Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Topline Results from the 24-Month Phase III BALANCE Clinical Trial of PRX-102 for the Treatment of Fabry Disease

April 4, 2022

PRX-102 successfully met the primary endpoint on kidney function in active control, non-inferiority study vs. agalsidase beta

Topline results demonstrated a favorable tolerability and immunogenicity profile for PRX-102

BLA resubmission planned for the second half of 2022

CARMIEL, Israel and BOSTON, April 4, 2022 /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 topline results from the BALANCE pivotal Phase III clinical trial evaluating pegunigalsidase alfa (PRX–102), 1 mg/kg, administered every two weeks, compared to agalsidase beta (Fabrazyme®) for the treatment of Fabry disease. PRX–102 is a novel, PEGylated enzyme replacement therapy (ERT) under development for the treatment of Fabry disease.

"We are pleased to announce positive topline results from the BALANCE Phase III clinical trial and would like to thank the Fabry disease patients and their families, as well as the study investigators and their teams. Our robust clinical development program, from the Phase I\II clinical trial, through the three Phase III clinical trials and the related extension studies, required substantial time and effort from study participants who showed a strong level of commitment allowing our clinical development program to move forward," said Dror Bashan, Protalix's President and Chief Executive Officer. "Based on results from our clinical program, we believe that PRX–102, as a PEGylated enzyme replacement therapy with potentially two different dosing regimens, may be a valuable new treatment option for individuals suffering from Fabry disease."

The pivotal Phase III BALANCE clinical trial has been completed and topline results from the final analysis are now available. This is a 24–month, randomized, double-blind, active control study of PRX–102 in adult Fabry patients with deteriorating renal function that was designed to evaluate the safety and efficacy of 1 mg/kg of PRX–102 administered every two weeks compared to agalsidase beta. The study enrolled 78 patients who were previously treated with agalsidase beta for at least one year with an estimated glomerular filtration rate (eGFR) slope at screening worse than –2 mL/min/1.73 m^2/year. Patients were randomized on a 2:1 ratio for switching to PRX–102 or continuing on agalsidase beta. A total of 77 patients were treated; 52 with PRX–102 and 25 with agalsidase beta.

"This is an important milestone both for the Fabry community and Protalix in a long and productive journey. We thank all of our collaborators for their contributions and support throughout this journey," said Einat Brill Almon, Ph.D., Protalix's Sr. Vice President and Chief Development Officer. "We believe that this multi-year study demonstrates the potential for switching from agalsidase beta to PRX–102 in the treatment of patients with Fabry disease. The study met our pre–defined criteria for non-inferiority of the primary endpoint of kidney function in a head–to–head active comparison on both the Intent–to–Treat (ITT) and Per Protocol (PP) analysis sets. These topline results show that PRX–102 was comparable to agalsidase beta in controlling eGFR decline, which is a key measure of Fabry disease progression, and continue to demonstrate a favorable tolerability profile for PRX–102. Combined with previous Phase III results from our BRIGHT and BRIDGE studies, as well as the results from our Phase I/II study and its long-term extension, we believe we have a compelling and consistent dataset from both treatment–naïve and ERT–experienced patients. Given these results, we plan, together with Chiesi, our commercialization partner, to work with regulatory agencies on the applicable submissions, hopefully bringing PRX–102 to approval as a new PEGylated enzyme replacement therapy for all adult Fabry patients."

As first announced in October 2021, as part of a Type A End–of–Review meeting, the U.S. Food and Drug Administration (FDA), in principle, agreed that the proposed analysis of the BALANCE study demonstrating non-inferiority to agalsidase beta included in the data package for the PRX–102 biologics license application (BLA) resubmission has the potential to support the approval of PRX–102 for the treatment of Fabry disease. Given the changed regulatory landscape in the United States with the full approval of agalsidase beta in March 2021, the primary analysis of the BALANCE study was changed from superiority to non-inferiority, as demonstrating superiority is no longer required under FDA guidelines. The primary endpoint of the BALANCE study compared the eGFR annualized changes (slope) between the two treatment arms in the ITT analysis set (77 patients). The study met its pre-specified primary endpoint and demonstrated that PRX-102 was statistically non-inferior to agalsidase beta.

The median (95% confidence interval) of the eGFR slope in the PRX-102 arm was –2.514 mL/min/1.73 m^2/year (–3.788, –1.240) and –2.155 mL/min/1.73 m^2/year (–3.805, –0.505) in the agalsidase beta arm, demonstrating a large overlap in the confidence intervals of the two arms. The difference in medians (95% confidence interval) is –0.359 mL/min/1.73 m^2/year (–2.444, 1.726). The prespecified non-inferiority margin was met. Topline results in the PP analysis set (72 patients) are consistent with the ITT results.

The study population (ITT analysis set) was composed of 47 males (61.0%) and 30 females (39.0%), with a mean (range) age of 44.3 (18-60) years. The mean duration of prior treatment with agalsidase beta was approximately six years. At baseline, mean (SD) eGFR was 73.33 ml/min/1.73m^2 (19.82) and median eGFR was 74.51 ml/min/1.73m^2; mean (SD) eGFR slope was –8.21 mL/min/1.73 m^2/year (5.88) and median eGFR slope was –7.32 ml/min/1.73m^2/year.

Forty-seven (90.4%) patients in the PRX–102 arm experienced at least one adverse event compared to 24 (96.0%) in the agalsidase beta arm. The number of events adjusted to 100 years of exposure is 572.36 events for the PRX–102 arm and 816.85 events for the agalsidase beta arm.

Treatment-related adverse events were reported for 21 (40.4%) patients in the PRX–102 arm compared to 11 (44.0%) in the agalsidase beta arm. The number of treatment-related events adjusted to 100 years of exposure is 42.85 events for the PRX-102 arm and 152.91 events for the agalsidase beta arm.

Usage of infusion pre-medication was tapered down during the study, if possible, for all patients. At baseline, 21 (40.4%) patients in the PRX–102 arm used infusion premedication compared to 16 (64.0%) in the agalsidase beta arm. At the end of the study, only three out of 47 (6.4%) patients in the PRX–102 arm used infusion premedication compared to three out of 24 (12.5%) in the agalsidase beta arm. Even with this reduction in use of premedication, there were fewer reported infusion-related reactions with PRX–102: 11 (21.2%) patients in the PRX–102 arm experienced a total of 13 events compared to six (24.0%) patients experiencing a total of 51 events in the agalsidase beta arm. The number of infusion-related reactions adjusted to 100 infusions is 0.5 for the PRX–102 arm and 3.9 for agalsidase beta arm.

Assessment of anti–PRX–102 antibodies or anti-agalsidase beta antibodies, respectively, in the study indicated that, for the PRX–102 arm, 18 (34.6%) patients were anti-drug antibody– (ADA–) positive at baseline, of which 17 (94.4%) had neutralizing antibody activity. For the agalsidase beta arm, eight (32.0%) patients were ADA–positive at baseline, of which seven (87.5%) had neutralizing antibody activity. At the end of the two-year study, 11 (23.4%) patients receiving PRX–102 were ADA–positive, of which seven (63.6%) had neutralizing antibody activity, while in the agalsidase beta arm six (26.1%) were ADA-positive and all six (100%) had neutralizing antibody activity.

Out of the 78 randomized patients, six patients discontinued the study: out of the five (9.4%) from the PRX–102 arm, one patient withdrew consent prior to the first infusion, two discontinued due to personal reasons, and two due to adverse events (one due to an unrelated adverse event and one due to a treatment–related adverse event); one (4%) patient from the agalsidase beta arm discontinued for personal reasons. There were no deaths.

Considering that in the trial, patients in the PRX-102 arm were exposed for the first time to the novel enzyme tolerability data appear favorable for PRX–102 and in line with what was observed in the previous clinical studies of PRX–102.

"The completion of the BALANCE study (NCT02795676), which represents the key pivotal study of the clinical PRX–102 program, is an important event for people with Fabry disease," said David Warnock, M.D., Professor of Medicine (Emeritus) at the University of Alabama at Birmingham. "As a physician and researcher who participated in the design of this trial, I want to emphasize that the development of this new enzyme replacement therapy (ERT) for Fabry disease has required the engagement and contribution of the patients and physicians who participated in the BALANCE study. This effort is the first randomized, head-to-head comparison in Fabry disease of a new ERT to an established, approved form of ERT. The topline results of the BALANCE study and the entire PRX–102 clinical program indicate that this novel PEGylated ERT has the potential for a long-term clinical benefit for adult Fabry patients. These topline results also indicate that PRX-102 was well-tolerated and support the potential to switch to this novel, investigational ERT from a currently approved ERT. As a physician, I believe having an alternative therapeutic option would be an important landmark, and, pending regulatory approval, will potentially improve access of Fabry patients to ERT."

Of the patients that completed the trial, 69 have opted, with the advice of the treating physician, to continue receiving PRX–102 1 mg/kg every other week in a long-term open-label extension study.

"We are pleased to share these positive topline results from the pivotal Phase III BALANCE study, which represent a significant milestone for our PRX-102 development program and the Fabry disease community," said Giacomo Chiesi, head of Chiesi Global Rare Diseases. "These data are especially encouraging following our recent announcement of the positive final results from our Phase III BRIGHT study of PRX-102 in Fabry disease and bring us one step closer towards potential approval of PRX-102 and launch in several countries as a much needed treatment option for patients. We believe the totality of the data observed suggests a favorable benefit-risk profile for the treatment of adult patients with a confirmed diagnosis of Fabry disease and the data will be included in our planned PRX–102 BLA resubmission to the FDA."

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 PRX-102

PRX–102 (pegunigalsidase alfa) is an investigational, plant cell culture-expressed, and chemically modified stabilized version of the recombinant α–Galactosidase–A enzyme. It is a novel, PEGylated enzyme replacement therapy (ERT) under development for the treatment of Fabry disease. 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 U.S. Food and Drug Administration (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 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 stabilized version of the recombinant human α–Galactosidase–A protein for the treatment of Fabry disease; alidornase alfa or PRX–110, for the treatment of various human respiratory diseases or conditions; PRX–115, a plant cell-expressed recombinant PEGylated uricase for the treatment of refractory gout; PRX–119, a plant cell-expressed long action DNase I for the treatment of NETs-related diseases; and others. Protalix has partnered with Chiesi Farmaceutici S.p.A., 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.chiesirarediseases.com.

About Chiesi Group

Based in Parma, Italy, Chiesi is an international research-focused pharmaceuticals and healthcare group with over 85 years' experience, operating in 30 countries with more than 6,000 employees (Chiesi Group). To achieve its mission of improving people's quality of life by acting responsibly towards society and the environment, the Group researches, develops and markets innovative therapeutic solutions in its three focus areas: AIR (products and services that promote respiration, from new-born to adult populations), RARE (treatment for patients with rare and ultra-rare diseases) and CARE (products and services that support specialty care and consumer-facing self-care). The Group's Research and Development centre is based in Parma and works alongside 6 other important research and development hubs in France, the U.S., Canada, China, the UK, and Sweden to pursue its pre-clinical, clinical, and regulatory programmes. In 2018 Chiesi has changed its legal status to a Benefit Corporation, according to the law in Italy, USA and, more recently, in France, by incorporating common benefit objectives into its bylaws, to generate value for its business, for the society and the environment. Since 2019, Chiesi has been the world's largest B Corp certified pharmaceutical group. B Corps are global leaders convinced to leverage business as a force for good. Moreover, as a Benefit Corporation, Chiesi Farmaceutici S.p.A. is required by law to report annually in a transparent way about its progress in achieving the common benefits objectives it has set forward. The Group is committed to becoming carbon neutral by the end of 2035.

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," "may," "plan," "will," "would," "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: risks related to the timing and progress of the preparation of a Biologics License Application (BLA) resubmission addressing the complete response letter; risks related to the timing, progress and likelihood of final approval by the FDA and European Medicines Agency (EMA) of a resubmitted BLA and of a Marketing Authorization Application, respectively, for PRX–102 and, if approved, whether the use of PRX–102 will be commercially successful; likelihood that the FDA, EMA or other applicable health regulatory authorities will approve an alternative dosing regimen; failure or delay in the commencement or completion of our preclinical studies and clinical trials, which may be caused by several factors, including: slower than expected rates of patient recruitment; unforeseen safety issues; determination of dosing issues; lack of effectiveness during clinical trials; inability to satisfactorily demonstrate non-inferiority to approved therapies; inability or unwillingness of medical investigators and institutional review boards to follow our clinical protocols; and inability to monitor patients adequately during or after treatment; delays in the approval or potential rejection of any applications we file with the FDA, EMA or other health regulatory authorities for our other product candidates, and other risks relating to the review process; risks associated with the novel coronavirus disease, or COVID–19, outbreak, which may adversely impact our business, preclinical studies and clinical trials; risks related to any transactions we may effect in the public or private equity markets to raise capital to finance future research and development activities, general and administrative expenses and working capital; the risk that the results of the clinical trials of our product candidates will not support the applicable claims of safety or efficacy, or 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 our collaborators, distributors or partners; risks related to the amount and sufficiency of our cash and cash equivalents; risks relating to our ability to make scheduled payments of the principal of, to pay interest on or to refinance our outstanding notes or any other indebtedness; 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; 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.

Investor Contact
Chuck Padala, Managing Director
LifeSci Advisors
+1-646-627-8390
chuck@lifesciadvisors.com

View original content:https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-topline-results-from-the-24-month-phase-iii-balance-clinical-trial-of-prx-102-for-the-treatment-of-fabry-disease-301516555.html

SOURCE Protalix BioTherapeutics, Inc.; Chiesi