Prothena Corp plc
Form 10-K
March 07, 2014

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, 2013

.. 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 (State or other jurisdiction of incorporation or organization)	98-1111119 (I.R.S. Employer Identification Number)
650 Gateway Boulevard South San Francisco, California (Address of principal executive offices)	94080 (Zip Code)

Registrant's telephone number, including area code: (650) 837-8550

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 o No x

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 28, 2013, 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 $187.1 million, based on the last reported sale of the registrant's ordinary shares on the NASDAQ Global Market on such date. 21,902,937 of the Registrant's ordinary shares, par value $0.01 per share, were outstanding as of March 3, 2014.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Proxy Statement to be delivered to shareholders in connection with the registrant's 2014 Annual General Meeting of Shareholders to be held on May 21, 2014 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, 2013.

PROTHENA CORPORATION PLC
Annual Report on Form 10K
For the Year Ended December 31, 2013
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PART I
ITEM 1. BUSINESS

Overview
We are a clinical stage biotechnology company focused on the discovery, development and commercialization of novel antibodies for the potential treatment of diseases that involve protein misfolding or cell adhesion. We focus on therapeutic monoclonal antibodies directed specifically to disease causing proteins. Our antibody-based product candidates target a number of potential indications including AL and AA forms of amyloidosis (NEOD001), Parkinson's disease and related synucleinopathies (PRX002) and novel cell adhesion targets involved in inflammatory diseases and cancers (PRX003). We initiated a Phase 1 clinical trial for NEOD001, with the first successful patient dosing in April 2013. The Phase 1 clinical trial of NEOD001 is evaluating its safety and tolerability in AL patients with amyloidosis. We also plan to initiate Phase 1 clinical trials for PRX002 and PRX003 in 2014 and 2015, respectively. Our strategy is to identify antibody candidates for clinical development and commercialization by applying our extensive expertise in generating novel therapeutic antibodies and working with collaborators having expertise in specific animal models of disease.
We are a public limited company formed under the laws of Ireland. On December 20, 2012, we separated from Elan Corporation Limited (formerly Elan Corporation, plc), or Elan, which subsequently became a wholly owned subsidiary of Perrigo Company plc, or Perrigo. 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 Approach
We focus on the discovery, development and commercialization of therapeutic monoclonal antibodies directed specifically to disease causing proteins. These product candidates target a number of potential indications including AL (primary) and AA (secondary) forms of amyloidosis (NEOD001), Parkinson's disease and other synucleinopathies (PRX002), and novel cell adhesion targets involved in inflammatory diseases and cancers (PRX003). Our strategy is to apply our extensive expertise in generating novel therapeutic antibodies and work with collaborators having expertise in specific animal models of disease, to identify antibody candidates for clinical development and commercialization.
An epitope is the molecular target recognized by an antibody. A neo-epitope is a site on a protein that becomes accessible only after modification, such as from cleavage or by misfolding into an abnormal shape. The neo-epitopes we target may occur as part of a disease-associated pathological process. For some of our products we are developing novel, specific monoclonal antibodies typically against neo-epitope targets for the potential treatment of patients having a disease associated with the neo-epitope.

Targeting Neo-epitopes of Misfolded Proteins Associated with Disease

In addition to antibodies directed to neo-epitope targets, we are developing antibodies directed to other targets. For example, we have generated antibodies against novel cell adhesion targets expressed on certain pathogenic Th17 immune cells and tumor cells. One specific cell adhesion protein, called melanoma cell adhesion molecule, or MCAM, interacts with another protein called

laminin near blood vessel walls which allows circulating tumor cells and a critical subset of T cells to leave the bloodstream and enter into tissues, sometimes initiating pathogenic processes that result in disease. Antibodies that interfere with the cell adhesion process may be useful for treating a range of inflammatory diseases and cancers.

Targeting Cell Adhesion Involved in Disease Processes

Research and Development Pipeline

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

The following table summarizes the status and anticipated upcoming milestones of our research and development pipeline for lead programs:

Our Lead Programs

NEOD001 for Amyloidosis

Systemic amyloidoses are a complex group of diseases caused by tissue deposition of misfolded proteins that result in progressive organ damage. The most common type, AL amyloidosis or primary systemic amyloidosis, involves a hematological disorder caused by plasma cells that produce misfolded AL protein resulting in deposits of abnormal AL protein (amyloid), in the tissues and organs of individuals with AL amyloidosis. Although little data are available on amyloidosis populations, AL amyloidosis is a rare disorder with an estimated incidence of 8.9 in 1,000,000 patient years. 1,200 to 3,200 new cases of AL amyloidosis are reported each year in the United States. The etiology of AL amyloidosis remains poorly understood.

Current treatments of patients with AL amyloidosis are organ transplants or treatments aimed at reducing or eliminating the bone marrow disorder, i.e. the plasma cells that are responsible for producing the AL protein, thereby limiting production of amyloid. There are no currently approved treatments for AL amyloidosis and no treatments that directly target potentially toxic forms of the AL protein. We believe that there are approximately 15,000 patients in the United States and Europe suffering from

AL amyloidosis.

A different form of systemic amyloidosis, AA amyloidosis or secondary systemic amyloidosis, occurs as a result of other illnesses, such as chronic inflammatory diseases (for example, rheumatoid arthritis and ankylosing spondylitis) or chronic infections (for example, tuberculosis or osteomyelitis). In secondary systemic amyloidosis, the depositing amyloid protein is amyloid A protein. Amyloid A protein is a cleaved fragment from the acute phase protein serum amyloid A that is produced in abundance by the liver as a result of chronic inflammation. The treatment of secondary amyloidosis is directed at treating the underlying illness, typically with broad acting anti- inflammatory agents such as tumor necrosis factor, or TNF, inhibitors. We believe that there are approximately 8,000 patients in the United States and Europe suffering from AA amyloidosis.

NEOD001 is a monoclonal antibody that specifically targets the amyloid that accumulates in both AL and AA forms of amyloidosis. The antibody was designed to not react with normal serum amyloid A and only with the aberrant cleaved form of the protein (amyloid A). 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 in 2013. An Investigational New Drug application, or IND, for NEOD001 in systemic amyloidosis (AL and AA forms of amyloidosis) was filed and accepted by the FDA in 2012. We have initiated a Phase 1 clinical trial for NEOD001 with the first successful patient dosed in April 2013. The primary objective of the Phase 1 clinical trial is evaluating the safety and tolerability of NEOD001 in patients with AL Amyloidosis and determining a recommended dose for testing in Phase 2/3 trials. The secondary and exploratory objective of the Phase 1 clinical trial includes assessments of pharmacokinetics and immunogenicity of NEOD001 and hematologic and organ response. We anticipate initiating a Phase 2/3 trial of NEOD001 in 2014 assuming a Phase 2/3 recommended dose is identified prior to that date.

PRX002 for Parkinson’s Disease

In December 2013, we entered into a License, Development, and Commercialization Agreement, or the License Agreement, with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or 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 “-Patents and Intellectual Property Rights.”

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 an unstructured 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 pathogenic forms of synuclein can be propagated and transmitted from neuron to neuron. Recent studies in cellular and animal models suggest that the spread of synuclein-associated neurodegeneration can be disrupted by targeting the pathogenic synuclein. Parkinson’s disease is a degenerative disorder of the central nervous system. Current treatments for Parkinson’s disease are 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.

We have generated proprietary antibodies targeting alpha-synuclein that may slow or reduce the neurodegeneration associated with synuclein misfolding and/or transmission. We have tested the efficacy of these antibodies in various cellular and animal models of synuclein-related disease. In a transgenic mouse model 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. The humanized antibody product candidate PRX002 has advanced into manufacturing and preclinical safety testing. We anticipate initiating a Phase 1 trial of PRX002 for Parkinson’s disease in 2014 pursuant to our collaboration with Roche.

License, Development, and Commercialization Agreement with Roche

In December 2013, we entered into a License, Development, and Commercialization Agreement, or the License Agreement, with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or collectively, 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 will collaborate to research and develop antibody products targeting alpha-synuclein. Roche will provide 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. After we file an investigational new drug application with the U.S. Food and Drug Administration for PRX002, Roche will be primarily responsible for developing, obtaining and maintaining regulatory approval for, and commercializing Licensed Products. 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, the License Agreement provides that Roche will pay a near-term clinical milestone payment of $15.0 million. For PRX002, 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 United States, 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 United States in the Parkinson's disease indication. If we exercise such option, we may also elect to co-promote additional Licensed Products in the United States approved for Parkinson's disease. Outside the United States, Roche will have responsibility for developing and commercializing the Licensed Products.

For more information on the License Agreement, see "-Patents and Intellectual Property Rights."

PRX003 for Inflammatory Diseases and Cancers

We are developing PRX003, a monoclonal antibody targeting MCAM for the potential treatment of inflammatory diseases and cancers.

MCAM is a cell adhesion molecule that allows certain cells traveling in the blood stream to leave the circulation and enter tissues. For example, MCAM is expressed on pathogenic Th-17 expressing immune cells that underlie inflammatory diseases and on tumor cells involved in metastatic cancer. 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 may block MCAM's VELCRO-like function as potential 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 rheumatoid arthritis, psoriasis, psoriatic arthritis, multiple sclerosis, sarcoidosis and Behcet's disease. Autoimmune and/or autoinflammatory diseases arise from an inappropriate immune response of the body against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. A substantial portion of the population suffers from these diseases, which are often chronic, debilitating, and life-threatening. There are more than eighty illnesses caused by autoimmunity. Current treatment for many types of inflammatory diseases typically entails 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.

MCAM antibodies may also be useful for treating several cancers, including melanoma. Melanoma is a malignant tumor of melanocytes, a potentially dangerous form of skin cancer. It was estimated that doctors in the United States

would diagnose about 76,250 new cases of melanoma in 2012, with approximately 9,000 melanoma-related deaths that are usually related to metastatic spread of the tumors. Normal melanocytes do not express MCAM, but expression is turned on and continues to increase as the cells become more malignant. Treatment with anti-MCAM antibodies may help patients with melanoma by inhibiting the growth and spread of the tumor.

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 multiple sclerosis known as experimental autoimmune encephalomyelitis. Our antibodies are currently being tested in additional animal models of inflammatory diseases and cancers. Based on early results from these studies, we have identified a lead clinical candidate, PRX003. We have advanced this antibody into manufacturing and intend to advance this antibody into preclinical safety testing. We anticipate that we will file an IND and initiate a Phase 1 trial of PRX003 in 2015.

Our Discovery Programs

Our pipeline also includes several late discovery stage programs for which we are testing efficacy of antibodies in preclinical models of disease. We are also generating additional novel antibodies against other targets involved in protein misfolding or cell adhesion for characterization in vivo and in vitro. If promising, we expect that these antibodies will advance to preclinical development.

Our Strategy

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

- Continue to discover antibodies directed against novel targets involved in protein misfolding or cell adhesion.

We will continue to leverage our core scientific expertise and proprietary technology to develop innovative antibody-based therapeutics for the potential treatment of a range of diseases. 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 typically 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 and Parkinson's disease. We plan to maintain a broad and diverse pipeline of antibodies with multiple potential indications.

- 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 to rapidly advance to manufacturing and preclinical testing. We have contracted with Boehringer Ingelheim for cell line development and antibody drug substance production. In 2012, we filed an IND with the FDA for NEOD001 for AL and AA amyloidosis and we initiated a Phase 1 clinical trial of NEOD001 in patients with amyloidosis in April 2013.

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

We will leverage our insight of pathology in diseases involving protein misfolding 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 smaller indications having more well-established endpoints in order to demonstrate proof of concept as a basis for further investment in clinical trials, potentially in larger indications, by us or potential partners.

- Strategically collaborate or out-license select programs.

For some therapeutic antibody programs we may seek to collaborate or license to biotechnology or pharmaceutical companies for preclinical and clinical development and commercialization. We may also pursue strategic alliances in which we would provide our research and development services for our collaborators as part of our plan to generate revenue. In December 2013, we entered into the License Agreement with Roche, to develop and commercialize certain antibodies that target alpha-synuclein, including PRX002.

- Highly leverage external talent and resources.

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 outsourcing 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 execute our preclinical and clinical development programs.

- Evaluate commercialization strategies on a product-by-product basis 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; and out-licensing our product, whereby another pharmaceutical or biotechnology company sells and markets our product and pays us a royalty on sales. Our decision will be made separately for each product and will be based on a number of factors including 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. It is too early for us to know which of these options we will pursue for our drug candidates, assuming their successful development.

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 United States.

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, or FFDCA, and its implementing regulations, and the Public Health Service Act, or PHSA, 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 United States, 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

In the United States, our drug candidates are regulated as biologic pharmaceuticals, or biologics. The FDA regulates biologics under the FFDCA, PHSA 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 United States generally involves the following:

- submission to the FDA of an Investigational New Drug Application, or 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, or 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 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 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 United States.

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 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.

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, or 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 United States 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.

Post-Approval Requirements

Any products manufactured or distributed by us or on our behalf pursuant to FDA approvals are subject to continuing regulation by the FDA, including requirements for record-keeping, reporting of adverse experiences with the biologic, and submitting biological product deviation reports to notify the FDA of unanticipated changes in distributed products. Additionally, any significant change in the approved product or in how it is manufactured, including changes in formulation or the site of manufacture, generally require prior FDA approval. The packaging and labeling of all products developed by us are also subject to FDA approval and ongoing regulation.

Manufacturers are required to register their facilities with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP standards, which impose certain quality processes, manufacturing controls and documentation requirements upon us and our third-party manufacturers in order to ensure that the product is safe, has the identity and strength, and meets the quality, purity and potency characteristics that it purports to have. Certain states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Noncompliance with cGMP or other requirements can result in issuance of warning letters, civil and criminal penalties, seizures, and injunctive action.

FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

The FDA and other federal and state agencies closely regulate the labeling, marketing and promotion of drugs. While doctors are free to prescribe any product approved by the FDA for any use, a company can only make claims relating to safety and efficacy of a product that are consistent with FDA approval, and the company is allowed to market a drug only for the particular use and treatment approved by the FDA. In addition, any claims we make for our products in advertising or promotion must be appropriately balanced with important safety information and otherwise be adequately substantiated. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising, injunctions, potential civil and criminal penalties, criminal prosecution, and agreements with governmental agencies that materially restrict the manner in which a company promotes or distributes drug products. Government regulators, including the Department of Justice and the Office of the Inspector General of

the Department of Health and Human Services, as well as state authorities, recently have increased their scrutiny of the promotion and marketing of drugs.

The FDA also enforces the requirements of the Prescription Drug Marketing Act, which, among other things, imposes various requirements in connection with the distribution of product samples to physicians. Sales, marketing and scientific/educational grant programs must comply with the Federal Anti-Kickback Statute, the False Claims Act, and similar state laws, each as amended from time to time. Pricing and rebate programs must comply with the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990, as amended. We may also be subject to the Physician Payment Sunshine Act, or Sunshine Act, which regulates disclosure of payments to healthcare professionals and providers.

The FCPA and UK Bribery Act prohibit companies and their representatives from offering, promising, authorizing or making payments to foreign officials (and certain private individuals under the U.K. Bribery Act) for the purpose of obtaining or retaining business abroad. In many countries, the healthcare professionals we interact with may meet the definition of a foreign government official for purposes of the FCPA. Failure to comply with domestic or foreign laws could result in various adverse consequences, including possible delay in approval or refusal to approve a product, recalls, seizures, withdrawal of an approved product from the market, the imposition of civil or criminal sanctions and the prosecution of executives overseeing our international operations.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally defined as a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting a BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first BLA/NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same orphan indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or if FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. As a result, even if one of our drug candidates receives orphan exclusivity, the FDA can still approve other drugs that have a different active ingredient for use in treating the same indication or disease. Furthermore, the FDA can waive orphan exclusivity if we are unable to manufacture sufficient supply of our product.

Pharmaceutical Coverage, Pricing and Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as federal, state, and foreign government health care programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly reducing reimbursements for medical products, drugs and services. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our drug candidates or a decision by a third-party payor to not cover our drug candidates could reduce physician usage of our products once approved and have a material adverse effect on our sales, results of operations and financial condition.

Other Healthcare Laws

Although we currently do not have any products on the market, if our drug candidates are approved and we begin commercialization, we may be subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which we conduct our business. Such laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security and physician sunshine

laws and regulations. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Patents and Intellectual Property Rights

We take actions to protect the proprietary technology that we believe is important to our business, including seeking and maintaining domestic and international patents intended to cover our products and compositions, their methods of use, and processes for their manufacture, as well as any other inventions that may be commercially important to the development of our business. We also rely on trade secrets to protect our business. Our competitive position depends on our ability to obtain patents on our technologies and our potential products, to defend our patents, to protect our trade secrets and to operate without infringing valid and enforceable patents or trade secrets of others. We seek licenses from others as appropriate to enhance or maintain our competitive position.

We or our affiliates own or hold licenses to a number of issued U.S. patents and pending U.S. patent applications, as well as issued foreign patents and pending Patent Corporation Treaty applications and foreign counterparts.

In connection with our program targeting AL and AA amyloid for the potential treatment of amyloidosis, we or our affiliates own U.S. Patent No. 7,928,203, which is a composition of matter patent and expires in 2029, U.S. Patent No. 8,124,081, which is a method of treatment patent and expires in 2020, U.S. Patent No. 8,268,973, which is a composition of matter patent that expires in 2028, and U.S. Patent No. 8,404,815, which is a composition of matter patent that expires in 2028. In addition, we or our affiliates jointly own with the University of Tennessee Research Foundation, or the University of Tennessee, issued patents in New Zealand and South Africa, and have exclusively licensed the University of Tennessee's joint ownership interest in these patents.

In connection with our program targeting alpha-synuclein, we or our affiliates own U.S. Patent No. 8,609,820, which is a composition of matter patent that expires in 2032. In addition, we or our affiliates jointly own with the Regents of the University of California, or the University of California, U.S. Patent Nos. 7,919,088, 8,092,801, 8,147,833 and 8,506,959, which are method of treatment patents that expire in 2025, 2029, 2027 and 2028, respectively. We have exclusively licensed the University of California's joint ownership interest in these patents.

We or our affiliates also hold an exclusive, royalty-free sublicense from Elan and certain of its affiliates under foreign patent rights owned by Janssen Alzheimer Immunotherapy relating to immunotherapeutic approaches targeting certain proteins solely for research, development and commercialization activities directed to the use, in the diagnosis, prevention and treatment of diseases, of active and passive immunotherapeutic approaches directly targeting certain targets, but specifically excluding amyloid beta peptide, or the Projects. In connection with our program targeting synuclein for the potential treatment of Parkinson's disease and other synucleinopathies, we or our affiliates hold an exclusive, royalty-free license from Elan and certain affiliates of Elan to U.S. Patent No. 7,910,333, which is a composition of matter patent that expires in 2024, and we or our affiliates own or hold exclusive, royalty-free licenses from Elan and certain of its affiliates, solely for the Projects, under patent rights relating to research tools such as animal models and assay technology.

We or our affiliates also own patent applications relating to AL and AA, synuclein, MCAM and various discovery programs that are pending in the United States and other countries, which, if issued, would have expiration dates in the range of 2020 through 2034, excluding any available patent term adjustment.

University of Tennessee License Agreement

Under our affiliate's exclusive, sublicensable, worldwide license agreement with the University of Tennessee entered into on December 31, 2008, we are required to pay to the University of Tennessee an amount equal to 1% of net sales of any product covered by any licensed patent, plus certain additional payments in the event that all or a portion of the license is sublicensed. To date, we have not paid or incurred any royalties to the University of Tennessee under our agreement. The agreement is effective on a country-by-country basis for the longer of (i) a period of twenty years from the date of execution of the agreement, or (ii) in each country in which a valid claim for any licensed patent or patent application exists, expiration of such valid claim. The agreement will terminate prior to the end of its term if we become insolvent unless the University of Tennessee elects to allow the agreement to remain in effect. The University of Tennessee may terminate the agreement prior to the end of its term upon our failure to make payment under the agreement within 120 days of notice of such failure or upon our material breach of the agreement, which breach has not been cured within 60 days of written notice of such breach. We may terminate the agreement prior to the end of its term if we have paid all amounts due to the University of Tennessee through the effective date of the termination and provide three months' written notice to the University of Tennessee or upon material breach of the agreement by the University of Tennessee, which breach has not been cured within 60 days of written notice of such breach.

License, Development, and Commercialization Agreement with Roche

On December 11, 2013, we entered into the License Agreement with Roche to develop and commercialize the Licensed Products. The License Agreement became effective on January 22, 2014 following the expiration of the applicable Hart-Scott-Rodino waiting period on January 17, 2014.

Under the License Agreement, we grant to Roche an exclusive, worldwide license to develop, make, have made, use, sell, offer to sell, import, and export the Licensed Products. We retain certain rights to conduct development of the Licensed Products and an option to co-promote PRX002. During the term of the License Agreement, we and Roche will work exclusively with each other to research and develop antibody products targeting alpha-synuclein.

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.

Competition

The pharmaceutical industry is highly competitive. Our principal competitors consist of major international companies, all of which are larger and have greater financial resources, technical staff, manufacturing, R&D and marketing capabilities than we have. We also compete with smaller research companies and generic drug and biosimilar manufacturers. The degree of competition varies for each of our programs.

A drug may be subject to competition from alternative therapies during the period of patent protection or regulatory exclusivity and thereafter it may be subject to further competition from generic products or biosimilars. Governmental and other pressures toward the dispensing of generic products or biosimilars may rapidly and significantly reduce, slow or reverse the growth, sales and profitability of any product not protected by patents or regulatory exclusivity, and may adversely affect our future results and financial condition. If we successfully discover, develop and commercialize any products, the launch of competitive products, including generic or biosimilar versions of any such products, may have a material adverse effect on our revenues and results of operations.

Our competitive position depends in part upon our ability to discover and develop innovative and cost-effective new products. If we fail to discover and develop new products, our business, financial condition and results of operations will be materially and adversely affected.

Product Supply

While supplies of raw materials and clinical supplies of our main product candidate are generally available in quantities adequate to meet the needs of our business, we are dependent on Boehringer Ingelheim to manufacture our clinical supplies for our therapeutic antibody programs. An inability to obtain product supply could have a material adverse effect on our business, financial condition and results of operations.