Prothena Reports Positive 9 Month Results from Phase 1 Long-term Extension Study of PRX004, the First Investigational Anti-Amyloid Immunotherapy for the Treatment of ATTR Amyloidosis

December 9, 2020

- **Slowing of neuropathy progression for all 7 evaluable patients, evidenced by a +1.29 point mean change in NIS, was more favorable than expected progression of +9.2 points**
- **Improvement in neuropathy for 3 of these 7 evaluable patients demonstrated by a mean change in NIS of –3.33 points**
- **Improvement in cardiac function for all 7 evaluable patients demonstrated by a decrease in global longitudinal strain (GLS)**
- **Investor conference call and webcast scheduled today at 8:30 AM ET**

DUBLIN, Ireland, Dec. 09, 2020 (GLOBE NEWSWIRE) -- Prothena Corporation plc (NASDAQ:PRTA) today reported positive results from the Phase 1 study of PRX004, the first anti-amyloid immunotherapy designed to deplete amyloid to demonstrate efficacy in ATTR amyloidosis. In the first report of clinical results with this depleter mechanism of action, PRX004 showed favorable results as demonstrated by slowing of neuropathy progression for all 7 evaluable patients at 9 months, including improvement in neuropathy in 3 of the 7 patients, and improved cardiac systolic function for all 7 patients. In this Phase 1 study, PRX004 was found to be generally safe and well tolerated across all dose levels. Prothena management will host a webcast to discuss the Phase 1 results today at 8:30 AM ET and will be joined by Dr. Ole Suhr, Senior Professor, Department of Public Health and Clinical Medicine, Umeå University, gastroenterologist and internist who was a principal investigator in the study, and Dr. Daniel Lenihan, Director, Cardio-Oncology Center of Excellence Advanced Heart Failure, Clinical Research Cardiovascular Division, Washington University in St. Louis.

As previously reported, the long-term extension portion of the Phase 1 study was disrupted by the COVID-19 pandemic. As a result, 7 patients received all infusions through 9 months and were considered evaluable for efficacy. For all of the evaluable patients, slowing of neuropathy progression was demonstrated by a mean change from baseline in Neuropathy Impairment Score (NIS) of +1.29 points at 9 months. This compares favorably to a calculated mean change in NIS of +9.2 points at 9 months in untreated and placebo-treated patients with hereditary ATTR peripheral neuropathy (hATTR-PN) based on analysis of published historical data. In addition, the change in NIS for each of these evaluable patients was more favorable than the published historical data. In this highly progressive disease, it was encouraging to see 3 of 7 patients demonstrate improvement in neuropathy with a mean change in NIS of –3.33 points at 9 months. These positive results were observed in patients with or without concomitant use of stabilizer therapy. PRX004 also demonstrated improvement in cardiac systolic function in each of the 7 evaluable patients, with a mean change in GLS of –1.21% at 9 months (centrally read). For the 3 patients who improved on NIS, GLS improvement was more pronounced, with a mean change of –1.51% at 9 months. Taken together, these positive clinical findings suggest PRX004's depleter mechanism of action can result in benefits in both neuropathy and cardiac function.

"We are pleased to see evidence of both a slowing of disease progression as well as a rapid improvement in neuropathy after only 9 months of treatment with PRX004. In this progressive disease, the more favorable than expected change in NIS for all 7 patients is an encouraging finding, as is PRX004's favorable safety and tolerability profile," stated Radhika Tripuraneni, MD, MPH Chief Development Officer and ATTR Program Head, Prothena. "The improvement on GLS, a key measure of cardiac systolic function, in all evaluable patients was even more pronounced in the 3 patients who improved on NIS. These results demonstrate the potential of PRX004's depleter mechanism of action as uniquely suited for patients at high risk of early mortality due to amyloid deposition in vital organs. We look forward to advancing PRX004 in 2021 to address this high unmet medical need."

"Given the expected clinical progression in patients with ATTR, this first report of clinical results for PRX004 are particularly encouraging," stated Ole Suhr, MD. "These consistent results on neuropathy and cardiac assessments demonstrate the potential of this novel depleter mechanism to provide a new treatment paradigm that is highly needed to treat this deadly disease, especially for patients with more advanced ATTR cardiomyopathy, where amyloid removal is needed to improve heart function."

PRX004 Phase 1 Study

The Phase 1, open-label, multicenter dose-escalation study (NCT03336580) enrolled 21 patients with hereditary ATTR Amyloidosis (hATTR) to receive PRX004 intravenously once every 28 days for up to 3 infusions in the dose escalation phase of the study. Patients were enrolled into 1 of the following 6 PRX004 dose cohorts: 0.1, 0.3, 1, 3, 10, and 30 mg/kg, starting with the lowest dose. Eligible patients who completed dose-escalation were provided the opportunity to enroll in the long-term extension (LTE) portion of the study. All 21 patients enrolled in the Phase 1 study successfully completed dose-escalation and 17 patients subsequently enrolled in the LTE.

In order to inform dose selection, a pharmacokinetic/pharmacodynamic (PK/PD) model was developed and subsequently confirmed by observed reductions in free non-native TTR (transthyretin) in plasma of patients following PRX004 administration. Based on this model, dose levels ≥3 mg/kg were predicted to saturate (occupy ≥90%) amyloid deposits. Therefore, cohorts 4, 5 and 6 were considered equivalent, and efficacy was assessed in these patients and pooled. Out of 12 patients, 7 from cohorts 4 (n=3), 5 (n=3), and 6 (n=1) received all infusions through 9 months and were therefore considered evaluable for efficacy. The remaining 5 patients did not meet these criteria due to COVID-19 pandemic-related disruptions.

PRX004 demonstrated a PK profile consistent with an lgG1 monoclonal antibody and exposures increased proportionally with dose.

Monthly intravenous (IV) infusions of PRX004 were generally safe and well tolerated at all dose levels tested, with 233 separate infusions and up to 17 infusions per patient in the study. No drug-related serious adverse events (SAEs), drug-related ≥grade 3 adverse events, deaths or dose-limiting

toxicities were reported. The most frequent treatment-emergent AEs (≥10%) were fall, anemia, upper respiratory tract infection, back pain, constipation, diarrhea and insomnia. No clinically relevant anti-drug antibodies were observed. Consistent with the proposed mechanism of action, PRX004 administration did not impact levels of native, normal tetrameric TTR.

About ATTR Amyloidosis

Transthyretin amyloidosis (ATTR amyloidosis) is a rare, progressive and fatal disease characterized by deposition of abnormal, non-native forms of TTR protein (amyloid) in vital organs. ATTR amyloidosis can be hereditary (hATTR) when caused by a mutation in the TTR gene, or wild-type (wtATTR) when it occurs sporadically. Patients can experience a spectrum of clinical manifestations due to deposition of amyloid that can affect multiple organs, most commonly the heart and/or nervous system. It is estimated that between 400,000 to 1.4 million patients suffer from ATTR-cardiomyopathy (ATTR-CM). Within this population, between 130,000 to 490,000 patients are estimated to be moderate-to-advanced and categorized as New York Heart Association Class III and IV. TTR protein is produced primarily in the liver, pancreas and choroid plexus and in its native tetrameric form serves as a carrier for thyroxin and retinol binding protein (a transporter for vitamin A) and has been proposed to have neuroprotective effects.

About PRX004 and Depleter Mechanism of Action

PRX004 is an investigational humanized monoclonal antibody designed to deplete amyloid associated with disease pathology that underlies hereditary and wild type ATTR amyloidosis (hATTR and wtATTR, respectively), without affecting the native, normal tetrameric form of the protein.

It is generally accepted that at the time of diagnosis, affected organs in ATTR patients contain extracellular amyloid deposits. These deposits, together with prefibrillar species, are believed to cause organ dysfunction. PRX004 has been shown in preclinical studies to promote clearance of insoluble amyloid fibrils through antibody-mediated phagocytosis and inhibit amyloid formation. This depleter mechanism of action has the potential to provide benefit for ATTR patients at high risk for early mortality due to amyloid deposition in vital organs.

Conference Call Details

Prothena management will discuss results from the Phase 1 study of PRX004 during an audio webcast and conference call today, at 8:30AM ET. The webcast will be made available on the Company's website at www.prothena.com under the Investors tab in the Events and Presentations section. Following the live audio webcast, a replay will be available on the Company's website for at least 90 days.

To access the call via dial-in, please dial (877) 887-5215 (U.S. and Canada toll free) or (315) 625-3069 (international) five minutes prior to the start time and refer to conference ID number 3038486. A replay of the call will be available until December 23, 2020 via dial-in at (855) 859-2056 (U.S. and Canada toll free) or (404) 537-3406 (international), Conference ID Number 3038486.

About Prothena

Prothena Corporation plc is a late-stage clinical company with expertise in protein dysregulation and a diverse pipeline of novel investigational therapeutics with the potential to change the course of devastating neurodegenerative and rare peripheral amyloid diseases. Fueled by its deep scientific expertise built over decades of research, Prothena is advancing a pipeline of therapeutic candidates for a number of indications and novel targets for which its ability to integrate scientific insights around neurological dysfunction and the biology of misfolded proteins can be leveraged. Prothena's partnered programs include prasinezumab (PRX002/RG7935), in collaboration with Roche for the potential treatment of Parkinson's disease and other related synucleinopathies, and programs that target tau (PRX005), TDP-43 and an undisclosed target in collaboration with Bristol-Myers Squibb for the potential treatment of Alzheimer's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) or other neurodegenerative diseases. Prothena's wholly-owned programs include PRX004 for the potential treatment of ATTR amyloidosis, and a portfolio of programs for the potential treatment of Alzheimer's disease including PRX012 that targets Aβ (Amyloid beta). For more information, please visit the Company's website at www.prothena.com and follow the Company on Twitter @ProthenaCorp.

Forward-looking Statements

This press release contains forward-looking statements. These statements relate to, among other things, the treatment potential and proposed mechanisms of action of PRX004; the design and capabilities of our misTTR assay for hereditary ATTR; and advancing PRX004 into late-stage clinical development. These statements are based on estimates, projections and assumptions that may prove not to be accurate, and actual results could differ materially from those anticipated due to known and unknown risks, uncertainties and other factors, including but not limited to the effects on our business of the worldwide COVID-19 pandemic and the risks, uncertainties and other factors described in the "Risk Factors" sections of our Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 3, 2020, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. Prothena undertakes no obligation to update publicly any forward-looking statements contained in this press release as a result of new information, future events or changes in Prothena's expectations.

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Source: Prothena Corporation plc