Prothena Corp plc
Form 10-K
March 13, 2015

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the year ended December 31, 2014

.. TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission file number: 001-35676

PROTHENA CORPORATION PUBLIC LIMITED COMPANY
(Exact name of registrant as specified in its charter)

Ireland	98-1111119
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

Alexandra House
The Sweepstakes, Ballsbridge
Dublin 4, Ireland

(Address of principal executive offices including Zip Code)
Registrant's telephone number, including area code: 011-353-1-902-3519
Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Ordinary Shares, par value $0.01 per share	The Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

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Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes x No o

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	o	Accelerated filer	x
Non-accelerated filer	¨ (Do not check if a smaller reporting company)	Smaller reporting company	o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ¨ No x

As of June 30, 2014, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the voting shares held by non-affiliates of the registrant was approximately $600.7 million, based on the last reported sale of the registrant's ordinary shares on the Nasdaq Global Market on such date. 27,399,535 of the Registrant's ordinary shares, par value $0.01 per share, were outstanding as of February 27, 2015.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Proxy Statement to be delivered to shareholders in connection with the registrant's Annual General Meeting of Shareholders to be held on May 21, 2015 are incorporated by reference into Part III of this Form 10-K. The registrant intends to file its Proxy Statement within 120 days after its fiscal year ended December 31, 2014.

PROTHENA CORPORATION PLC
Annual Report on Form 10-K
For the Year Ended December 31, 2014
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PART I
ITEM 1. BUSINESS

Overview
We are a late-stage clinical biotechnology company focused on the discovery, development and commercialization of novel protein immunotherapy programs for the potential treatment of diseases that involve amyloid or cell adhesion. We are developing antibody-based product candidates that target a number of potential indications including AL amyloidosis (NEOD001), Parkinson's disease and other related synucleinopathies (PRX002) and psoriasis and other inflammatory diseases (PRX003).
We are conducting The VITAL Amyloidosis Study, a Phase 3 global registrational trial, and a concurrent Phase 1/2 trial for our lead antibody, NEOD001, for the potential treatment of patients with AL amyloidosis. NEOD001 received Fast Track designation from the U.S. Food and Drug Administration (the "FDA") in December 2014.
In collaboration with Roche, we are developing PRX002 for the treatment of Parkinson's disease and other related synucleinopathies. During 2014, we advanced PRX002 into clinical development with the initiation of two Phase 1 studies. Results for the first Phase 1 study, a single ascending dose trial in healthy volunteers, are expected in March 2015. We continue to enroll patients with Parkinson's disease in the second Phase 1 multiple ascending dose study, with results expected in first half of 2016.
For PRX003, we expect to initiate a Phase 1 single ascending dose study in healthy volunteers during the first half of 2015, with a multiple ascending dose study in patients with psoriasis beginning in 2016 to establish potential clinical proof-of-biology in Phase 1. Beyond psoriasis, we may further develop PRX003 for the potential treatment of orphan and/or other inflammatory diseases.
We are a public limited company formed under the laws of Ireland. On December 20, 2012, we separated from Elan Corporation, plc ("Elan"). Our ordinary shares began trading on The Nasdaq Global Market under the symbol "PRTA" on December 21, 2012 and currently trade on The Nasdaq Global Select Market.

Our Strategy

Our goal is to be a leading biotechnology company focused on the discovery, development and commercialization of novel protein immunotherapy programs for the treatment of diseases that involve amyloid or cell adhesion. Key elements of our strategy to achieve this goal are to:

- Continue to discover antibodies directed against novel targets related to amyloid or cell adhesion.

We leverage our core scientific expertise and proprietary technology to develop innovative antibody-based therapeutics for the potential treatment of major unmet medical needs. Once we formulate a novel hypothesis or approach to a known target, we generate antibodies against that target. Specific and selective antibodies are characterized in vitro, then used to test the initial hypothesis in vivo using animal models of disease. We often rely on the use of animal models that have been extensively developed by external laboratories, as we have already done with our programs for AL amyloidosis, Parkinson's disease and psoriasis.

- Quickly translate our research discoveries into clinical development.

Once we establish in vivo proof of concept for our antibody candidates, we use animal models to identify potential clinical candidates and to rapidly advance these candidates into manufacturing and preclinical testing. In 2012, we filed an Investigational New Drug Application ("IND") with the FDA for NEOD001 for AL and AA amyloidosis and less than two years later, in December 2014, we initiated The VITAL Amyloidosis Study, a Phase 3 global registrational clinical trial in patients with AL amyloidosis and cardiac dysfunction.

- Establish early clinical proof of concept with our therapeutic antibodies.

We leverage our insight of disease pathology related to amyloid or cell adhesion to employ biomarker endpoints as a way to detect signals of biological activity early in the clinical development process. We may elect to start clinical testing of our antibodies in indications that have well-established endpoints in order to demonstrate proof of concept as a basis for further investment in clinical trials, by us or potential partners.

- Focus on diseases that lack effective therapies.

We focus on the development and commercialization of therapies for serious and/or life-threatening diseases that lack effective therapies. NEOD001 received Fast Track designation in December 2014, and has received orphan drug designation in both the U.S. and Europe for the treatment of AL amyloidosis. We have initiated The VITAL Amyloidosis Study, a Phase 3 clinical trial for NEOD001 for the treatment of newly-diagnosed, treatment-naïve patients with AL amyloidosis and cardiac dysfunction. To date, there are no approved therapies for the treatment of AL amyloidosis.

In collaboration with Roche, we are developing PRX002 as a potential disease-modifying treatment of Parkinson's disease and other related synucleinopathies. During 2014, we advanced PRX002 into clinical development with the initiation of two Phase 1 studies. Results for the first Phase 1 study, a single ascending dose trial in healthy volunteers, are expected in March 2015. We continue to enroll patients with Parkinson's disease in the second Phase 1 multiple ascending dose study, with results expected in the first half of 2016. To date, all approved therapies for patients with Parkinson's disease focus on the alleviation of disease symptoms.

We expect to initiate a Phase 1 single ascending dose study for PRX003 in healthy volunteers in the first half of 2015, with a multiple ascending dose trial enrolling patients with psoriasis in 2016. While therapies exist today that treat psoriasis and other inflammatory disorders, we believe our antibody has the potential to improve the outcome for patients who do not receive adequate benefit from existing therapies.

Moving forward, we intend to advance new discovery-stage monoclonal antibody therapeutics that show promise in orphan disease indications.

- Strategically collaborate or out-license select programs.

Our robust discovery engine generates monoclonal antibodies that may be useful in treating unmet medical needs. For therapeutic antibody programs targeting broad patient populations that may require large clinical trials and development investment, we may seek to collaborate or license these potential antibody therapeutics to biotechnology or pharmaceutical companies for development and/or commercialization. In line with our strategy, in December 2013, we entered into the License, Development and Commercialization Agreement with Roche (described below), to develop and commercialize certain antibodies that target alpha-synuclein, including PRX002 for the potential treatment of Parkinson's disease and other related synucleinopathies.

- Highly leverage external talent and resources.

Although we plan to maintain strong talent internally having expertise in our core areas of focus and as needed to execute efficiently on our clinical development and business objectives, we will leverage external resources to meet our operational and business needs while maintaining flexibility as those needs may change over time. We plan to continue to rely on the very extensive experience of our management team to execute on our objectives.

- Collaborate with scientific and clinical experts in disease areas of interest.

We collaborate with highly regarded scientists having expertise in our disease areas of interest to test and characterize our potential therapeutic antibody candidates. We also collaborate with leading clinical experts in our disease areas of interest for feedback and guidance on our programs. In addition, we engage a number of consultants having specific functional and/or disease area expertise to help us execute on our preclinical and clinical development programs.

- Evaluate commercialization strategies in order to maximize the value of our product candidates or future potential products.

As we move our drug candidates through development toward regulatory approval, we will evaluate several options for each drug candidate's commercialization strategy. These options include building our own internal sales force; entering into a joint marketing partnership with another pharmaceutical or biotechnology company, whereby we jointly sell and market the product; regional licensing for markets where we do not have expertise or infrastructure; and out-licensing our product, whereby another pharmaceutical or biotechnology company sells and markets our product and pays us a royalty on sales. We evaluate options for each product based on a number of factors including commercial synergies and expertise, capital necessary to execute on each option, size of the market to be addressed and terms of potential offers from other pharmaceutical and biotechnology

companies.

Research and Development Pipeline

Our research and development pipeline includes three therapeutic antibody programs that we intend to advance: NEOD001 for the potential treatment of AL amyloidosis; PRX002 in collaboration with Roche, for the potential treatment of Parkinson's disease and other related synucleinopathies; and PRX003 for the potential treatment of psoriasis and other inflammatory diseases.

The following table summarizes the status of our research and development pipeline for our lead programs:
Our Lead Programs

NEOD001 for AL Amyloidosis

Our most advanced product development program, NEOD001, targets AL amyloidosis. Systemic amyloidoses, including AL, AA and ATTR amyloidosis, are a complex group of diseases caused by tissue deposition of amyloid proteins that result in progressive organ damage. The most common type, AL amyloidosis or primary systemic amyloidosis, results from hematological disorder involving abnormal plasma cells. Plasma cells normally produce light chains that pair with heavy chains to make functional antibodies. But in AL amyloidosis, something goes awry - the cause remains unknown. A subset of plasma cells begin overproducing a single light chain in great abundance. These light chains then misfold in blood and eventually aggregate into tissues, such as heart and kidneys, causing extensive organ damage and fatigue.

AL amyloidosis is a grievous disease and there are no approved treatments that directly target the toxic forms of the AL protein that build up in the organs. AL amyloidosis is a rare disorder with about 15,000 patients in the U.S. and Europe, however, we believe this disease is significantly underdiagnosed. Both the cause and origins of AL amyloidosis remain poorly understood.

Current treatment for patients with AL amyloidosis include organ transplants or the administration of off-label chemotherapeutic and/or oncologic therapies targeted at killing plasma cells to decrease the production of light chain circulating in the blood, called the hematologic burden. These chemotherapeutic and/or oncologic agents are associated with a known adverse event profile and patients often become refractory to their hematologic effect and/or relapse. In addition, the target of these therapies remains the plasma cells responsible for production of light chain, rather than the toxic light chain in circulation or built up in the organs. There remains a significant unmet need to directly target and remove the insoluble amyloid deposited on organs, to improve organ function and mortality, without increasing adverse events.

NEOD001 is a humanized monoclonal antibody that specifically targets the circulating misfolded soluble light chain and deposited insoluble amyloid that accumulates in AL amyloidosis. NEOD001 received Fast Track designation from the FDA in December 2014. The purpose of the Fast Track designation is to make important new drugs available to patients earlier. The Fast Track program also provides a company with the ability to submit sections of the Biologics License Applications ("BLA") for review before the company submits the complete BLA. This enables the FDA to review sections of the BLA as they are received, rather than waiting until every section of the application is completed, and also allows for Priority Review, which can shorten the standard review of the final BLA to six months. A drug program with Fast Track designation permits the company to have

early and frequent communications with the FDA in the development and review of the product candidate, potentially leading to faster drug approval.

In addition, NEOD001 was granted orphan drug designation for the treatment of AL and AA amyloidosis by the FDA in 2012 and for the treatment of AL amyloidosis by the European Medicines Agency (the "EMA") in 2013.

The VITAL Amyloidosis Study, a Phase 3 Clinical Trial

In December 2014, we initiated The VITAL Amyloidosis Study, a Phase 3 clinical trial for NEOD001 in patients with AL amyloidosis. The trial is designed to support global regulatory approvals. We intend to enroll approximately 230 newly-diagnosed, treatment-naïve patients with AL amyloidosis and cardiac dysfunction. Patients will be randomized on a 1:1 basis to receive 24 mg/kg of NEOD001 or placebo via intravenous infusion every 28 days, with both groups receiving concurrent standard of care therapy.

The composite primary endpoint is event-based, with all-cause mortality or cardiac hospitalizations as qualifying events. Secondary endpoints of the study include evaluation of the cardiac biomarker NT-proBNP, renal biomarker proteinuria, six-minute walk test, and multiple quality of life evaluations including the Short Form-36 and the Kansas City Cardiomyopathy Questionnaire. Prothena designed the study with 90% power to detect a 30% change in the event rate between the treatment and placebo groups with a two-sided alpha of 0.05. The trial allows for an interim analysis to assess the primary endpoint for efficacy and futility.

Cardiac and Renal Biomarker Responses in Phase 1/2 Study

The VITAL Amyloidosis Study, a Phase 3 clinical trial, was initiated following report of positive data in the ongoing Phase 1/2 clinical trial. In December 2014, we reported results from the ongoing Phase 1/2 study that showed 7 of 14 cardiac-evaluable patients (50%) treated with NEOD001 demonstrated a cardiac response, defined as more than 30% and 300 pg/mL decrease in levels of NT-proBNP from baseline (a validated cardiac biomarker associated with mortality). Cardiac responders, on average, showed more NT-proBNP decline with added monthly NEOD001 infusions. The 50% cardiac response rate compares favorably with the expected results of a 26.5% cardiac response rate from historical data in patients treated solely with standard of care that is not approved specifically for AL amyloidosis (Comenzo, et al., Leukemia. 2012;26:2317-2325). As noted in numerous peer-reviewed publications, increasing levels of NT-proBNP predicts higher mortality rates in patients with AL amyloidosis. Conversely, decreasing levels of NT-proBNP predicts lower mortality rates.

In a best response analysis of renal-evaluable patients treated with NEOD001, 6 of 14 renal-evaluable patients (42.9%) demonstrated a response, defined as more than 30% decrease in proteinuria in the absence of greater than 25% worsening of estimated glomerular filtration rate ("eGFR"). The 42.9% renal response rate compares favorably with the expected results of an approximately 24% renal response rate from historical data in patients treated solely with standard of care that is not approved specifically for AL amyloidosis (Palladini, et al., Blood. 2014 124: 2325-2332). Increased levels of proteinuria and decreased eGFR predicts faster progression to dialysis where decreased levels of proteinuria and increased eGFR predicts delayed time to dialysis.

Safety, Tolerability, Pharmacokinetics and Immunogenicity

Data from the Phase 1/2 study also continued to demonstrate that chronic monthly infusions of NEOD001 are safe and well-tolerated in patients with AL amyloidosis and persistent organ dysfunction. A database analysis as of September 30, 2014 showed a total of 27 patients in seven dosing cohorts received 209 infusions, with each patient treated on average for approximately eight months. No hypersensitivity reactions or drug-related serious adverse events were reported and no anti-NEOD001 antibodies were detected. NEOD001 demonstrated excellent pharmacokinetic

properties, supporting a dose level of 24 mg/kg every 28 days. The most frequently reported adverse events (more than 10% of subjects) were fatigue, cough, dyspnea, diarrhea, upper respiratory infection, anemia, headache, hyponatremia, nausea and edema. All adverse events were mild to moderate and no dose limiting toxicities have been observed. As of September 30, 2014, 19 patients continued on therapy (eight patients discontinued). No patient discontinued due to drug-related adverse events. Following selection of 24 mg/kg as the Phase 3 recommended dose, in consultation with their treating physician, all 14 eligible patients continuing in the dose escalation portion of the Phase 1/2 study have chosen to escalate to 24 mg/kg.

Expansion Portion of Phase 1/2 Study

Concurrent with The VITAL Amyloidosis Study, a Phase 3 clinical trial, we are enrolling up to an additional 25 patients, with AL amyloidosis and selected persistent organ dysfunction, in an open-label expansion portion of the Phase 1/2 study. We plan to enroll 10 patients with cardiac dysfunction, 10 patients with renal dysfunction and five patients with peripheral neuropathy,

all of whom will receive 24 mg/kg intravenously every 28 days. The expansion phase will continue to evaluate safety, tolerability, pharmacokinetics and immunogenicity of NEOD001 as well as the specific clinical activity against cardiac, renal and neuropathy endpoints.

PRX002 for Parkinson’s Disease

In December 2013, we entered into a License, Development, and Commercialization Agreement (the "License Agreement”) with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (collectively, “Roche”) to develop and commercialize certain antibodies that target alpha-synuclein, including PRX002. Together, we and Roche aim to develop PRX002 as a disease-modifying treatment for Parkinson’s disease and potentially other synucleinopathies. For more information on the License Agreement, see the information below.

Alpha-synuclein is found extensively in neurons and is a major component of pathological inclusions that characterize several neurodegenerative disorders, including Parkinson’s disease, dementia with Lewy bodies, and multiple system atrophy, which collectively are termed synucleinopathies. While the normal function of synuclein is not well understood, the protein normally occurs in a soluble form. In synucleinopathies, the synuclein protein can misfold and aggregate to form soluble aggregates and insoluble fibrils that contribute to the pathology of the disease.

There is genetic evidence for a causal role of synuclein in Parkinson’s disease. In rare cases of familial forms of Parkinson’s disease, there are mutations in the synuclein gene, or duplication and triplications of the gene that may cause synuclein protein to form amyloid-like fibrils that contribute to the disease. There is also increasing evidence that this disease-causing synuclein can be propagated and transmitted from neuron to neuron, resulting in an infection-like spread of neuronal death. Recent studies in cellular and animal models suggest that the spread of synuclein-associated neurodegeneration can be disrupted by targeting aberrant forms of synuclein.

Parkinson’s disease is a degenerative disorder of the central nervous system that affects one in 100 people over age 60. Current treatments for Parkinson’s disease are only effective at managing the early motor symptoms of the disease, mainly through the use of levodopa and dopamine agonists. As the disease progresses and dopaminergic neurons continue to be lost, these drugs eventually become less effective at treating the symptoms. The goal of our approach is to slow down the progressive neurodegenerative consequences of disease, a current unmet need. PRX002 targets alpha-synuclein and may slow or reduce the neurodegeneration associated with synuclein misfolding and/or transmission.

During 2014, we and Roche advanced PRX002 into clinical development with the initiation of two Phase 1 studies. The first study, a Phase 1 double-blind, placebo-controlled, single ascending dose trial, enrolled 40 healthy volunteers, all of which were randomized 3:1 into five escalating dose cohorts to receive PRX002 or placebo every 28-days. Results for this trial are expected in March 2015.
In addition, we are enrolling patients with Parkinson’s disease in a Phase 1 multiple ascending dose study. The Phase 1 randomized, double-blind, placebo-controlled, multiple ascending dose study of PRX002 is expected to enroll up to 60 patients with Parkinson's disease at multiple centers across the U.S. and is designed to evaluate the safety, tolerability, pharmacokinetics and immunogenicity of PRX002. The multiple ascending dose study will also evaluate multiple clinical and exploratory biomarker endpoints. Patients will be enrolled in escalating dose cohorts of PRX002 or placebo and will be observed for up to 6 months.

Prior to initiating clinical trials, we tested the efficacy of PRX002 in various cellular and animal models of synuclein-related disease. In transgenic mouse models of Parkinson’s disease, passive immunization with 9E4, the murine version of PRX002, reduced the appearance of synuclein pathology, protected synapses and improved performance by the mice in behavioral testing.

License, Development, and Commercialization Agreement with Roche

In December 2013, we entered into the License Agreement with Roche to develop and commercialize certain antibodies that target alpha-synuclein, including PRX002, which are referred to in this report collectively as “Licensed Products.” The License Agreement became effective following the expiration of the applicable Hart-Scott-Rodino waiting period on January 17, 2014, which triggered an upfront payment to us of $30.0 million from Roche, which we received in February 2014.

Pursuant to the License Agreement, we and Roche are collaborating to research and develop antibody products targeting alpha-synuclein. Roche is providing funding for a research collaboration between us and Roche focused on optimizing early stage antibodies targeting alpha-synuclein, potentially including incorporation of Roche’s proprietary Brain Shuttle™ technology

to increase delivery of therapeutic antibodies to the brain. Roche is primarily responsible for developing, obtaining and maintaining regulatory approval for, and commercializing Licensed Products under the collaboration including PRX002. Roche will also become responsible for the clinical and commercial manufacture and supply of Licensed Products within a defined time period following the effective date of the License Agreement.

In addition to the $30.0 million upfront payment and a clinical milestone payment of $15.0 million paid in 2014, Roche is also obligated to pay:

- up to $380.0 million upon the achievement of development, regulatory and various first commercial sales milestones;
- up to an additional $175.0 million in ex-U.S. commercial sales milestones; and
- tiered, high single-digit to high double-digit royalties in the teens on ex-U.S. annual net sales, subject to certain adjustments.

In the U.S., the parties will share all development and commercialization costs, as well as profits, all of which will be allocated 70% to Roche and 30% to us, for PRX002 in the Parkinson's disease indication, as well as any other Licensed Products and/or indications for which we opt in to co-develop and co-fund. We may opt out of the co-development and cost and profit sharing on any co-developed Licensed Products and instead receive U.S. commercial sales milestones totaling up to $155.0 million and tiered, single-digit to high double-digit royalties in the teens based on U.S. annual net sales, subject to certain adjustments, with respect to the applicable Licensed Product. In addition, we have an option under the License Agreement to co-promote PRX002 in the U.S. in the Parkinson's disease indication. If we exercise such option, we may also elect to co-promote additional Licensed Products in the U.S. approved for Parkinson's disease. Outside the U.S., Roche will have responsibility for developing and commercializing the Licensed Products.

Under the License Agreement with Roche, we granted to Roche an exclusive, worldwide license to develop, make, have made, use, sell, offer to sell, import and export the Licensed Products. The License Agreement continues on a country-by-country basis until the expiration of all payment obligations thereunder. The License Agreement may also be terminated (i) by Roche at will after the first anniversary of the effective date of the License Agreement, either in its entirety or on a Licensed Product-by-Licensed Product basis, upon 90 days' prior written notice to us prior to first commercial sale and 180 days' prior written notice to us after first commercial sale, (ii) by either party, either in its entirety or on a Licensed Product-by-Licensed Product or region-by-region basis, upon written notice in connection with a material breach uncured 90 days after initial written notice, and (iii) by either party, in its entirety, upon insolvency of the other party. The License Agreement may be terminated by either party on a patent-by-patent and country-by-country basis if the other party challenges a given patent in a given country. Our rights to co-develop Licensed Products under the License Agreement will terminate if we commence certain studies for certain types of competitive products. Our rights to co-promote Licensed Products under the License Agreement will terminate if we commence a Phase 3 study for such competitive products.

PRX003 for Psoriasis and Other Inflammatory Diseases

We are developing PRX003, a monoclonal antibody targeting melanoma cell adhesion molecule ("MCAM") for the potential treatment of psoriasis and other inflammatory diseases, and expect to initiate a Phase 1 single ascending dose study in the first half of 2015. Beyond psoriasis, we may further develop this antibody for the potential treatment of orphan and/or other inflammatory diseases.

Within the immune system, white blood cells play an important role. T-cells are a subset of white blood cells that express either CD4 glycoprotein (CD4+) or CD8 glycoprotein (CD8+) on their surface. CD4+ T-cells are called "helper"

cells as they do not neutralize the infection, but rather initiate the body's response to infections. Th-17 cells are a subset of CD4+ T-cells characterized by the production of IL-17, and are known to be key participants in inflammatory reactions and various autoimmune diseases.

MCAM is a cell adhesion molecule that allows certain cells traveling in the blood stream to leave the circulation and enter tissues. MCAM is expressed on pathogenic Th-17 immune cells. These immune cells are believed to underlie many inflammatory diseases. MCAM functions like VELCRO™ hook-and-loop fasteners, allowing these cells to stick to the blood vessel wall, so that they can migrate into the surrounding tissues to initiate and/or maintain their pathogenic process.

Our research in the area of cell adhesion has uncovered unique insights into MCAM function, allowing us to develop specific and novel antibodies that block MCAM's VELCRO™-like function and may serve as therapeutics to prevent disease causing cells from spreading into tissue.

Anti-MCAM antibodies may be useful for treating a variety of inflammatory diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, multiple sclerosis, sarcoidosis, uveitis, and Behcet's disease. Autoimmune and/or autoinflammatory diseases arise from the body's inappropriate immune response against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a foreign pathogen and attacks its own cells. A substantial portion of the population suffers from these diseases, which are often chronic, debilitating, and life-threatening.

Current treatment for many types of inflammatory diseases may entail the use of broad acting immunosuppressive agents that weaken the body's ability to fight infection. Only 3 to 5% of CD4+ T-cells in the circulation express MCAM, yet these cells appear to be disproportionately involved in the propagation of inflammatory diseases. Hence, anti-MCAM based therapy may provide a more specific way to target the disease-causing immune cells while not interfering with normal function of the majority of the immune system.

We have generated monoclonal antibodies that selectively block MCAM-mediated cell adhesion and have been shown to delay relapse and severity of relapse in a mouse model of autoimmune inflammation.

We expect to initiate a Phase 1 single ascending dose trial of PRX003 in the first half of 2015, with a multiple ascending dose study beginning in 2016. Our clinical strategy is to pursue psoriasis initially to allow for potential rapid feedback on the biological activity of our therapeutic agent and establish a solid clinical foundation to inform our decisions as we explore the full development potential of this antibody in psoriasis and other inflammatory indications. We may elect to license or partner PRX003 for disease areas that would require larger clinical trials and investment.

Our Discovery Programs

Our pipeline also includes several late discovery-stage programs for which we are testing the efficacy of antibodies in preclinical models of diseases related to amyloid or cell adhesion. If promising, we expect that these antibodies will advance to preclinical development. New target discovery will focus on the potential treatment of orphan indications involving amyloidosis or cell-adhesion where we can bring these therapies to patients expeditiously through our internal expertise and resources. Existing late discovery-stage programs with non-orphan indications may be partnered or out-licensed.

Regulation

We anticipate that if we commercialize any products, the U.S. market will be our most important market. For this reason, the laws and regulations discussed below focus on the requirements applicable to biologic products in the U.S.

Government Regulation

Governmental authorities, including the FDA and comparable regulatory authorities in other countries, regulate the design, development, testing, manufacturing, safety, efficacy, labeling, storage, record-keeping, advertising, promotion and marketing of pharmaceutical products, including biologics, under the Federal Food, Drug, and Cosmetic Act and its implementing regulations, and the Public Health Service Act and its implementing regulations. Non-compliance with applicable requirements can result in fines and other judicially imposed sanctions, including product seizures, import restrictions, injunctive actions and criminal prosecutions of both companies and individuals. In addition, administrative remedies can involve requests to recall violative products; the refusal of the government to enter into supply contracts; or the refusal to approve pending product approval applications until manufacturing or other alleged deficiencies are brought into compliance. The FDA also has the authority to cause the withdrawal of approval of a marketed product or to impose labeling restrictions.

The pricing of pharmaceutical products is regulated in many countries and the mechanism of price regulation varies. In the U.S., while there are limited indirect federal government price controls over private sector purchases of drugs, it is not possible to predict future regulatory action on the pricing of pharmaceutical products.

Product Approval

United States. In the U.S., our drug candidates are regulated as biologic pharmaceuticals, or biologics. The FDA regulates biologics under the Federal Food, Drug and Cosmetics Act, Public Health Safety Act and its implementing regulations. Biologics are also subject to other federal, state and local statutes and regulations. The process required by the FDA before biologic product candidates may be marketed in the U.S. generally involves the following:

- submission to the FDA of an IND, which must become effective before human clinical trials may begin and must be

updated annually;

- completion of extensive preclinical laboratory tests and preclinical animal studies, all performed in accordance with the FDA's Good Laboratory Practice ("GLP") regulations;

- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product for each proposed indication, all performed in accordance with FDA's current good clinical practices ("cGCP") regulations;

- submission to the FDA of a BLA for a new biologic, after completion of all pivotal clinical trials;

- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities at which the product is produced and tested to assess compliance with current good manufacturing practices ("cGMP") regulations; and

- FDA review and approval of a BLA for a new biologic, prior to any commercial marketing or sale of the product in the U.S.

Preclinical tests assess the potential safety and efficacy of a product candidate in animal models. The results of these studies must be submitted to the FDA as part of an IND before human testing may proceed. An IND is a request for authorization from the FDA to administer an investigational drug or biologic product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human studies. The IND also includes results of animal studies or other human studies, as appropriate, as well as manufacturing information, analytical data and any available clinical data or literature to support the use of the investigational new drug. An IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical trials. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before clinical trials can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with cGCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Additionally, approval must also be obtained from each clinical trial site's Institutional Review Board ("IRB") before the trials may be initiated, and the IRB must monitor the study until completed. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries.

The clinical investigation of a pharmaceutical, including a biologic, is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The three phases of an investigation are as follows:

- Phase 1. Phase 1 includes the initial introduction of an investigational product into humans. Phase 1 clinical trials are typically closely monitored and may be conducted in patients with the target disease or condition or in healthy volunteers. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational product in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During Phase 1 clinical trials, sufficient information about the investigational product's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and

scientifically valid Phase 2 clinical trials. The total number of participants included in Phase 1 clinical trials varies, but is generally in the range of 20 to 80;

- Phase 2. Phase 2 includes controlled clinical trials conducted to preliminarily or further evaluate the effectiveness of the investigational product for a particular indication(s) in patients with the disease or condition under study, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks associated with the product. Phase 2 clinical trials are typically well-controlled, closely monitored, and conducted in a limited patient population, usually involving no more than several hundred participants; and

- Phase 3. Phase 3 clinical trials are generally controlled clinical trials conducted in an expanded patient population generally at geographically dispersed clinical trial sites. They are performed after preliminary evidence suggesting effectiveness of the product has been obtained, and are intended to further evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational product, and to provide an adequate basis

for product approval. Phase 3 clinical trials usually involve several hundred to several thousand participants.

The clinical trial process can take three to ten years or more to complete, and there can be no assurance that the data collected will support FDA approval of the product. The FDA may place clinical trials on hold at any point in this process if, among other reasons, it concludes that clinical subjects are being exposed to an unacceptable health risk. Trials may also be terminated by IRBs, which must review and approve all research involving human subjects. Side effects or adverse events that are reported during clinical trials can delay, impede or prevent marketing authorization.

The results of the preclinical and clinical testing, along with information regarding the manufacturing of the product and proposed product labeling, are evaluated and, if determined appropriate, submitted to the FDA through a BLA. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators.

Once the BLA submission has been accepted for filing, the FDA's standard goal is to review applications within ten months of the filing date or, in the case of Priority Review, six months from the filing date. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe, pure and potent, which includes determining whether it is effective for its intended use, and whether the product is being manufactured in accordance with cGMP, to assure and preserve the product's identity, strength, quality, potency and purity. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations.

The FDA has four program designations - Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review - to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of serious or life-threatening conditions. The Fast Track designation provides pharmaceutical manufacturers with opportunities for frequent interactions with FDA reviewers during the product's development and the ability for the manufacturer to do a rolling submission of the BLA. A rolling submission allows completed portions of the application to be submitted and reviewed by the FDA on an ongoing basis. The Breakthrough Therapy designation provides manufacturers with all of the features of the Fast Track designation as well as intensive guidance on implementing an efficient development program for the product and a commitment by the FDA to involve senior managers and experienced review staff in the review. The Accelerated Approval designation allows the FDA to approve a product based on an effect on a surrogate or intermediate endpoint that is reasonably likely to predict a product's clinical benefit and generally requires the manufacturer to conduct required post-approval confirmatory trials to verify the clinical benefit. The Priority Review designation means that the FDA's goal is to take action on the BLA within six months, compared to ten months under standard review.

After the FDA evaluates the BLA and conducts inspections of manufacturing facilities where the candidate product and/or its API will be produced, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the biologic with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. Even if such additional information is submitted, the FDA may ultimately decide that the BLA does not satisfy the criteria for approval. The FDA could approve the BLA with a Risk Evaluation and Mitigation Strategy ("REMS") plan to mitigate risks, which could include medication guides, physician

communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. Such post- market testing may include Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

There can be no marketing in the U.S. of a biologic until a BLA has been submitted and approved by the FDA. Until an application is actually approved, there can be no assurance that the information requested and submitted will be considered adequate by the FDA.