June 9, 2016

Prothena Reports Results of Phase 1 Single Ascending Dose Study of PRX003, Demonstrating Target Engagement of the Novel Anti-MCAM Antibody for Inflammatory Diseases

- **All doses of PRX003 found to be safe and well tolerated, meeting the primary objective of the Phase 1 single ascending dose study in healthy volunteers**
- **Neutralization of Th17 cells of greater than 95 percent and statistically significant dose-dependent duration of MCAM downregulation observed at PRX003 exposure levels that saturate MCAM**
- **Investor conference call and webcast planned today at 4:30 PM ET**

DUBLIN, Ireland, June 09, 2016 (GLOBE NEWSWIRE) -- Prothena Corporation plc (Nasdaq:PRTA), a late-stage clinical biotechnology company focused on the discovery, development and commercialization of novel protein immunotherapies, today announced new clinical results from a Phase 1 double blind, placebo controlled, single ascending dose study of PRX003 in healthy volunteers. PRX003 is a monoclonal antibody targeting melanoma cell adhesion molecule (MCAM), believed to be an integral mediator of Th17 cell pathogenesis, for the potential treatment of inflammatory diseases where multiple cytokines play a role. PRX003 is designed to address inflammation by targeting Th17 cells upstream of the process that releases disease-causing cytokines into tissue.

The data, being presented on June 10th at 11:20 AM BST in an oral session at The European League Against Rheumatism (EULAR) 17th Annual European Congress of Rheumatology in London, demonstrated that PRX003 was safe and well-tolerated following a single infusion, up to and including the highest dose level tested of 30 mg/kg. Further, results from this study showed that administration of PRX003 led to greater than 95 percent neutralization of MCAM at saturating drug exposures. The data also showed a statistically significant ($p<0.0001$) dose-dependent duration of downregulation of MCAM on Th17 cells.

"Drawing on our team's strong track record in the development of therapies for immune-related diseases we have designed PRX003 as an approach to uniquely target and intervene in inflammatory diseases by targeting Th17 cells through blockade of MCAM on their cell surface," said Gene Kinney, Ph.D., Chief Scientific Officer and Head of Research and Development for Prothena. "We believe PRX003 represents a new approach to achieve robust neutralization of Th17 cells upstream of the release of multiple cytokines implicated in inflammatory diseases. Because cells that express MCAM represent only a small fraction of T cells, PRX003 leaves the vast majority of immune cells unaffected. We look forward to assessing clinical endpoints in patients with psoriasis in the ongoing proof-of-biology Phase 1b multiple ascending dose study of PRX003."

Phase 1 Single Ascending Dose Trial Design

The Phase 1 double-blind, placebo-controlled, single ascending dose study enrolled 40 healthy volunteers and was designed to assess the safety, tolerability, pharmacokinetics and immunogenicity of PRX003. All subjects enrolled were randomized 3:1 into five escalating dose cohorts (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg) to receive either PRX003 or placebo. No drug-related serious or severe adverse events, dose-limiting toxicity or anti-drug antibodies were reported. No infusion related or systemic hypersensitivity reactions were reported. The only treatment-emergent adverse events that were reported in ≥ 5 percent of subjects (≥2 of 30 PRX003 treated subjects) were headache, balance disorder, seasonal allergies and viral upper respiratory tract infection.

PRX003 demonstrated favorable pharmacokinetic properties with evidence of target mediated disposition, supporting the current dosing frequency in the ongoing Phase 1b multiple ascending dose study in patients with psoriasis. Data from this study is expected in the second half of 2017. More information about this trial can be found at clinicaltrials.gov (NCT02458677).

PRX003 Occupancy, Demargination, and Downregulation of MCAM

PRX003 is a novel approach to address immune-mediated diseases and is thought to work through multiple mechanisms. Pharmacodynamic endpoints in this study suggest that by occupying MCAM on Th17 cells, PRX003 may demarginate Th17 cells and down regulate MCAM expression.

Occupancy:

PRX003 is designed to bind to the specific MCAM epitope that interacts with laminin α4, disrupting this binding event and preventing adhesion of Th17 cells to the blood vessels and subsequent migration of cells that can — in a disease state — release multiple pathogenic cytokines into tissue. Occupancy of MCAM with PRX003 refers to the ability of PRX003 to bind to this epitope and directly neutralize MCAM's ability to interact with laminin. When saturating PRX003 levels were maintained in circulation, near complete occupancy of the laminin binding epitope of MCAM was demonstrated in a subset of dosed subjects.

***Demargination*:**
The majority of T cells in the body exist in various tissues, outside of circulation. Disease induction mediated by Th17 cells is largely caused by the ability of Th17 cells to leave the circulation, and initiate uncontrolled inflammation in tissue — a process that is facilitated by MCAM. Margination of cells is a critical first step in this process, and is characterized by adhesion of the cells to the blood vessel wall. Demargination is the process of interfering with this adhesion, resulting in increased numbers of the target cells (in this case MCAM expressing Th17 cells) being drawn away from blood vessel walls or tissue and sequestered in circulation. In this study, immediately upon PRX003 administration, an increase in the percentage of MCAM expressing cells in circulation was observed, consistent with a mechanism whereby PRX003 demarginated Th17 cells. This process has been noted in drugs such as glucocorticoids and natalizumab (Tysabri®), which also target components of the immune cell adhesion cascade.

***Downregulation*:**
As a result of occupancy, study data showed that PRX003 binding caused downregulation, the reduction of MCAM expression on the surface of Th17 cells, thereby potentially further limiting the ability of cells that would normally express MCAM to migrate into tissue. In this study, a statistically significant ($p < 0.0001$) dose-dependent duration of MCAM downregulation was observed.

Conference Call and Webcast Details

Prothena management will discuss the clinical trial results from the Phase 1 single ascending dose study of PRX003 during a live audio webcast and conference call on June 9, 2016 at 4:30 PM ET. The webcast and slide presentation 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 of the webcast will be available on the Company's website for 90 days.

To access the conference call via dial-in, please dial (877) 887-5215 (U.S. toll free) or (315) 625-3069 (international) five minutes prior to the start time and refer to conference ID number 10657612. A replay of the call will be available until June 16th via dial-in at (855) 859-2056 (U.S. toll free) or (404) 537-3406 (international), Conference ID Number 10657612.

About MCAM and Inflammatory Disease

Within the immune system, a small population of approximately three to six percent of T cells known as Th17 cells, are known to be a key participant in both normal inflammatory reactions as well as pathogenic autoimmune diseases. MCAM is a cell adhesion molecule expressed on the surface of Th17 cells, and facilitates their interaction with vasculature and subsequent migration from circulation into tissues, in some cases to initiate or perpetuate a disease process. While only a small percentage of T cells in circulation express MCAM, these cells secrete the Th17 signature cytokines, IL-17A and IL-17F, but can also produce other cytokines such as such as IFNγ, GM-CSF, TNFα and IL-22 that may play a role in disease pathogenesis.

About PRX003

PRX003 is a monoclonal antibody being developed for the potential treatment of inflammatory diseases where multiple cytokines play a role, including psoriasis. PRX003 is designed to occupy and down-regulate MCAM, a cell adhesion molecule expressed on the surface of Th17 cells, thereby sequestering cells that secrete disease-causing cytokines in the bloodstream and preventing their migration into tissues. As MCAM expressing T cells appear to be disproportionately involved in propagation of inflammation, targeting the T cell, rather than any individual cytokine, may provide a highly specific way to impact multiple pathogenic processes, while leaving the vast majority of immune function intact. PRX003 may be useful for the treatment of a variety of inflammatory diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, giant cell arteritis and sarcoidosis. For more information about Prothena's ongoing Phase 1b clinical study of PRX003 in patients with psoriasis please visit www.clinicaltrials.gov and search identifier NCT02630901.

About Prothena

Prothena Corporation plc is a global, late-stage clinical biotechnology company seeking to fundamentally change the course of progressive diseases with its clinical pipeline of novel therapeutic antibodies. Fueled by its deep scientific understanding

built over decades of research in protein misfolding and cell adhesion — the root causes of many serious or currently untreatable amyloid and inflammatory diseases — Prothena has advanced several drug candidates into clinical trials while pursuing discovery of additional novel therapies. Our clinical pipeline of antibody-based product candidates targets a number of potential indications including AL amyloidosis (NEOD001), Parkinson's disease and other related synucleinopathies (PRX002) and inflammatory diseases, including psoriasis (PRX003). For more information, please visit the company's web site at www.prothena.com.

Forward-looking Statements

This press release contains forward-looking statements. These statements relate to, among other things, the timing of announcing data from the Phase 1b multiple ascending dose study of PRX003; the potential for PRX003 to represent a new approach to neutralization of Th17 cells; the design and proposed mechanism of action of PRX003; and the potential for PRX003 to be useful for the treatment of a variety of inflammatory diseases. 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 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 February 25, 2016 and our subsequent Quarterly Reports on Form 10-Q filed 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.

Contacts

Investors: Tran Nguyen, CFO
650-837-8535, IR@prothena.com

Media: Ellen Rose, Head of Communications
650-922-2405, ellen.rose@prothena.com