Prothena Presents New Data for Alzheimer's and Parkinson's Disease Programs at AD/PD 2022

- Oral presentation on preclinical data demonstrates Prothena's dual Aβ/tau vaccine, for the potential treatment and prevention of Alzheimer's, generated anti-Aβ and anti-tau antibodies to enable phagocytosis of Aβ and to neutralize tau
- Preclinical data from poster presentation demonstrates that Prothena's tandem C-terminal α-synuclein vaccine, for the potential treatment and prevention of Parkinson's, produces robust binding to pathogenic α-synuclein and inhibition of uptake of soluble α-synuclein aggregates into cells
- Oral presentation by partner Roche on the Phase 2 PASADENA study of prasinezumab, an α-synuclein antibody being developed for the treatment of Parkinson's, further supports a potential effect on delaying motor progression in patients
- Prothena leadership will participate in and sponsor two AD/PD 2022 Forum Discussions: *Amyloid-Removing Therapies* and *Anti-Tau Approaches In Clinical Trials*
- AD/PD 2022 honors the legacy of late Prothena Co-founder and CEO, Dale Schenk Ph.D., celebrating his hallmark discoveries in the biology and advancement of therapeutics for Alzheimer's

DUBLIN, Ireland, March 16, 2022 -- Prothena Corporation plc (NASDAQ:PRTA), a late-stage clinical biotechnology company with a robust pipeline of investigational therapeutics built on protein dysregulation expertise, presented new preclinical data from both its dual Aβ/tau vaccine for the potential treatment and prevention of Alzheimer's disease (AD) and from its tandem C-terminal α-synuclein vaccine programs for the potential treatment and prevention of Parkinson's disease (PD) and related synucleinopathies. The data were presented at the International Conference on Alzheimer's and Parkinson's Diseases (AD/PD 2022), taking place March 15-20, 2022, in Barcelona, Spain.

Additionally, the scientific legacy of Dr. Dale Schenk, late Co-Founder and CEO of Prothena, was honored at the AD/PD 2022 opening ceremony. During this memorial, Dr. Dennis Selkoe, the Vincent and Stella Coates Professor of Neurologic Diseases at Harvard Medical School, Co-Director of the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital and Director on Prothena's Board of Directors, celebrated the impact of Dr. Schenk's pioneering research. Dr. Schenk's work spans fundamental discoveries elucidating the roles that amyloid, gamma secretase and beta secretase contribute to AD, to research that has paved the way for multiple scientific and therapeutic breakthroughs for patients suffering from AD and PD.

"The need for vaccines to prevent Alzheimer's and Parkinson's diseases from ever occurring is urgent. We are making exciting progress in that direction by combining our unbiased Biology-Directed Engine and our know-how with the many learnings from the development of therapies in Alzheimer's and Parkinson's over

the last several decades," said Wagner M. Zago, Ph.D., Chief Scientific Officer of Prothena. "At AD/PD 2022, we are excited to present a wealth of data highlighting potential advances across the therapeutic spectrum, from active treatment to prevention of these devastating neurodegenerative diseases. Specifically in Alzheimer's, our dual Aβ/tau vaccine demonstrated, in a preclinical setting, simultaneous generation of antibodies against Aβ and tau with the proper quantity and quality of response, while avoiding engagement of cytotoxic immune responses. We continue to build momentum toward our ultimate goal of eradicating Alzheimer's disease and plan for an IND for this AD vaccine candidate in 2023."

Dual Aβ/tau vaccine for the treatment and prevention of Alzheimer's disease

Preclinical data on Prothena's dual Aβ/tau vaccine were presented in an oral presentation titled: *Development of a Dual Aβ/tau Vaccine for the Treatment and Prevention of Alzheimer's Disease* (Oral Presentation SO007 / #814).

Prothena's dual Aβ/tau vaccines were described as linear peptide conjugates designed to prevent the two key processes associated with AD: 1) the formation of Aβ-plaque and 2) the development of intraneuronal tau tangles. The incremental results from preclinical studies support the continued development of this dual-epitope vaccine for the treatment and prevention of AD.

Specifically, the findings presented at AD/PD 2022 provide proof of concept in multiple preclinical species for Prothena's dual Aβ/tau vaccine to address the desirable attributes of *quantity, quality and safety* that have prevented the advancement of safe and effective vaccines for the treatment or prevention of AD. From a *quantity* standpoint, results demonstrated both the generation of robust and balanced immunogenic responses against pathogenic Aβ and tau in multiple animal species, demonstrating the ability to overcome immunodominance. For *quality*, sera from immunized animals inhibited the binding of soluble Aβ aggregates to cultured hippocampal neurons and bound to Aβ plaques and tau tangles in human AD brain sections at titers expected to be achieved in the central nervous system *in vivo*, potentially demonstrating strong immunoreactivity to Aβ and tau pathology. The antibodies generated by these vaccines also induced phagocytosis and blocked binding of tau to heparin, an analog of heparan sulfate (HS). Tau-HS interactions are believed to be involved in both the secretion of tau and its subsequent internalization into neurons. For *safety*, the sera from immunized non-human primates did not generate measurable cytotoxic T-cell responses to endogenous Aβ or tau proteins.

Tandem C-terminal α-synuclein vaccine for the treatment and prevention of Parkinson's disease and other synucleinopathies

Prothena presented preclinical data from a study of Prothena's tandem C-terminal α-synuclein vaccine in a poster presentation titled: *Development of C-Terminal α-Synuclein Vaccine for Treatment and Prevention of Parkinson's Disease and Other Synucleinopathies* (Poster P563 / #156*)*.

The findings demonstrate that the lead vaccine candidate with tandem C-terminal α-synuclein peptides resulted in titers, with robust binding to pathogenic α-synuclein and inhibition of uptake of soluble α-synuclein aggregates into cells, when compared to immunization with vaccines containing a single peptide sequence. The robust and functional characteristics of the immune response following vaccination support

the further development of this approach for the potential treatment and prevention of PD and related synucleinopathies.

Prothena leadership will participate in two AD/PD 2022 Forum Discussions

Anti-Tau Approaches In Clinical Trials
Co-Moderators: Luc Buee (France), William Jagust (USA)
Wagner M. Zago, Ph.D., Chief Scientific Officer
Wednesday, March 16, 2022 - 17:30–18:30 CET

Amyloid-Removing Therapies: The Beginning Of The End Or The End Of The Beginning?
Co-Moderators: Al Sandrock (USA), Philip Scheltens (The Netherlands)
Gene Kinney, Ph.D., President and Chief Executive Officer
Saturday, March 19, 2022 - 15:50–16:50 CET

Roche (partner) Presentations on Prasinezumab

Results from the delayed-start analysis of Phase 2 PASADENA study of prasinezumab for the treatment of Parkinson's disease

Data from Phase 2 PASADENA study of prasinezumab, first-in-class anti-α-synuclein antibody and the focus of a worldwide collaboration with Roche, were presented in an oral presentation titled: *A 104-Week Delayed-Start Analysis of PASADENA (Phase 2 Study Evaluating the Safety and Efficacy of Prasinezumab in Early Parkinson's Disease* (Oral Presentation SO309 / #408).

Results presented by Roche showed that participants with PD who were treated with prasinezumab for two years (early-start group) showed slower decline of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 3 scores relative to participants treated with prasinezumab for one year (delayed-start group).

Additional Roche (partner) presentations on prasinezumab include:

Oral - *Delayed Start Analysis of Roche PD Mobile Application V2 In Pasadena Shows Persistent Positive Effects of Prasinezumab on Bradykinesia Progression* (Oral Presentation SO307 / #123)

Poster - *Estimating the Meaningful Within-Patient Change Threshold for the MDS-UPDRS PART III* (Poster P595 / #407)

Poster - *Non-motor Symptoms In Parkinson's Disease: A Systematic Review and Meta-analysis of Prevalence* (Poster OO229 / #418)

About Alzheimer's Disease

Alzheimer's disease is the most common form of dementia causing increasingly serious symptoms, including confusion, disorientation, mood and behavioral changes, difficulty speaking, swallowing, and walking. Approximately 50 million people worldwide are estimated to be living with Alzheimer's disease or other dementias. Alzheimer's disease is the most common neurodegenerative disorder. There is an urgent need for therapies that slow the progression and ultimately prevent Alzheimer's disease to address this global healthcare crisis. Prothena's Alzheimer's disease portfolio spans next generation antibody immunotherapy, small molecule, and vaccine approaches, geared toward building upon first generation treatments to advance the treatment paradigm.

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 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 Prothena

Prothena Corporation plc is a late-stage clinical company with a robust pipeline of novel investigational therapeutics built on protein dysregulation expertise 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 potentials, designs, and proposed mechanisms of action of our dual Aβ/tau vaccine, our α-synuclein vaccine, and prasinezumab; plans for future clinical studies of our dual Aβ/tau vaccine; and the continued advancement of our discovery, preclinical, and clinical 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 those 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, 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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