Prasinezumab Slows Progression on Measures of Parkinson's Disease in Phase 2 Study

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- **First potentially disease-modifying, anti-alpha-synuclein antibody to demonstrate signals of efficacy on multiple pre-specified secondary and exploratory clinical endpoints, including measures of motor function and biomarkers, in patients with early Parkinson's disease**
- **Significantly reduced decline in motor function by 35% vs. placebo at one year and delayed time to clinically meaningful worsening of motor progression over one year**
- **Results support further clinical development of prasinezumab**
- **Investor webcast scheduled for Tuesday, September 15 at 1:30PM ET following Top Abstract oral presentation at the MDS Virtual Congress 2020**

DUBLIN, Ireland, Sept. 11, 2020 (GLOBE NEWSWIRE) -- Prothena Corporation plc (NASDAQ:PRTA), announced that results from the Phase 2 PASADENA study of prasinezumab are being highlighted today at the International Parkinson and Movement Disorder Society's MDS Virtual Congress 2020 (MDS Congress). Prasinezumab is the first potentially disease-modifying, anti-alpha-synuclein antibody to demonstrate signals of efficacy on multiple pre-specified secondary and exploratory clinical endpoints in patients with early Parkinson's disease. As previously reported, the study did not meet the primary objective, but signals of efficacy showing a reduction in disease progression were observed in both of the prasinezumab arms when compared to placebo. In the study, prasinezumab significantly reduced decline in motor function by 35% (pooled dose levels) vs. placebo after one year of treatment on the centrally rated assessment of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, a clinical examination of motor function. Motor symptoms associated with Parkinson's disease include slowness of movement (bradykinesia), tremor, rigidity, and gait. Prasinezumab-treated patients also demonstrated a significant delay in time to clinically meaningful worsening of motor progression on the site rated assessment of time to at least a 5-point progression on MDS-UPDRS Part III vs. placebo over one year, with a hazard ratio of 0.82 (pooled dose levels). There are currently no treatments available that target the underlying cause of Parkinson's disease and can slow its progression.

The clinical results will be posted online today on the MDS Virtual Congress website as an ePoster in the Virtual Poster Hall and will also be presented by Roche on Tuesday, September 15, as a Top Abstract oral presentation. Prothena will conduct an investor webcast on Tuesday, September 15 at 1:30PM ET. Prasinezumab is being developed through a worldwide collaboration between Prothena and Roche.

"Our expectation that both dose levels tested would saturate aggregated alpha-synuclein in the brain was confirmed by the similar outcomes across multiple endpoints in both prasinezumab arms of the study after a single year of treatment, including a significant 35% reduction in motor function decline in patients with early Parkinson's disease versus placebo, a significant delay in time to clinically meaningful worsening of motor progression, and other clinical endpoints such as bradykinesia, that assess activities impacted in patients with Parkinson's disease," stated Gene Kinney, PhD, president and chief executive officer of Prothena. "We are further encouraged to see consistent signals favoring prasinezumab across other secondary and exploratory endpoints. In totality, these clinical results support further clinical development of prasinezumab to assess its potential as a first-in-class disease-modifying therapy to slow progression of Parkinson's disease, and add to the growing body of clinical evidence that selective and specific targeting of pathogenic proteins implicated in a wide variety of central and peripheral disorders has the potential to fundamentally change the course of these devastating diseases."

Phase 2 PASADENA Study Results

These clinical results are consistent with the expectation that both tested dose levels of prasinezumab saturate the target of aggregated alpha-synuclein in the brain of patients as was predicted based on preclinical studies and CNS exposure in the Phase 1b clinical study. Comparing the results of the pooled treatment arms vs. placebo, a prespecified exploratory analysis of MDS-UPDRS, increases the overall sample size of prasinezumab-treated patients and thereby increases the confidence in the observed effect. The statistical analyses were conducted in alignment with the powering to detect changes at a two-sided alpha of 0.20; thus p-values below 0.20 are considered significant. As previously reported, the primary endpoint of the study – change from baseline in the MDS-UPDRS total score (Parts I, II and III) at 52 weeks in each treatment group vs. the placebo group – was not met (pooled dose levels: –14.0%, –1.30, 80% CI=(–3.18, 0.58), p=0.38; low dose level: –21.5%, –2.02, 80% CI=(–4.21, 0.18); and high dose level: –6.6%, –0.62, 80% CI=(–2.82, 1.58)). As a result of the primary objective not meeting the criteria for statistical significance, subsequent nominal p-values are for descriptive purposes, without alpha control for multiple comparison.

Signals of efficacy were observed on multiple pre-specified secondary and exploratory clinical endpoints including change from baseline in MDS-UPDRS Part III in prasinezumab-treated patients vs. placebo at 52 weeks by central rating (pooled dose levels: –35.0%, –1.88, 80% CI=(–3.31, –0.45), p=0.09; low dose level: –45.4%, –2.44, 80% CI=(–4.09, –0.78); and high dose level: –24.7%, –1.33, 80% CI=(–2.99, 0.34)) and by site rating (pooled dose levels: –25.0%, –1.44, 80% CI=(–2.83, –0.06), p=0.18; low dose level: –33.8%, –1.88, 80% CI=(–3.49, –0.27); and high dose level: –18.2%, –1.02, 80% CI=(–2.64, 0.61)). MDS-UPDRS Part III is a clinical examination of motor function that assesses motor symptoms associated with Parkinson's disease. Prasinezumab also delayed time to clinically meaningful worsening of motor progression in prasinezumab-treated patients vs. placebo over 52 weeks as demonstrated by site rating of time to at least a 5-point progression in MDS-UPDRS Part III (pooled dose levels: HR=0.82, 80% CI=0.64 to 0.99, p=0.17; low dose level: HR=0.77, 80% CI=0.63 to 0.96; and high dose level: HR=0.87, CI=0.70 to 1.07).

Additional signals of efficacy on bradykinesia and, separately, a digital motor score developed by Roche using a novel smartphone technology further extended the results shown on MDS-UPDRS Part III. Signals of efficacy were observed on change from baseline on bradykinesia in prasinezumab-treated patients vs. placebo at 52 weeks by site rating (pooled dose levels: –27.0%, –0.75, 80% CI=(–1.62, 0.11); low dose level: –38.3%, –1.07, 80% CI=(–2.07, –0.07); and high dose level: –15.7%, –0.44, 80% CI=(–1.45, 0.56)). Bradykinesia is one of the cardinal symptoms of Parkinson's disease and is assessed as a component of the MDS-UPDRS Part III clinical motor examination. Positive signals on motor function were also confirmed by

digital measures of progression as assessed by the digital motor score, a composite score built from 80% bradykinesia features and 20% resting tremor features. Prasinezumab-treated patients demonstrated reduced motor progression as measured by a slope analysis of the digital motor score vs. placebo at 52 weeks (pooled dose levels: –25.0%, –0.030, 80% CI=(–0.050, –0.010); low dose level: –30.3%, –0.040, 80% CI=(–0.063, –0.017); and high dose level: –21.5%, –0.029, 80% CI=(–0.052, –0.006)).

"These results are extremely encouraging for patients with Parkinson's disease and the clinicians who treat them and warrant additional clinical investigation to confirm and extend these findings," commented Joseph Jankovic, M.D., professor, neurology, distinguished chair in movement disorders and director, Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine. "There is an urgent need for new therapies that target the underlying cause of this debilitating disease and, unlike symptomatic therapies, slow its relentless progression."

Dr. Kinney added, "This step forward in developing new treatments for Parkinson's disease would not be possible without the many patients, caregivers, clinicians and site staff participating in the Phase 2 PASADENA signal detection study, and we want to thank them for their significant contributions."

Consistent signals favoring prasinezumab were also demonstrated at both dose levels on Montreal Cognitive Assessment (MoCA), a screening assessment of cognitive function. On average, patients in the PASADENA study were in the cognitively normal range at baseline and prasinezumab-treated patients showed an improvement in MoCA score. MoCA is a 30 point-scale and a higher score indicates better cognitive performance. Consistent signals favoring prasinezumab were also demonstrated with both dose levels on Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Change (PGI-C), two assessments of global impression of change. On both the CGI-I and PGI-C, assessments that measure change in health state by the clinician and patient respectively, prasinezumab-treated patients demonstrated a reduced risk of worsening.

In an analysis of cerebral blood flow, assessed by changes in magnetic resonance-arterial spin labeling (MRI-ASL) in a subset of patients, prasinezumab-treated patients showed improvement in cerebral blood flow in the putamen, an area of the brain associated with the loss of dopaminergic terminals and presence of alpha-synuclein pathology in Parkinson's disease, suggesting an impact on the underlying biology implicated in disease progression. On endpoints that minimally progressed over 52 weeks, signals favoring prasinezumab were not observed, including on MDS-UPDRS Part I or Part II, the The Schwab and England Activities of Daily Living scale, and DaT-SPECT endpoints.

Prasinezumab was found to be generally safe and well tolerated, with the majority of adverse events reported as mild or moderate and similar across placebo and both treatment arms. The majority of reported Adverse Events (AE) (92%) were mild (grade 1-2). A single grade 4 AE was reported and deemed to be unrelated to study drug. There were no grade 5 AEs.

"This first report of an anti-alpha synuclein antibody to show clinical benefit in patients with early Parkinson's disease is an important advancement for patients," commented Todd Sherer, PhD, chief executive officer, The Michael J. Fox Foundation for Parkinson's Research. "With these signals of functional improvement, targeting alpha-synuclein continues to represent a promising path in the development of disease-modifying treatments for Parkinson's disease and I look forward to further investigation of this approach."

Phase 2 PASADENA Study Design

PASADENA is a two-part Phase 2 clinical study in early Parkinson's disease patients that is being conducted by Roche. Part 1 is a randomized, double-blind, placebo-controlled, three-arm study that enrolled 316 patients to evaluate the efficacy and safety of prasinezumab in patients over 52-weeks. In Part 1, patients were randomized on a 1:1:1 basis to receive one of two active doses (1500 mg or 4500/3500 mg, depending on body weight) of prasinezumab or placebo via intravenous infusion once every 4 weeks. Eligible patients were not on dopaminergic therapy and were not expected to require dopaminergic therapy for at least 52 weeks. Part 2 of the study, which is ongoing, is a 52-week blinded extension phase in which patients from the placebo arm of the study have been re-randomized onto one of two active doses on a 1:1 basis, so that all participants are on active treatment. Patients who were originally randomized to an active dose will continue at that dose level for an additional 52 weeks. In Part 2, patients are allowed to start dopaminergic therapy. Any patient who medically required initiation of dopaminergic therapy during Part 1 has had their subsequent data censored for the primary endpoint analysis.

The primary endpoint of this study is change from baseline in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score (Parts I, II and III) at the completion of Part 1 (52-weeks) in each treatment group vs the placebo group. The signal-detection study was designed to include 100 patients per arm, resulting in 80% power and two-sided alpha of 0.20, to detect a 37.5% relative change in MDS-UPDRS total score between groups from baseline to week 52. A prespecified exploratory analysis will compare the results of the two pooled treatment arms vs. placebo. Secondary endpoints can be found on clinicaltrials.gov by searching NCT #03100149.

The 52-week blinded extension of the study (Part 2 of the Phase 2 PASADENA Study) is ongoing. COVID-19 has caused some participants to miss assessments in Part 2 of the study. Mitigation efforts have been put in place to ensure patient safety, and the situation is improving in most geographies. Roche continues to monitor the situation carefully to minimize patient risk and the impact on the study.

For more information on the Phase 2 PASADENA study, please visit clinicaltrials.gov and search NCT #03100149.

Conference Call Details

Prothena management will discuss results from Part 1 of the Phase 2 PASADENA study during a live audio webcast and conference call on September 15, at 1:30PM 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 1185004. A replay of the call will be available until September 29, 2020 via dial-in at (855) 859-2056 (U.S. and Canada toll free) or (404) 537-3406 (international), Conference ID Number 1185004.

About Parkinson's Disease

Parkinson's disease is a progressive degenerative disorder of the entire nervous system that affects one in 100 people over age 60. An estimated seven to 10 million people are living with Parkinson's disease worldwide. It is the second most common neurodegenerative disorder after Alzheimer's disease. The disease is characterized by the neuronal accumulation of aggregated alpha-synuclein in the CNS and peripheral nervous system that results in a wide spectrum of worsening progressive motor and non-motor symptoms. While diagnosis relies on motor symptoms classically associated

with Parkinson's disease, non-motor symptoms may present many years earlier. Current treatments for Parkinson's disease are symptomatic and only address a subset of symptoms such as motor impairment, dementia, or psychosis. There are currently no treatments available that target the underlying cause of the disease and can slow its progression.

About Alpha-synuclein

Alpha-synuclein, a protein found in neurons and other cells, is a major component of pathology that characterizes several neurodegenerative disorders including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, which collectively are termed synucleinopathies. The understanding of the normal physiological function of alpha-synuclein is limited, but evidence indicates that soluble forms of the protein may interact with other proteins and certain intracellular membranes. In synucleinopathies, the alpha-synuclein protein appears to be abnormally aggregated intracellularly, which contributes to disease pathology. There is increasing evidence that certain aggregated forms of alpha-synuclein can be transmitted from neuron to neuron, resulting in a propagation of pathology that causes neuronal dysfunction and loss. Recent studies in cellular and animal models of synucleinopathy suggest that the spread of alpha-synuclein-associated neuronal pathology can be disrupted by targeting aberrant forms of alpha-synuclein.

About Prasinezumab

Prasinezumab is a humanized monoclonal antibody under development for the potential treatment of Parkinson's disease. Prasinezumab targets alpha-synuclein and is designed to block the cell-to-cell transmission of the aggregated pathogenic forms of alpha-synuclein in Parkinson's disease, thereby slowing clinical decline. Prior to initiating clinical trials, the efficacy of prasinezumab was evaluated in various cellular and animal models of alpha-synuclein-related disease. In alpha-synuclein transgenic mice, the murine version of prasinezumab reduced the appearance of alpha-synuclein pathology, protected synapses and halted the worsening of behavioral phenotypes. In December 2013, Prothena and Roche entered into a worldwide collaboration to develop and commercialize antibodies that target alpha-synuclein, including prasinezumab. Prothena has an option to co-promote prasinezumab in the U.S., where the companies share all development and commercialization costs, as well as profits, on a 30/70 basis (30 percent Prothena, 70 percent Roche). Outside the U.S., Roche has sole responsibility for developing and commercializing prasinezumab and has agreed to pay Prothena up to double-digit royalties on net sales. To date, Prothena has earned $75 million of a total potential $600 million in milestone payments that includes clinical, regulatory and sales milestones. For more information on the Phase 2 PASADENA clinical study of prasinezumab in patients with early Parkinson's disease, visit clinicaltrials.gov and search NCT #03100149.

About Prothena

Prothena Corporation plc is a clinical-stage 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, 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 programs that target Aβ (Amyloid beta) for the potential treatment of Alzheimer's disease. 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 prasinezumab; plans for the ongoing Phase 2 clinical study of prasinezumab; plans for future clinical studies of prasinezumab; and the continued advancement of our discovery and preclinical pipeline. 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 on March 3, 2020, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. 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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