Pfizer’s New Phase 1b Results of Gene Therapy in Ambulatory Boys with Duchenne Muscular Dystrophy (DMD) Support Advancement into Pivotal Phase 3 Study

Friday, May 15, 2020 - 08:00am

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NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced updated Phase 1b clinical data on PF-06939926, an investigational gene therapy being developed to treat Duchenne muscular dystrophy (DMD). The preliminary data from 9 ambulatory boys with DMD, aged 6 to 12 (mean age: 8 years) indicate that the intravenous administration of PF-06939926 was well-tolerated during the infusion period, with encouraging efficacy and manageable safety events, even when considering those adverse events that were more severe in nature. The treatment provided durable and statistically significant improvements across multiple efficacy-related endpoints measured at 12 months post-infusion, including sustained levels of mini-dystrophin expression and improvements on the North Star Ambulatory Assessment (NSAA) rating scale, which is a validated measure of muscle function. Three serious adverse events (SAEs) were recorded, two of which reflected likely complement activation. While these two SAEs were severe in nature, all three events fully resolved within 2 weeks, providing encouragement that close monitoring and early intervention can help mitigate the effects of complement activation. This new dataset, which includes updated 12-month results on safety, dystrophin expression, and exploratory functional endpoints for 3 additional boys, was presented for the first time during a virtual oral session today at the American Society of Gene & Cell Therapy (ASGCT) Annual Meeting.

DMD is a devastating and life-threatening X-linked disease that is caused by mutations in the gene encoding dystrophin, which is needed for proper muscle membrane stability and function. Patients present with muscle degeneration that progressively worsens with age to the extent that they require wheelchair assistance when they are in their early teens, and unfortunately, usually succumb to their disease by the time they are in their late twenties. It is estimated that there are ~10-12,000 individuals affected with DMD in the US.

“Based on the encouraging preliminary efficacy data and manageable safety events from our Phase 1b study, we believe we may have a potential breakthrough therapy for boys with Duchenne muscular dystrophy, a devastating disease for which there remains a significant medical need,” said Seng Cheng, PhD, Chief Scientific Officer, Pfizer Rare Disease Research Unit. “ We are advancing our Phase 3 program as quickly as possible and plan to begin dosing patients in the second half of 2020 pending regulatory approval. Our program has the potential to be the first DMD gene therapy Phase 3 trial start using a commercial-scale manufacturing process. If the program is successful, this manufacturing capability is expected to help position us to deliver this medicine to patients quickly following regulatory approval.”

Data presented at the ASGCT virtual meeting included results from the study of 9 ambulatory boys with DMD, aged 6 to 12 (mean age: 8 years). Three of those 9 patients received a one-time intravenous infusion of PF-06939926 at 1E14 vector genomes per kilogram (vg/kg) (considered to be the low dose) and the other 6 received a one-time intravenous dose of 3E14 vg/kg (considered to be the high dose).

Preliminary Safety Results

The primary endpoint of the Phase 1b study is to assess the safety and tolerability of this investigational gene therapy in ambulatory boys with Duchenne muscular dystrophy through 12 months following treatment. Based on the data to date, the most common adverse events (AEs) suspected to be related to PF-06939926 (occurring in >40% of patients) were vomiting, nausea, decreased appetite, and pyrexia. There was no evidence of clinically relevant anti-dystrophin responses or hepatic dysfunction with the protocol-defined daily glucocorticoid regimen.

Among the 9 patients, 3 serious adverse events (SAEs) were reported in the first 14 days following administration, one more SAE than at Pfizer’s previous update. Importantly, each of these SAEs was fully resolved and at their last clinic visits, all patients were doing well. The first SAE involved persistent vomiting resulting in dehydration, which required

admission for IV anti-emetics and fluids. The second SAE involved acute kidney injury with atypical hemolytic uremic syndrome (aHUS)-like complement activation, which required hemodialysis and treatment with eculizumab. The most recent SAE involved thrombocytopenia with aHUS-like complement activation which required platelet transfusion and treatment with eculizumab. Based on safety observations over the course of the study, Pfizer amended the clinical study protocol to include increased monitoring and management regimes, which helped enable timely intervention and mitigation in the case of the third SAE.

Results from Secondary and Exploratory Endpoints

Secondary endpoints of the clinical study included measurement of mini-dystrophin concentration by liquid chromatography mass spectrometry (LCMS) and distribution within muscle fibers by immunofluorescence.

Dystrophin concentration

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” level. 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. This novel LCMS assay isan anti-peptide antibody enriched, immunoaffinity liquid chromatography tandem mass spectrometry (IA LCMS/MS) assay that has been validated by Pfizer in preclinical species and human tissues and discussed with the United States Food and Drug Administration (FDA).

Using this LCMS assay, “normal” concentrations of dystrophin were established to compare to secondary endpoint results in patients. These “normal” reference levels were based on pooled skeletal muscle biopsies from 60 pediatric samples. In the Phase 1b trial, new results from open muscle biopsies of the biceps of the 3 patients in the low dose cohort showed that the mean percent normal dystrophin at 12 months was 24.0%. For the 3 patients in the high-dose cohort for whom 12-month data are available, the mean percent normal dystrophin at 12 months was 51.6%. Comparisons between baseline and post-treatment measures were significant ($p < 0.005$ at 2 months [N=9], and $p < 0.05$ at 12 months [N=6]). The increases in dystrophin levels observed at 2 months were generally sustained at 12 months, and 5 of the 6 boys showed an increase in mini-dystrophin concentration between the 2- and 12-month time points.

Dystrophin distribution

New results from open muscle biopsies of the biceps at both dose levels using an updated digital platform and analysis with a new quantitative imaging algorithm show dystrophin immunofluorescence, measured as the proportion of muscle fibers expressing dystrophin. Of the 3 patients in the low dose cohort, the mean percent positive fibers was 28.5% at 2 months and 21.2% at 12 months. Of the 6 patients in the high dose cohort, the mean percent positive fibers at 2 months was 48.4%. For the 3 patients in the high dose cohort for whom 12-month data are available, the mean percent positive fibers was 50.6% at 12 months.

Functional assessment

Functional assessments are considered exploratory in this study, due to the small number of planned patients and the risk for bias in an open-label study. However, preliminary results for the North Star Ambulatory Assessment (NSAA) are available for the six patients with at least 1 year of follow-up, 3 of whom received PF-06939926 at the low dose and 3 of whom received it at the high dose. While baseline natural history NSAA scores are variable, generally scores are stable or decline in DMD patients over 6 years old, with the rate of progression associated with the baseline age and function. This pattern has been reported in a natural history database from the UK (Muntoni et al, PLoS ONE, 2019). The patients in Pfizer’s Phase 1b study, showed a significant functional improvement from baseline NSAA scores after one year, compared with the scores in an independent, external control group derived from recent prior clinical trials involving boys with DMD, who were matched specifically by age, weight and function (i.e. median loss of 4 points in NSAA total score for external placebo group [N=61] vs. improvement of 3.5 points in the Phase 1b patients [N=6], p = 0.003).

A second exploratory analysis using MRI showed a reduction in fat fraction in the thighs of boys treated with the high dose at 12 months post-treatment. Boys with DMD typically exhibit a progressive loss of contractile or lean muscle and replacement with fat and fibrotic tissue. In this study, a reduction in fat fraction was observed in boys from the high dose-treated cohort when compared to an external placebo group, suggesting that gene therapy may have improved muscle fiber health and quality in these boys. No reduction in fat fraction was seen in the low dose group.

“Taken together, we believe these data support the view that administration of PF-06939926 at a dose of 3E14 vg/kg can lead to expression of potentially therapeutic levels of mini-dystrophin that may translate to a measurable improvement in muscle function

and health in DMD patients," said Cheng. "We also want to give our heartfelt thanks to all the patients, their families, the researchers, investigators, other clinicians and advocacy organizations for their passion, expertise and engagement in helping to advance clinical research and care for the Duchenne muscular dystrophy community."

About PF-06939926

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 vector 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.

About Pfizer: Breakthroughs That Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 170 years, we have

worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

DISCLOSURE NOTICE: The information contained in this release is as of May 15, 2020. 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 a potential Phase 3 study for PF-06939926, that involve 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 regulatory authorities will approve the commencement of our planned Phase 3 study; 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; uncertainties regarding the impact of COVID-19 on our business, operations and financial results; 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, 2019 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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