NEWS RELEASE

Prothena Presents Data Demonstrating Consistent Survival Benefit Observed with Birtamimab in Mayo Stage IV AL Amyloidosis Patients in Phase 3 VITAL Study at ASH 2022

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- Significant improvement in time to all-cause mortality at month 9 was observed in the post hoc analysis and remained consistent across all key baseline variables in Mayo Stage IV patients
- Birtamimab is currently being studied in the confirmatory Phase 3 study AFFIRM-AL in patients with Mayo Stage IV AL amyloidosis; topline data is expected in 2024

DUBLIN--(BUSINESS WIRE)-- Prothena Corporation plc (NASDAQ:PRTA), a late-stage clinical biotechnology company with a robust pipeline of investigational therapeutics built on protein dysregulation expertise, today presented data from the completed phase 3 VITAL study demonstrating that in a post hoc analysis of patients with Mayo Stage IV AL amyloidosis, a statistically significant survival benefit was observed in those treated with birtamimab at 9 months. The survival benefit of birtamimab in VITAL remained consistent across all key baseline variables in patients with Mayo Stage IV AL amyloidosis. The data were presented in an oral presentation at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans, LA.

Birtamimab is a potential best-in-class amyloid depleter treatment for AL amyloidosis. Based on the totality of the VITAL study data, Prothena has advanced birtamimab into the confirmatory Phase 3 AFFIRM-AL study in patients with Mayo Stage IV AL amyloidosis under a Special Protocol Assessment (SPA) agreement with the U.S. FDA with a primary endpoint of all-cause mortality at p≤0.10. Confirmatory Phase 3 AFFIRM-AL topline data is expected in 2024.

A post hoc analysis of patients with Mayo Stage IV AL amyloidosis showed a statistically significant survival benefit of 74 percent in patients treated with birtamimab versus a survival benefit of 49 percent in patients on placebo at 9 months (HR 0.413, p=0.021). The survival benefit of birtamimab in VITAL remained consistent across all key baseline variables in Mayo Stage IV patients, reinforcing the strength of the survival data in these patients at high risk of early mortality.

“AL amyloidosis is a rare and life-threatening disease without any treatment options that address resident amyloid deposits at the time of diagnosis,” said Morie Gertz, MD, Hematologist, Chair emeritus Internal Medicine, Mayo Clinic. “The significant and consistent survival benefits of birtamimab in the VITAL study’s post hoc analysis of patients with Mayo Stage IV AL amyloidosis offers us hope that the removal of amyloid deposits leads to a survival benefit and affirms the potential of birtamimab as a safe, well-tolerated and meaningful therapy. We believe that the VITAL study results set the stage for the AFFIRM-AL trial which we hope will continue to show that birtamimab can help patients with Mayo Stage IV AL amyloidosis, who have the highest risk of early death.”

The sensitivity analysis was performed as part of the post hoc analysis of patients with Mayo Stage IV AL amyloidosis. After adjusting for baseline demographic, clinical, and laboratory variables, the adjusted hazard ratios ranged from 0.336 to 0.465, with no upper bounds of the 90% confidence interval crossing 1, indicating a consistent survival benefit with birtamimab at 9 months.

Birtamimab also demonstrated statistically significant improvement over placebo in post hoc analyses of quality of life (assessed with the Short Form-36 version 2 physical component score, SF-36v2 PCS) and cardiac function (assessed with the 6-minute walk test). Patients treated with birtamimab showed a mean difference of 4.65 in the SF-36v2 PCS over placebo at 9 months (p=0.046). Mayo Stage IV patients treated with birtamimab after 9 months demonstrated an increase of 15.22 meters in the 6-minute walk test, whereas patients treated with placebo had a decrease of 21.15 meters (a difference of 36.37; p=0.022).

Birtamimab was generally safe and well tolerated in the overall patient population and in Mayo Stage IV patients. The rates of treatment emergent adverse events (TEAEs) were balanced between treatment arms. The rates of treatment-related TEAEs were similar or lower with birtamimab than in the placebo arm of both the overall population and in Mayo Stage IV patients. Consistent with AL amyloidosis, cardiac disorder was the most common class of fatal TEAEs. There were no fatal TEAEs that were considered treatment related.

Slides from today’s oral presentation at ASH 2022 will be made available on **www.prothena.com** under the Investors tab in the Events and Presentations section.

About VITAL Phase 3 Study

VITAL was a phase 3 multicenter, randomized, double-blind, placebo-controlled clinical trial that evaluated the efficacy and safety of birtamimab plus standard of care versus placebo plus standard of care in newly diagnosed, treatment-naïve patients with AL amyloidosis. The study was terminated early based on a futility analysis. The primary endpoint in the full study population was the composite of time to all-cause mortality and cardiac hospitalization in patients with AL amyloidosis. The primary endpoint in the overall study population favored birtamimab over placebo, but the difference was not statistically significant at the time of early study termination. The primary study population included 260 patients with AL amyloidosis, of which patients who received birtamimab and placebo were evenly split. Approximately one-third of patients in the study had Mayo Stage IV AL amyloidosis (n=77). Patient demographics were generally balanced between the birtamimab and placebo groups in the study population and the Mayo Stage IV sub population.

About Birtamimab

Birtamimab is an investigational monoclonal antibody designed to specifically and selectively target and clear the amyloid that accumulates and causes organ dysfunction and failure in patients with AL amyloidosis. Birtamimab specifically binds to a defined epitope on kappa and lambda AL protein involved in the disease process. Birtamimab is the only investigational therapeutic that has shown a significant survival benefit in patients with Mayo Stage IV AL amyloidosis post-hoc in a placebo-controlled study. Birtamimab has been granted orphan drug designation for AL Amyloidosis by both the U.S. FDA and the European Medicines Agency and has been granted Fast Track designation by the FDA. A SPA was agreed to between Prothena and the FDA for the AFFIRM-AL trial which represents FDA's agreement that the design and planned analysis for the primary endpoint of time to all-cause mortality adequately address the objectives necessary to support a regulatory submission. Results from the AFFIRM-AL trial are anticipated in 2024. Final marketing approval is predicated upon FDA's complete review of the entire application.

About AL Amyloidosis

AL amyloidosis is a rare, progressive and fatal disease where clonal plasma cells overproduce light chain proteins that misfold, aggregate and deposit as amyloid in vital organs such as the heart. It is estimated that there are 60,000 – 120,000 patients worldwide living with Mayo Stage IV AL amyloidosis. Patients with AL amyloidosis can present with a wide range of general symptoms that are common to other conditions such as fatigue, shortness of breath or edema. Current treatment strategies target plasma cells to reduce production of new amyloid, but do not address the amyloid already deposited in organs. Mortality is driven primarily by cardiac failure. There is an urgent unmet medical need for therapies that improve survival in patients at risk for early mortality due to amyloid deposition.

About Prothena

Prothena Corporation plc is a late-stage clinical biotechnology company with expertise in protein dysregulation and a pipeline of 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 pipeline includes both wholly-owned and partnered programs being developed for the potential treatment of diseases including AL amyloidosis, ATTR amyloidosis, Alzheimer's disease, Parkinson's disease and a number of 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 treatment potential, design, proposed mechanism of action, and potential administration of birtamimab; and the expected timing of reporting data from clinical studies of birtamimab. 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 those described in the "Risk Factors" sections of our Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 8, 2022, and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. We undertake 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 our expectations.

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