NEWS RELEASE

Prothena Provides Update on PRX012 and Announces Results from the Phase 1 ASCENT Clinical Program

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- As previously communicated, Prothena plans to explore potential partnership interest to advance PRX012 and its preclinical PRX012-TfR (transferrin receptor) antibody
- Phase 1 ASCENT clinical program established proof-of-mechanism for PRX012 as a once-monthly, subcutaneous anti-amyloid beta antibody with high binding potency, dose- and time-dependent reduction of amyloid plaque, although with a non-competitive ARIA-E profile in patients with early symptomatic Alzheimer's disease

DUBLIN--(BUSINESS WIRE)-- Prothena Corporation plc (NASDAQ:PRTA), today announced results from the Phase 1 ASCENT clinical program in participants with early symptomatic Alzheimer's disease (AD). As previously communicated, Prothena plans to explore potential partnership interest to advance PRX012 and its preclinical PRX012-TfR (transferrin receptor) antibody.

The Phase 1 ASCENT clinical program results demonstrated PRX012 as a potential once-monthly, subcutaneous anti-amyloid beta (Aβ) antibody with stable pharmacokinetics, low anti-drug antibodies, low injection site reactions, and dose- and time-dependent reductions in amyloid plaque. At the 400 mg dose level, PRX012 demonstrated a mean reduction in amyloid PET to 27.47 centiloids (CL) at month 12; FDA approved anti-Aβ antibodies have defined amyloid negativity thresholds of ≤30 CL or ≤24.1 CL. However, PRX012 was associated with higher overall ARIA-E rates relative to FDA approved anti-Aβ antibodies, making PRX012 less appropriate for the patients studied in the ASCENT clinical program. When ARIA-E did occur, the characteristics were similar to those reported following treatment with other anti-Aβ antibodies.

Based on the profile observed in the ASCENT clinical program and feasibility work already completed on its preclinical Aβ-transferrin receptor antibody surrogate, Prothena believes this approach may represent an opportunity to significantly lower the risk of ARIA and quickly reduce amyloid plaque with a once-monthly subcutaneous administration. Initial preclinical studies have demonstrated substantially increased brain exposure and facilitated rapid targeting of Aβ plaques in an APP/PS1 transgenic mouse model.

“On behalf of our entire team, we extend our continued appreciation to the patients, families, investigators, and staff whose dedication and collaboration enabled the Phase 1 ASCENT clinical program to achieve its objectives," said Chad Swanson, Ph.D., Chief Development Officer, Prothena. “We plan to explore potential partnership interest to further develop PRX012 and PRX012-TfR.”

Prothena does not plan to publicly share additional data from the ASCENT clinical program while it expects to explore potential partnership interest to advance PRX012 and PRX012-TfR.

Phase 1 ASCENT Clinical Program

The Phase 1 ASCENT clinical program includes ASCENT-1: a randomized, double-blind, placebo-controlled single-ascending-dose trial; ASCENT-2: a randomized, double-blind, placebo-controlled six-month multiple-dose trial; and ASCENT-3: a twelve-month open-label extension trial. The objectives of the ASCENT clinical program were to determine the safety, tolerability, immunogenicity, and pharmacokinetics of PRX012. The ASCENT-2 and ASCENT-3 trials also evaluated the pharmacodynamics of PRX012, including amyloid plaque deposition as measured by positron emission tomography (PET), in participants with early symptomatic AD.

The results include data from the five ASCENT-2 Group A cohorts in 228 participants with early symptomatic AD who are either APOε4 non-carriers or heterozygous carriers ranging in doses of PRX012 from 45 mg to 400 mg, randomized to PRX012 or placebo in a 3:1 ratio. Additional amyloid plaque reduction data from an interim read-out of ASCENT-3, the open-label extension (OLE) trial, was included.

ASCENT-2 Group A: Adverse Events[1]

	Placebo (n=57)	45 mg (n=25)	70 mg (n=24)	200 mg[2] (n=97)	400 mg (n=24)
Treatment Emergent Adverse Events (TEAE)	33 (57.9%)	10 (40.0%)	13 (54.2%)	66 (68.0%)	18 (75.0%)
Treatment Emergent Serious Adverse Event (TESAE)	5 (8.8%)	2 (8.0%)	1 (4.2%)	7 (7.2%)	1 (4.2%)
Study drug related TESAE	0	0	1 (4.2%)	5 (5.2%)	1 (4.2%)

TEAE Leading to Withdrawal of Study Drug	0	0	1 (4.2%)	4 (4.1%)	0
TEAE Leading to Withdrawal from the Study	0	0	1 (4.2%)	1 (1.0%)	0
Death	0	1 (4.0%)	0	0	0
Death due to Study Drug	0	0	0	0	0
Overall ARIA	4 (7.0%)	4 (16.0%)	5 (20.8%)	41 (42.3%)	10 (41.7%)
ARIA-E	1 (1.8%)3	3 (12.0%)	2 (8.3%)	37 (38.1%)	10 (41.7%)
ARIA-H	4 (7.0%)	3 (12.0%)	4 (16.7%)	29 (29.9%)	8 (33.3%)
Concurrent ARIA-E and ARIA-H	0	2 (8.0%)	1 (4.2%)	24 (24.7%)	8 (33.3%)

1 Safety population includes all randomized participants who received at least one dose of study drug
2 Participants received 200 mg dose level in two separate cohorts (a core and an expansion cohort)
3 The one placebo participant with ARIA-E was in the 70 mg cohort: 1 of 8 participants (12.5%)

PRX012 was generally well-tolerated across all dose cohorts of the trial. Injection site reactions in participants treated with PRX012 were low (4.1%). Treatment emergent anti-drug antibodies were low and generally transient with titer values close to the assay's detection threshold. There was one death in the study in the 45 mg dose cohort, which was determined by the investigator to be not related to study drug.

Group A: Amyloid PET Centiloid (CL) Values

ASCENT-2 and ASCENT-3 Interim Data

	Placebo	45 mg	70 mg	200 mg1	400 mg
Baseline Mean CL	77.74 (n=49)	75.64 (n=22)	75.62 (n=19)	75.47 (n=86)	70.95 (n=23)
6 Months Mean CL (double-blind placebo controlled)	77.84 (n=49)	77.39 (n=22)	67.44 (n=19)	68.83 (n=85)	58.66 (n=23)
12 Months Mean CL2 (OLE)	n/a	78.86 (n=18)	61.60 (n=13)	52.88 (n=57)	27.47 (n=13)

1 Participants received 200 mg dose level in two separate cohorts (a core and an expansion cohort)
2 12 months mean CL data includes only participants who were randomized to PRX012 in ASCENT-2 and rolled over to ASCENT-3 (OLE) as the majority of those participants had the opportunity to reach month 12 dosing at each dose level by the time of the interim data cut

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 ATTR amyloidosis with cardiomyopathy, 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 X (formerly Twitter) @ProthenaCorp.

Forward-Looking Statements

This press release contains forward-looking statements. These statements relate to, among other things, the treatment potential, design, and proposed mechanism of action of our Aβ-transferrin receptor antibody program; and our exploration of potential partnership interest to advance our PRX012 and PRX012-TfR programs. 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 uncertainties related to the completion of operational and financial closing procedures, audit adjustments and other developments that may arise that would require adjustments to the preliminary financial results included in this press release, as well as 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 4, 2025, 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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