Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of BRIDGE Phase III Open-Label, Switch-Over Clinical Trial Evaluating Pegunigalsidase Alfa for the Treatment of Fabry Disease

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Phase III BRIDGE open-label, switch-over clinical trial met key objectives for safety and efficacy
Final analysis confirmed substantial improvement in renal function as measured by mean annualized estimated Glomerular Filtration Rate (eGFR slope) in patients switched from agalsidase alfa to pegunigalsidase alfa (PRX-102)
A decline trend in patients' renal function on agalsidase alfa was attenuated and improved to be similar to normal renal function decline when switched to PRX-102

CARMIEL, Israel and BOSTON, Dec. 30, 2020 /PRNewswire/ -- Protalix BioTherapeutics, Inc. (NYSE American:PLX) (TASE:PLX), a biopharmaceutical company focused on the development, production and commercialization of recombinant therapeutic proteins produced by its proprietary ProCellEx® plant cell-based protein expression system, and Chiesi Global Rare Diseases, a business unit of Chiesi Farmaceutici S.p.A., an international research-focused healthcare Group (Chiesi Group), today announced final study results from the BRIDGE Phase III Open-Label, Switch-Over Clinical Trial Evaluating Pegunigalsidase Alfa for the Treatment of Fabry Disease. Pegunigalsidase alfa is a plant cell-expressed recombinant, PEGylated, cross-linked α-galactosidase-A product candidate under development for the treatment of Fabry disease. Topline results from the BRIDGE study were announced in May 2020.

The BRIDGE study was a Phase III 12 month open-label, single arm switch-over study evaluating the safety and efficacy of pegunigalsidase alfa, 1 mg/kg infused every two weeks, in up to 22 Fabry patients previously treated with agalsidase alfa, marketed by Takeda Pharmaceutical Company Limited (formerly Shire Plc) as Replagal®, for at least two years and on a stable dose for at least six months.

Final results of the data generated in the study showed substantial improvement in renal function as measured by mean annualized estimated Glomerular Filtration Rate (eGFR slope) in both male and female patients who were switched from agalsidase alfa to PRX-102.

Twenty of twenty-two patients completed the 12-month treatment duration. Eighteen of the patients who completed the study opted to roll over to a long-term extension study and continue to be treated with PRX-102.

As announced in May 2020, in the study, the mean annualized eGFR slope of the study participants improved from -5.90 mL/min/1.73m^2/year while on agalsidase alfa to -1.19 mL/min/1.73m^2/year on PRX-102 in all patients. Male patients improved from -6.36 mL/min/1.73m^2/year to -1.73 mL/min /1.73m^2/year and female patients improved from -5.03 mL/min/1.73m^2/year to -0.21 mL/min/1.73m^2/year.

Following the switch to PRX-102, there was a decrease in patients with progressing or fast progressing kidney disease, and most patients achieved a stable status post-switch.

PRX-102 was well-tolerated in the study, with all adverse events being transient in nature without sequelae. Of the 22 patients enrolled in the BRIDGE study, the majority of treatment emergent adverse events were mild or moderate in severity, with two patients (9.1%) withdrawing from the therapy due to hypersensitivity reaction that was resolved. The most common moderate treatment emergent adverse events were nasopharyngitis, headache and dyspnea.

An immunogenicity assessment indicated that four out of 20 patients (20%) developed persistent antidrug antibodies over the course of the study, of which two had neutralizing activity.

Baseline characteristics of the 20 patients that completed the study, ranging from ages 28 to 60 years, were as follows: mean eGFR 75.87 mL/min /1.73m^2 in males, and 86.14 mL/min/1.73m^2 in females and plasma lyso-Gb_3 mean levels were 51.81 nM and 13.81 nM in males and females, respectively. While lyso-Gb_3 levels remain slightly high, particularly within the male cohort, continuous reduction in lyso-Gb_3 levels was observed of 19.55nM (32.35%) in males and 4.57nM (29.81%) in females.

"We are excited to have completed the final analysis of our Phase III BRIDGE study," said Dror Bashan, Protalix's President and Chief Executive Officer. "We anticipate that the BRIDGE study results will be used to support the filing of a Marketing Authorization Application (MAA) with the

European Medicines Agency, and having completed the analysis, we have taken an important step in the preparations for the application."

The Phase III clinical development program consists of three studies, the BRIDGE study, the BALANCE study and the BRIGHT study. The ongoing BALANCE study is a fully enrolled, randomized, double blind, head-to-head, active control study which aims to demonstrate PRX-102's superiority in renal function as measured by the comparison of the mean annualized change (slope) in estimated glomerular filtration rate (eGFRCKD-EPI) between treatment groups over 24 months of treatment as compared to agalsidase beta, marketed by Sanofi Genzyme as Fabrazyme®. The BRIGHT study is a fully enrolled open-label, switch-over study designed to evaluate the safety, efficacy and pharmacokinetics of PRX-102, 2 mg/kg dosed once every 4 weeks, and to assess whether patients maintain clinical stability as measured by certain Fabry disease parameters after being switched to this regimen from an enzyme replacement therapy (ERT), agalsidase alfa or agalsidase beta, dosed every two weeks. The treatment period of the BRIGHT study was completed in July 2020.

"These important final results confirm the topline results announced last May," said Einat Brill Almon, Ph.D., Protalix's Senior Vice President and Chief Development Officer. "We look forward to the continued findings from our other ongoing Phase III studies of PRX-102, with the final results from the BRIGHT study expected in the first quarter of 2021, and interim results from the BALANCE study expected in the first half of 2021."

In May 2020, Protalix and Chiesi Global Rare Diseases announced the submission of a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for pegunigalsidase alfa for the proposed treatment of adult patients with Fabry disease via the FDA's Accelerated Approval pathway. Subsequently, the FDA accepted the BLA and granted Priority Review designation for PRX-102 for the proposed treatment of adult patients with Fabry disease. The FDA also indicated in the BLA filing communication letter that it is not currently planning to hold an advisory committee meeting to discuss the application. The action date under the Prescription Drug User Fee Act (PDUFA) for the BLA has been updated to April 27, 2021.

"It is clear that many people who are living with Fabry disease are seeking new treatments," said Giacomo Chiesi, Head of Chiesi Global Rare Diseases. "We continue to be encouraged by the clinical data generated by this robust Phase III program and look forward to advancing through the final stages of the regulatory review process in the U.S."

Additional Details about the BRIDGE Study

Patients in the BRIDGE study were screened and evaluated over three months while continuing agalsidase alfa treatment. Following the screening period, each patient was enrolled and switched from agalsidase alfa treatment to receive intravenous infusions of PRX-102, 1 mg/kg every two weeks, for 12 months. Patients had the option to receive PRX-102 infusions in a home care setting based on infusion tolerability and country regulation.

About Fabry Disease

Fabry disease is an X-linked inherited disease that results from deficient activity of the lysosomal α-Galactosidase-A enzyme resulting in progressive accumulation of abnormal deposits of a fatty substance called globotriaosylceramide (Gb_3) in blood vessel walls throughout a person's body. Fabry disease occurs in one person per 40,000 to 60,000. Fabry patients inherit a deficiency of the α-Galactosidase-A enzyme, which is normally responsible for the breakdown of Gb_3. The abnormal storage of Gb_3 increases with time and, accordingly, Gb_3 accumulates, primarily in the blood and in the blood vessel walls. The ultimate consequences of Gb_3 deposition range from episodes of pain and impaired peripheral sensation to end-organ failure – particularly of the kidneys, but also of the heart and the cerebrovascular system.

About Pegunigalsidase Alfa

Pegunigalsidase alfa (PRX-102) is an investigational, plant cell culture-expressed, and chemically modified stabilized version of the recombinant α-Galactosidase-A enzyme. Protein sub-units are covalently bound via chemical cross-linking using short PEG moieties, resulting in a molecule with unique pharmacokinetic parameters. In clinical studies, PRX-102 has been observed to have a circulatory half-life of approximately 80 hours. The Company designed PRX-102 to potentially address the continued unmet clinical need in Fabry patients.

About Protalix BioTherapeutics, Inc.

Protalix is a biopharmaceutical company focused on the development and commercialization of recombinant therapeutic proteins expressed through its proprietary plant cell-based expression system, ProCellEx®. Protalix was the first company to gain FDA approval of a protein produced through plant cell-based in suspension expression system. Protalix's unique expression system represents a new method for developing recombinant proteins in an industrial-scale manner.

Protalix's first product manufactured by ProCellEx, taliglucerase alfa, was approved for marketing by the FDA in May 2012 and, subsequently, by the regulatory authorities of other countries. Protalix has licensed to Pfizer Inc. the worldwide development and commercialization rights for taliglucerase alfa, excluding Brazil, where Protalix retains full rights.

Protalix's development pipeline consists of proprietary versions of recombinant therapeutic proteins that target established pharmaceutical markets, including the following product candidates: pegunigalsidase alfa, a modified version of the recombinant human α-Galactosidase-A protein for the proposed treatment of Fabry disease; OPRX-106, an orally- delivered anti-inflammatory treatment; alidornase alfa for the treatment of Cystic Fibrosis; and others. Protalix has partnered with Chiesi Global Rare Diseases, both in the United States and outside the United States, for the development and commercialization of pegunigalsidase alfa.

About Chiesi Global Rare Diseases

Chiesi Global Rare Diseases is a business unit of the Chiesi Group established in February 2020 and focused on research and development of treatments for rare and ultra-rare disorders. The Global Rare Diseases unit works in collaboration with Chiesi Group to harness the full resources and capabilities of our global network to bring innovative new treatment options to people living with rare diseases, many of whom have limited or no treatments available. The unit is also a dedicated partner with global leaders in patient advocacy, research and patient care. For more information visit www.chiesiglobalrarediseases.com.

About Chiesi Group

Based in Parma, Italy, Chiesi Farmaceutici is an international research-focused healthcare group with 85 years of experience in the pharmaceutical industry and a global presence in 29 countries. Chiesi researches, develops, and markets innovative drugs in the respiratory therapeutics, specialist medicine, and rare disease areas. Its R&D organization is headquartered in Parma (Italy), and is integrated with R&D groups in France, the USA, the UK, and Sweden to advance Chiesi's pre-clinical, clinical, and registration programs. Chiesi employs nearly 6,000 people.
Chiesi Group is a certified Benefit corporation. For more information, please visit www.chiesi.com.

Forward-Looking Statements

To the extent that statements in this press release are not strictly historical, all such statements are forward-looking, and are made pursuant to the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. The terms "expect," "anticipate," "believe," "estimate," "project," "plan," "should" and "intend," and other words or phrases of similar import are intended to identify forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual future experience and results to differ materially from the statements made. These statements are based on our current beliefs and expectations as to such future outcomes. Drug discovery and development involve a high degree of risk and the final results of a clinical trial may be different than the preliminary findings for the clinical trial. Factors that might cause material differences include, among others: failure or delay in the commencement or completion of our preclinical and clinical trials which may be caused by several factors, including: risks that the FDA will not accept an application for accelerated approval of PRX-102 with the data generated to date or will request additional data or other conditions of our submission of any application for accelerated approval of PRX-102; unforeseen safety issues; determination of dosing issues; lack of effectiveness during clinical trials; inability to monitor patients adequately during or after treatment; inability or unwillingness of medical investigators and institutional review boards to follow our clinical protocols; and slower than expected rates of patient recruitment; risks associated with the novel coronavirus disease (COVID-19) outbreak, which may adversely impact our business, preclinical studies and clinical trials; the risk that the results of the clinical trials of our product candidates will not support our claims of safety or efficacy, that our product candidates will not have the desired effects or will be associated with undesirable side effects or other unexpected characteristics; risks related to our ability to maintain and manage our relationship with Chiesi Farmaceutici and any other collaborator, distributor or partner; risks related to the amount of our future revenues and expenditures; the risk that despite the FDA's grant of fast track designation for PRX-102, we may not experience a faster development process, review or approval compared to applications considered for approval under conventional FDA procedures; risks related to the FDA's ability to withdraw the fast track designation at any time; our dependence on performance by third party providers of services and supplies, including without limitation, clinical trial services; delays in our preparation and filing of applications for regulatory approval; delays in the approval or potential rejection of any applications we file with the FDA or other health regulatory authorities, and other risks relating to the review process; the inherent risks and uncertainties in developing drug platforms and products of the type we are developing; the impact of development of competing therapies and/or technologies by other companies and institutions; potential product liability risks, and risks of securing adequate levels of product liability and other necessary insurance coverage; and other factors described in our filings with the U.S. Securities and Exchange Commission. The statements in this press release are valid only as of the date hereof and we disclaim any obligation to update this information, except as may be required by law.

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