# Pfizer Presents Initial Clinical Data on Phase 1b Gene Therapy Study for Duchenne Muscular Dystrophy (DMD)

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Pfizer Inc. (NYSE:PFE) will present initial Phase 1b clinical data on PF-06939926, an investigational gene therapy to potentially treat Duchenne muscular dystrophy (DMD) at the 25th Annual Parent Project Muscular Dystrophy (PPMD) Connect Conference in Orlando, FL. These are preliminary data drawn from a small number of participants in an ongoing study.

The primary endpoint of the ongoing Phase 1b study is to assess the safety and tolerability of this investigational gene therapy. Secondary endpoints of the clinical study include measurement of expression of mini-dystrophin distribution within muscle fibers by immunofluorescence and concentration by liquid chromatography mass spectrometry (LCMS). Pfizer aims to enroll approximately 12 boys with DMD who are ambulatory and aged 5 to 12. To date, 6 study participants ranging in age from 6 to 12 years have received the one-time intravenous dose of PF-06939926 at either 1E14 vector genomes/kilogram (vg/kg) or 3E14 vg/kg, as quantified using an inverted terminal repeat-based quantitative polymerase chain reaction (qPCR) drug product titer assay.

“Gene therapy for single-gene disorders is at a formative stage in its evolution, and the initial data we’ve seen in our study for Duchenne muscular dystrophy may exemplify the potential for this modality to change patients’ lives,” said Seng Cheng, Senior Vice President and Chief Scientific Officer of Pfizer’s Rare Disease Research Unit. “We are looking forward to building on these initial data and advancing the development of this therapeutic modality.”

## Preliminary Safety Results

Preliminary safety results show that the most common adverse events suspected to be related to PF-06939926 are nausea, vomiting, decreased appetite, tiredness and/or fever, which were reported within a few days of dosing by 4 of 6 study participants. Nausea and vomiting symptoms were managed with oral antiemetics for 3 of the participants, but one was hospitalized for 2 days for intravenous antiemetics and replacement fluids. In all cases, vomiting and fever symptoms resolved within 2 to 5 days and the other symptoms resolved within 1 to 3 weeks.

As expected, immune responses occurred in all participants and varied in specificity and magnitude as measured by neutralizing antibody levels and T-cell responses on enzyme-linked immune absorbent spot (ELISPOT). One of the 6 participants, however, developed a rapid antibody response with activation of the complement system associated with acute kidney injury, hemolysis, and reduced platelet count. This participant was promptly admitted to a pediatric intensive care unit and received intermittent hemodialysis, as well as 2 intravenous doses of a complement inhibitor. He was discharged from the hospital after 11 days, and his renal function returned to normal within 15 days. None of the other dosed participants had immune-related clinical events. Regardless, in accordance with the original study design, no other participants will be dosed until the specific additional safety monitoring, which has been endorsed by the external data monitoring committee, has obtained all appropriate approvals at the clinical research sites.

## Preliminary Results from Secondary and Exploratory Endpoints

Preliminary results from open muscle biopsies of the biceps taken 2 months after dosing show detectable mini-dystrophin immunofluorescence signals with a mean of 38% positive fibers taken from participants who received PF-06939926 at 1E14 vg/kg and a mean of 69% positive fibers taken from participants who received PF-06939926 at 3E14 vg/kg.

Dystrophin concentrations in healthy or “normal” muscle, or muscle with no known disease, vary widely between samples and individuals, and no industry standard currently exists for defining a “normal” range or threshold. Historically, dystrophin concentration was measured by Western Blot. However, due to limitations of this methodology, Pfizer leveraged its internal expertise in immuno-affinity mass spectrometry protein quantification and developed a proprietary assay to measure dystrophin concentration with a wide dynamic range and low variability. Using this FDA-reviewed LCMS assay, “normal” concentrations of dystrophin were based on pooled skeletal muscle biopsies

from 20 pediatric samples, which resulted in mean concentration of just below 3,000 fmol/mg of protein, while levels in the individual samples differed from the mean approximately 50 to 150%. In the ongoing Phase 1b study, mini-dystrophin concentrations 2 months after dosing for all 6 DMD study participants showed a range of 300-1800 fmol/mg of protein, or 10-60% of “normal”. The mean expression level of mini-dystrophin was 23.6% for participants who received PF-06939926 at 1E14 vg/kg and 29.5% for those who received at 3E14 vg/kg.

Although functional assessments are considered exploratory, due to the small number of planned study participants and the risk for bias in an open-label study, preliminary results for the NorthStar Ambulatory Assessment (NSAA) are available for the only 2 participants with at least 1 year of follow-up, both of whom received PF-06939926 at 1E14 vg/kg. These participants, who were 7 and 8 years upon study entry with baseline NSAA total scores of 24 and 25, respectively, showed mean increases of 4.5 points at the 12-month timepoint. While baseline natural history NSAA scores are variable, generally scores are stable or decline in DMD patients of the same age as these participants, with the rate of progression associated with the baseline age and function (UK NSAA/cTAP; Muntoni et al, PLoS ONE, in press).

As Pfizer continues to collect data from this ongoing open-label study in boys with DMD, it is also in the planning stages for a global, randomized, placebo-controlled Phase 3 study. This study is expected to begin in the first half of 2020 with commercial-scale manufacturing processes using multiple 2000-liter bioreactors. The anticipated Phase 3 study intends to leverage the learnings from the ongoing Phase 1b study in order to inform Pfizer’s decisions regarding the optimal dose, assay, method of administration, concomitant medications, participant selection and safety monitoring.

“The emerging field of gene therapy has collaboration at its core as patients, scientists, clinicians, regulators, and payors all need to come together to share their experiences,” said Debra Miller, CEO and Founder of CureDuchenne. “Without that collaboration, we wouldn’t have made the progress in our community’s understanding of the science that we’re proud is being presented today.”

PPMD Connect Conference is a meeting that brings together families, caregivers, physicians, researchers, industry partners, and those living with DMD to discuss recent studies and opportunities in DMD research, as well as health care priorities impacting the DMD community.

About PF-06939926

DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. In the absence of dystrophin, muscle cells deteriorate. PF-06939926 is an investigational, recombinant adeno-associated virus serotype 9 (AAV9) capsid carrying a shortened version of the human dystrophin gene (mini-dystrophin) under the control of a human muscle-specific promotor. The AAV9 capsid was chosen as the delivery mechanism because of its potential to target muscle tissue. Pfizer initiated the Phase 1b multi-center, open-label, non-randomized, ascending dose study of a single intravenous infusion of PF-06939926 in 2018. The goal of the study is to assess the safety and tolerability of this investigational gene therapy. Other objectives of the clinical study include measurement of dystrophin expression and distribution, as well as assessments of muscle strength, quality and function.

About Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a serious genetic disease characterized by progressive muscle degeneration and weakness. Symptoms usually manifest in early childhood between the ages of 3 and 5. The disease primarily affects boys. Muscle weakness can begin as early as age 3, first affecting the muscles of the hips, pelvic area, thighs and shoulders, and later the skeletal (voluntary) muscles in the arms, legs and trunk. By the early teens, patients typically lose their ability to walk and the heart and respiratory muscles are also affected, ultimately resulting in premature death. DMD is the most common form of muscular dystrophy worldwide with incidence of 1 in every 3500 to 5000 live male births.

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DISCLOSURE NOTICE: The information contained in this release is as of June 28, 2019. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about gene therapy and PF-06939926, an investigational gene therapy to potentially treat Duchenne muscular dystrophy, including their potential benefits and the timing of a potential Phase 3 study for PF-06939926, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risks associated with initial and preliminary data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when drug applications may be filed in any jurisdictions for any potential indication for PF-06939926; whether and when any such applications may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether PF-06939926 will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of PF-06939926; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer’s Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned “Risk Factors” and “Forward-Looking Information and Factors That May Affect Future Results”, as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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