Prothena Announces Confirmatory Phase 3 AFFIRM-AL Study of Birtamimab in Mayo Stage IV Patients with AL Amyloidosis under SPA Agreement with FDA

February 1, 2021

- **Significant survival benefit observed in VITAL study for birtamimab-treated patients with AL amyloidosis at high risk for early mortality (Mayo Stage IV, HR=0.413, p=0.025, over 9 months)**
- **SPA agreement with FDA to enable registration of birtamimab at unprecedented p≤0.10 for primary endpoint of all-cause mortality in Mayo Stage IV patients with AL amyloidosis**
- **AFFIRM-AL study of birtamimab expected to initiate mid-2021**
- **Investor conference call and webcast scheduled Feb. 2 at 8:00am ET, Prothena management will be joined by Morie Gertz, MD, MACP, Division of Hematology, Mayo Distinguished Clinician, Mayo Clinic**

DUBLIN, Ireland, Feb. 01, 2021 (GLOBE NEWSWIRE) -- Prothena Corporation plc (NASDAQ:PRTA) today announced that following further analyses by the Company and multiple in-depth discussions with the U.S. Food and Drug Administration (FDA) regarding the previous analysis of patients categorized as Mayo Stage IV at baseline in the VITAL study, Prothena is advancing birtamimab into the confirmatory Phase 3 AFFIRM-AL study in this category of patients with AL amyloidosis. This registration-enabling study will be conducted with a primary endpoint of all-cause mortality at p≤0.10 under a Special Protocol Assessment (SPA) agreement with FDA. Birtamimab is the only investigational therapeutic that has shown a significant survival benefit in Mayo Stage IV patients with AL amyloidosis in a placebo-controlled study, with 74% of birtamimab-treated patients alive at 9 months versus 49% of patients in the control group in VITAL (hazard ratio (HR)=0.413, p=0.025, over 9 months). AFFIRM-AL is expected to initiate mid-2021.

The significant survival benefit observed in VITAL with birtamimab was further supported by evidence of clinical benefit on secondary endpoints, including significant changes observed on both the Short Form-36 version 2 Physical Component Score (SF-36v2 PCS), a measure of quality of life (p=0.026), and 6 Minute Walk Test (6MWT) distance, an assessment of functional capacity (p=0.046).

“Our analysis of the previously disclosed VITAL results revealed a greater than 50% relative risk reduction for all-cause mortality in Mayo Stage IV patients treated with birtamimab,” said Gene Kinney, Ph.D., President and Chief Executive Officer of Prothena. “We have extensively reviewed these results during a series of formal and informal interactions with the FDA and are appreciative of the close collaboration that led to this unprecedented SPA agreement for the AFFIRM-AL study. Birtamimab becomes our most advanced late-stage program and now has a defined path forward in this orphan patient population.”

Early Mortality in AL Amyloidosis Remains an Urgent Unmet Medical Need

- Recent clinical results for plasma-cell directed therapeutic approaches for AL amyloidosis that target CD38 have demonstrated that daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (DARA-CyBorD) resulted in significantly higher complete hematologic (CR) and organ response rates (best response of hematologic CR: 53% DARA-CyBorD versus 18% CyBorD p<0.0001 and cardiac response rate at 6 months: 42% DARA-CyBorD versus 22% CyBorD p=0.0029).[1]

- Despite these significant hematologic and organ response rates, results reported to date from the ANDROMEDA study have not demonstrated a survival benefit:

  ° In the first 6 months: 25 deaths with DARA-CyBorD versus 20 deaths with CyBorD. More than 90% of these deaths were related to underlying AL amyloidosis across both arms.[1]

  ° In the 11.4-month median follow-up period: 27 deaths with DARA-CyBorD versus 29 deaths with CyBorD.[2]

- An urgent need remains for treatments that improve survival in patients with AL amyloidosis who are at high risk for early mortality.

Confirmatory Phase 3 AFFIRM-AL Study Design

- To be conducted under an SPA agreement with FDA and supported by the significant survival benefit observed in the previous analysis of birtamimab-treated patients categorized as Mayo Stage IV at baseline in the VITAL study (HR=0.413, p=0.025, over 9 months).

- Global, multi-center, double-blind, placebo-controlled, 2:1 randomized, time-to-event study expected to enroll approximately 150 newly diagnosed, treatment naïve patients with AL amyloidosis categorized as Mayo Stage IV.

- Designed to evaluate the primary endpoint of all-cause mortality with a significance level of p≤0.10.

- Includes an interim analysis to be conducted when approximately 50% of the events have occurred, allowing the independent data monitoring committee to recommend either continuing the study or stopping early for overwhelming efficacy.

- Patients will receive 24 mg/kg of birtamimab or placebo by intravenous infusion every 28 days, with all patients receiving concurrent standard of care therapy consisting of a first line bortezomib-containing regimen.

“Birtamimab has a substantial clinical dataset informing its potential as an important therapeutic for patients with AL amyloidosis,” stated Isabelle Lousada, Founder and Chief Executive Officer of the Amyloidosis Research Consortium. “The burden of AL amyloidosis on patients and their families remains enormous and I am pleased to see this amyloid-targeting approach advancing into a registration-enabling clinical trial designed to assess patient-relevant endpoints in a subset of patients with an urgent unmet medical need.”

Kinney concluded, “We look forward to initiating the AFFIRM-AL study in mid-2021 as one of many milestones ahead. Our team delivered key clinical results across multiple programs in 2020 that further establish Prothena as a leader in addressing diseases caused by protein dysregulation. We look forward to continued execution on multiple milestones in 2021 and beyond to drive sustainable growth. With three late-stage clinical programs including the pivotal AFFIRM-AL study, an internal R&D engine expected to deliver multiple INDs, and significant potential partner payments that add to our strong cash position, we are well positioned to transition to a fully-integrated commercial biotechnology company.”

Fast Track and Orphan Drug Designation

- Birtamimab has been granted Fast Track Designation by the FDA for the treatment of Mayo Stage IV patients with AL amyloidosis to reduce the risk of mortality and has been granted Orphan Drug Designation by both the FDA and European Medicines Agency (EMA).

Conference Call Details

Prothena management will host a live audio webcast and conference call February 2, 2021 at 8:00am ET and will be joined by Dr. Morie Gertz. 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 9689499. A replay of the call will be available until February 16, 2021 via dial-in at (855) 859-2056 (U.S. and Canada toll free) or (404) 537-3406 (international), Conference ID Number 9689499.

Special Protocol Assessment

A Special Protocol Assessment (SPA) is a written agreement between a sponsor and the FDA that indicates concurrence between the parties regarding the adequacy and acceptability of specific design elements and planned analysis for a clinical trial intended to form the basis of a licensing application. An SPA does not indicate FDA concurrence on every detail in a particular trial protocol, and final marketing approval depends upon factors including the efficacy and safety results from the trial, the overall safety profile and an evaluation of the risk/benefit ratio for the product candidate as demonstrated across clinical trials.

About Birtamimab

Birtamimab is an investigational humanized immunoglobulin G1 designed to directly neutralize soluble toxic aggregates and promote clearance of amyloid via phagocytosis. Birtamimab’s depleter mechanism of action broadly targets misfolded kappa and lambda light chain to clear deposited amyloid that causes organ dysfunction and failure in patients with AL amyloidosis. Preclinical research has shown that birtamimab binds to both soluble and insoluble aggregated kappa and lambda immunoglobulin light chain by recognizing an epitope that is exposed at the earliest stages of abnormal light chain misfolding and through aggregation of deposited amyloid involved in AL amyloidosis. In clinical studies, birtamimab was generally safe and well tolerated, and has been evaluated in 302 patients receiving monthly intravenous infusions (including 294 patients who received the recommended 24 mg/kg dose), for an average of approximately 15 months.

Birtamimab was previously evaluated in the Phase 3 VITAL Study, a global multi-center, randomized, double-blind, placebo-controlled clinical study of newly diagnosed, treatment naïve patients with AL amyloidosis and cardiac involvement (N=260). Results from a post hoc analysis of the VITAL study revealed a significant survival benefit favoring birtamimab in a subset of patients categorized as Mayo Stage IV at baseline (n=77), with 74% of birtamimab-treated patients alive at 9 months versus 49% of patients in the control group (hazard ratio of 0.413 (95% CI: 0.191, 0.895; p=0.025, over 9 months). The randomization stratification factors in VITAL were Mayo Stage I-II vs III-IV, renal stage I vs II-III and 6MWD < 300 meters vs ≥ 300 meters.

Significant changes observed on secondary endpoints provided further evidence of clinical benefit in birtamimab-treated Mayo Stage IV patients in VITAL. For SF-36v2 PCS, an assessment of quality of life, the difference in mean change from baseline at 9 months between the birtamimab and control arms of the study was +5 points favoring the birtamimab arm (p=0.026). For 6MWT distance, an assessment of functional capacity, the difference in mean change from baseline at 9 months between the birtamimab and control arms was +27 meters favoring the birtamimab arm (p=0.046).

About AL Amyloidosis

AL amyloidosis is a rare, progressive, and fatal disease where immunoglobulin light chain proteins produced by clonal plasma cells misfold, aggregate, and deposit as amyloid in vital organs. These toxic aggregates and amyloid deposits cause progressive damage and failure of vital organs, including the heart. It is estimated that 200,000 to 400,000 patients globally suffer from this rare disease, with 60,000 to 120,000 patients being categorized as Mayo Stage IV. Patients categorized at diagnosis as Mayo Stage IV have poor outcomes with current standard-of-care that aims to reduce the production of new protein but do not directly target and clear the toxic amyloid that deposits in organs. There are no approved treatments for AL amyloidosis that have demonstrated a survival benefit and there remains an urgent unmet medical need for therapies that improve survival in

patients at high risk for early mortality due to amyloid deposition. For more information on AL amyloidosis, please visit the websites of the Amyloidosis Support Groups, The Amyloidosis Research Consortium, and the Amyloidosis Foundation.

About Prothena

Prothena Corporation plc is a late clinical-stage company with expertise in protein dysregulation and a 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 wholly-owned programs include birtamimab for the potential treatment of AL amyloidosis, 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). 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. 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 design, proposed mechanism of action and possible clinical benefits of birtamimab, and its potential as a treatment for Mayo Stage IV patients with AL amyloidosis; the design, expected enrollment and expected timing of the Phase 3 AFFIRM-AL study of birtamimab; the results from post hoc analyses that reveal a potential survival benefit of birtamimab in Mayo Stage IV patients; the continued advancement of our discovery, preclinical and clinical pipeline and the expected milestones in 2021 and beyond; and amounts we might receive under our collaborations with Roche and Bristol-Myers Squibb. 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.

[1]Primary Results from the Phase 3 ANDROMEDA Study presented at the European Hematology Association annual meeting, June 11-21, 2020. The ANDROMEDA study and the VITAL study were separate studies with different designs and no head-to-head studies have been conducted to evaluate birtamimab and daratumumab.

[2]Full prescribing information for **DARZALEX *FASPRO*®**.

Source: Prothena Corporation plc