen explained:

> "The accelerated approval pathway is appropriate for viltolarsen because [Duchenne] is clearly a serious and life-threatening disease, and viltolarsen has the potential to address an unmet medical need and provide an advantage over available therapy (deflazacort) in some patients. Deflazacort has a modest response rate, and there is evidence that a substantial proportion of [Duchenne] patients are not using steroids, in part because of their safety profile. Viltolarsen has a novel mechanism of action that has a well-understood relationship to the disease pathophysiology, and has been shown to increase dystrophin levels in [Duchenne] patients with a genetic mutation amenable to exon 53 skipping, thereby potentially improving muscle function. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for viltolarsen is similar in size or may be slightly

> greater to that established for eteplirsen and golodirsen, drugs that received accelerated approval based on a previous conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. Based on these precedents, and barring any evidence to suggest otherwise, the statistically significant increase in de novo (truncated) dystrophin protein…supports accelerated approval of viltolarsen."

Of note, FDA's Summary Review stated that "given the variability in the natural history of [Duchenne], comparisons to a natural history cohort, even when matched controls are utilized, does not appear reliable."

The Summary Review also noted that the study "rigorously established that viltolarsen is able to produce statistically significant increases in truncated dystrophin at dosages of 40 mg/kg and 80 mg/kg administered once weekly." The Summary Review also stated that "the positive and highly statistically persuasive results, with support across both dose levels and secondary endpoints, make reliance on a single efficacy study appropriate to support approval." With regard to safety, FDA observed in the Summary Review that "renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for serious renal toxicity in humans. No serious renal adverse reaction, however, was reported in viltolarsen clinical studies. The seriousness of the indication along with the unmet medical need make the risk for renal toxicity acceptable, and manageable through labeling and enhanced pharmacovigilance."

VI. Appendix 6 – Summary of Casimersen Data

The Clinical Review for casimersen[25] provided a detailed description and overview of the biomarker and safety data for casimersen from one arm of one study in the application (Study 4045-301). That information is summarized below:

- The effect of casimersen on dystrophin production was evaluated in the casimersen arm of one study (Study 1; NCT02500381; Study 4045-301) from which FDA determined patients who received casimersen showed a significantly greater increase in dystrophin protein levels from baseline to week 48 of treatment compared to those who received placebo. From this, FDA concluded that the data submitted demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in patients with Duchenne who have a confirmed mutation of the dystrophin gene amenable to exon 45 skipping.

- Study 1 is an ongoing, double blind, placebo-controlled, multicenter clinical study in ambulatory Duchenne patients with an open-label extension study to assess the efficacy and safety of casimersen and golodirsen. The golodirsen arm will serve as the confirmatory study for golodirsen, which was previously granted accelerated approval. The submission for casimersen contained data from the casimersen arm of Study 1. In the casimersen arm, Study 1 is enrolling ambulatory Duchenne patients amenable to exon 45 skipping, taking a stable dose of corticosteroids for at least 24 weeks, stable pulmonary function (FVC % of predicted $\geq$ 50% and no requirement for nocturnal ventilation), and a mean 6MWT distance of $\geq$ 300 to $\geq$ 450 meters (without assistance) at both screening and baseline visits. The study consists of a 96-week randomized, double blind, placebo-controlled period, followed by a 48-week open-label period. By the time of submission of the application for casimersen there were 76 patients exposed to casimersen, with 59 patients with > 48 weeks of exposure, and 19 patients with > 120 weeks of exposure. However, the accelerated approval of casimersen was based on the results from 43 patients randomized 2:1 (27 to casimersen, 16 to placebo).

- Dystrophin levels were assessed by the Sarepta western blot assay and increased from 0.93% (SD 1.67) of normal at baseline to 1.74% (SD 1.97) of normal after 48 weeks of treatment with casimersen. The mean change from baseline in dystrophin after 48 weeks of treatment with casimersen was 0.81% (SD 0.70) of normal levels ($p<0.001$). The mean change from baseline in dystrophin after 48 weeks of treatment with placebo was 0.22% (SD 0.49). In the Summary Review,[25] FDA noted that it determined that "the change in dystrophin level, albeit small, has a high level of statistical persuasiveness" and that "the increase in dystrophin level was statistically significantly greater in the casimersen group than in the placebo group."

- "The increases observed on western blot are also supported by confirmation of exon 45 skipping by measurement and sequence verification of exon 45 skipped mRNA. The casimersen group had a statistically significantly greater increase in percent exon skipping from baseline to week 48 than the placebo group (mean difference of 1.599; $p < 0.001$). Overall, the positive and highly statistically persuasive results, with support on the secondary endpoint of exon skipping, make reliance on a single efficacy study appropriate to support approval."

- With regard to safety, FDA observed in the Summary Review that "renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for renal toxicity in humans. No serious renal adverse reaction was reported in casimersen clinical studies. The seriousness of the indication along with the unmet medical need make the risk for renal toxicity acceptable, and manageable through labeling and enhanced pharmacovigilance."
- Following approval, the FDA is requiring the completion of the ongoing confirmatory randomized, double blind, placebo-controlled study with a 96-week placebo-controlled period followed by an open-label extension period to 144 weeks. The primary endpoint will be the 6MWT. The company expects the trial to conclude by 2024. Additionally, FDA issued PMRs for assessments of QT prolongation and immunogenicity.

Similar to its Summary Review of viltolarsen, FDA's Summary Review of casimersen explained:

> "The accelerated approval pathway is appropriate for casimersen because [Duchenne] is clearly a serious and life-threatening disease, and casimersen has the potential to address an unmet medical need and provide an advantage over available therapy (deflazacort) in some patients. Deflazacort has a modest response rate, and there is evidence that a substantial proportion of [Duchenne] patients are not using steroids, in part because of their safety profile. Casimersen has a novel mechanism of action that has a well-understood relationship to the disease pathophysiology, and is the first drug that has been shown to increase dystrophin levels in Duchenne patients with a genetic mutation amenable to exon 45 skipping, thereby potentially improving muscle function. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for casimersen is similar in size to other approved ASOs, such as eteplirsen and golodirsen, that have received accelerated approval based on a conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. Based on these precedents, and barring any evidence to suggest otherwise, the statistically significant increase in de novo (truncated) dystrophin protein…supports accelerated approval of casimersen for the treatment of [Duchenne] in patients with a genetic mutation amenable to exon 45 skipping. Study 4045-301 is ongoing, and the clinical outcomes from the study will serve to assess the clinical benefits of the observed increases in dystrophin."

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