Prothena Corp plc
Form S-1/A
September 30, 2013
Table of Contents

As filed with the Securities and Exchange Commission on September 30, 2013.

Registration No. 333-191218

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Amendment No. 1

to

FORM S-1

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

Prothena Corporation plc

(Exact name of Registrant as specified in its charter)

Ireland	**2834**	**43-1256213**
(State or other jurisdiction of incorporation or organization)	**(Primary Standard Industrial Classification Code Number)**	**(I.R.S. Employer Identification Number)**

650 Gateway Boulevard

South San Francisco, CA 94080

(650) 837-8550

(Address, including zip code, and telephone number, including area code, of Registrant s principal executive offices)

Dale B. Schenk

Chief Executive Officer

Prothena Corporation plc

650 Gateway Boulevard

South San Francisco, CA 94080

(650) 837-8550

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Alan C. Mendelson, Esq.	**Mark B. Weeks, Esq.**
Robert W. Phillips, Esq.	**John T. McKenna, Esq.**
Latham & Watkins LLP	**Cooley LLP**
140 Scott Drive	**3175 Hanover Street**
Menlo Park, CA 94025	**Palo Alto, CA 94304**
Telephone: (650) 328-4600	**Telephone: (650) 843-5000**
Facsimile: (650) 463-2600	**Facsimile: (650) 849-7400**

Approximate date of commencement of proposed sale to the public: As soon as practicable after the effective date of this Registration Statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. ¨

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

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 the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act.

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

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

Table of Contents

The information in this prospectus is not complete and may be changed. We and the selling shareholder may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

Subject to Completion

Prospectus dated September 30, 2013

5,000,000 Shares

Ordinary Shares

Prothena Corporation plc is offering 3,500,000 of its ordinary shares. The selling shareholder identified in this prospectus is offering 1,500,000 ordinary shares. We will not receive any of the proceeds from the sale of the ordinary shares offered by the selling shareholder.

Our ordinary shares are listed on The NASDAQ Global Market under the symbol PRTA. On September 27, 2013, the last reported sale price of our ordinary shares on The NASDAQ Global Market was $20.24 per ordinary share.

We are an emerging growth company as that term is defined under the federal securities laws of the United States and, as such, may elect to comply with certain reduced public company reporting requirements for this and future filings.

Investing in our ordinary shares involves risks that are described in the Risk Factors section beginning on page 11 of this prospectus.

	Per Share	Total
Public offering price	$	$
Underwriting discount (1)	$	$
Proceeds, before expenses, to Prothena Corporation plc	$	$
Proceeds, before expenses, to the selling shareholder	$	$

(1) See Underwriting for a description of the compensation payable to the underwriters.

We have granted to the underwriters the right to subscribe for up to 750,000 additional ordinary shares at the public offering price, less the underwriting discount, for 30 days after the date of this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the ordinary shares to investors on or about , 2013.

BofA Merrill Lynch **Credit Suisse** **RBC Capital Markets**

Wedbush PacGrow Life Sciences **Roth Capital Partners**

The date of this prospectus is , 2013.

Table of Contents

TABLE OF CONTENTS

	Page
Prospectus Summary	1
Risk Factors	11
Special Note Regarding Forward-Looking Statements	39
Market, Industry and Other Data	41
Use of Proceeds	42
Price Range of Our Ordinary Shares and Dividend Policy	42
Capitalization	43
Dilution	44
Selected Financial Data	46
Management s Discussion and Analysis of Financial Condition and Results of Operations	48
Business	57
Management	71
Executive Compensation	79
Certain Relationships and Related Party Transactions	89
Principal and Selling Shareholders	96
Description of Share Capital	99
Shares Eligible for Future Sale	112
Material United States Federal Income Tax Consequences to U.S. Holders	114
Certain Irish Tax Consequences Relating to the Holding of Our Ordinary Shares	119
Underwriting	121
Legal Matters	128
Experts	128
Where You Can Find More Information	128
Index to Consolidated Financial Statements	F-1

Neither we, the selling shareholder nor the underwriters have authorized anyone to provide you with information that is different from that contained in this prospectus or in any free writing prospectus we may authorize to be delivered or made available to you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We, the selling shareholder and the underwriters are offering to sell ordinary shares and seeking offers to buy ordinary shares only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date on the front of this prospectus, regardless of the time of delivery of this prospectus or any sale of our ordinary shares.

Prothena and our logo are our trademarks and are used in this prospectus. This prospectus also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, our trademarks and tradenames referred to in this prospectus appear without the symbol, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks and tradenames.

For investors outside the United States: Neither we nor any of the underwriters have taken any action that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons who have come into possession of this prospectus in a jurisdiction outside the United States are required to inform themselves about and to observe any restrictions relating to this offering and the distribution of this prospectus.

Table of Contents

PROSPECTUS SUMMARY

The items in the following summary are described in more detail later in this prospectus. This summary provides an overview of selected information and does not contain all of the information you should consider before buying our ordinary shares. Therefore, you should read the entire prospectus carefully, especially the Risk Factors section beginning on page 11 and our consolidated financial statements (which we refer to as our Financial Statements) and the related notes appearing at the end of this prospectus, before deciding to invest in our ordinary shares. In this prospectus, unless the context otherwise requires, references to we, us, our, or Prothena, refer to Prothena Corporation plc.

Overview

We are a clinical stage biotechnology company focused on the discovery, development and commercialization of novel antibodies for the treatment of a broad range of diseases that involve protein misfolding or cell adhesion. We focus on the discovery, development and commercialization of therapeutic monoclonal antibodies directed specifically to disease causing proteins. Our antibody-based product candidates target a broad range of potential indications including AL and AA forms of amyloidosis (NEOD001), Parkinson s disease and other synucleinopathies (PRX002) and inflammatory diseases and cancers (PRX003). We initiated a Phase 1 clinical trial for NEOD001, with the first patient dosing in April 2013. The Phase 1 clinical trial of NEOD001 is evaluating its safety and tolerability in AL amyloidosis patients. 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 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. We separated from Elan Corporation, plc, or Elan, on December 20, 2012 and our ordinary shares began trading on The NASDAQ Global Market under the symbol PRTA on December 21, 2012.

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 broad range of potential indications including AL (primary) and AA (secondary) forms of amyloidosis, Parkinson s disease and other synucleinopathies, and novel cell adhesion targets involved in inflammatory diseases and cancers. 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.

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 against neo-epitope targets for the potential treatment of patients having a disease associated with the neo-epitope.

Table of Contents

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

Table of Contents

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 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 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 transplant 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 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 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). Preclinical data has demonstrated survival benefits

and selectivity of NEOD001 for amyloid deposits in a mouse model of AA amyloidosis. This approach has the potential to be a first-in-class agent for this orphan disease with a significant unmet medical need. 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 patient dosed in April 2013. The primary objective of the Phase 1 clinical trial is evaluating the safety and tolerability of NEOD001 in AL Amyloidosis patients and determining a recommended dose for testing in Phase 2 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 trial of NEOD001 in 2014 assuming a Phase 2 recommended dose is identified prior to that date.

PRX002 for Parkinson s Disease

Alpha-synuclein is a protein that is a prominent component of Lewy bodies and neurites which are pathological hallmarks of Parkinson s disease, dementia with Lewy bodies, multiple system atrophy and certain other neurological disorders, collectively known as 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 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 ineffective 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, a 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 filing an IND and initiating a Phase 1 trial of PRX002 for Parkinson s disease in 2014.

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 travelling 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 and migrate into tissues to initiate their pathogenic process.

Table of Contents

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. Inflammatory disease arises 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 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 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 late 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 and 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 discovery, development and commercialization of novel antibodies for the treatment of a broad range 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 and cell adhesion;

Quickly translate our research discoveries into clinical development;

Establish early clinical proof of concept with our therapeutic antibodies;

Table of Contents

Strategically collaborate or out-license select programs;

Highly leverage external talent and resources;

Collaborate with scientific and clinical experts in disease areas of interest; and

Evaluate commercialization strategies on a product-by-product basis in order to maximize the value of each of our product candidates or future potential products.

Risks and Uncertainties Relating to Our Business

We are a clinical stage biotechnology company and our business and ability to execute our business strategy is subject to numerous risks and uncertainties that you should be aware of before making an investment decision. These risks and uncertainties are described more fully in the sections titled Risk Factors and Special Note Regarding Forward-Looking Statements in this prospectus. You should carefully consider all of the information set forth in this prospectus and, in particular, should evaluate the specific factors set forth under Risk Factors and Special Note Regarding Forward-Looking Statements in deciding whether to invest in our ordinary shares. Among these important risks and uncertainties that could adversely affect our results of operations and business condition are the following:

We have not generated any significant third party external revenue to date, and we anticipate that we will incur losses for the foreseeable future and we may never achieve or sustain profitability;

We will require additional capital to fund our operations, and if we are unable to obtain such capital, we will be unable to successfully develop and commercialize drug candidates;

Our success is largely dependent on the success of our research and development programs, which are at an early stage. Our drug candidates are still in early stages of development and we have only one drug candidate in its first Phase 1 clinical trials. We may not be able to successfully discover, develop, obtain regulatory approval for or commercialize any drug candidates;

Even if any of our drug candidates receives regulatory approval, if such approved product does not achieve broad market acceptance, the revenues that we generate from sales of the product will be limited;

The markets for our drug candidates are subject to intense competition. If we are unable to compete effectively, our drug candidates may be rendered noncompetitive or obsolete;

If clinical trials of our drug candidates are prolonged, delayed, suspended or terminated, we may be unable to commercialize our drug candidates on a timely basis, which would require us to incur additional costs and delay our receipt of any revenue from potential product sales;

We rely on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet established deadlines for the completion of any such clinical trials;

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our drug candidates, our business will be substantially harmed;

Even if our drug candidates receive regulatory approval in the United States, we may never receive approval or commercialize our products outside of the United States;

Table of Contents

We depend on third-party suppliers for key raw materials used in our manufacturing processes, and the loss of these third-party suppliers or their inability to supply us with adequate raw materials could harm our business;

If we are unable to adequately protect or enforce the intellectual property relating to our drug candidates our ability to successfully commercialize our drug candidates will be harmed; and

Other factors identified elsewhere in this prospectus, including those set forth under Risk Factors and Special Note Regarding Forward-Looking Statements.

Corporate Information

We were formed under the laws of Ireland as a private limited company under the name Neotope Corporation Limited on September 26, 2012. We subsequently re-registered as a public limited company and changed our name to Neotope Corporation plc. On November 1, 2012, our shareholders resolved to change our name to Prothena Corporation plc, and this was approved by the Irish Registrar of Companies on November 7, 2012.

Our business consists of a substantial portion of Elan s former drug discovery business platform, including Neotope Biosciences Limited and its wholly owned subsidiaries Onclave Therapeutics Limited and Prothena Biosciences Inc (which for the period prior to separation and distribution we refer to herein as the Prothena Business). Prior to December 21, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. After the separation from Elan, and the related distribution of our ordinary shares to Elan s shareholders (which we refer to as the Separation and Distribution), our ordinary shares began trading on The NASDAQ Global Market under the symbol PRTA on December 21, 2012.

Our principal executive offices are located at 650 Gateway Boulevard, South San Francisco, California 94080, and our telephone number is (650) 837-8550. We also maintain offices in Dublin, Ireland. Our website address is http://www.prothena.com. The information contained in, or that can be accessed through, our website is not part of this prospectus.

Implications of Being an Emerging Growth Company

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and are eligible to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. These include, but are not limited to, (i) reduced obligations with respect to the disclosure of selected financial data in registration statements filed with the Securities and Exchange Commission (including the registration statement on Form S-1 of which this information statement is a part), (ii) reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, (iii) an exception from compliance with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002 and (iv) exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and the requirement to obtain shareholder approval of any golden parachute payments not previously approved.

In addition, Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, or Securities Act, for complying with new or revised accounting standards. In other words, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We intend to take advantage of such extended transition period, and as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for private companies. Section 107 of the JOBS Act provides that we can elect to opt out of the extended transition period at any time and that election is irrevocable.

Table of Contents

THE OFFERING

Issuer	Prothena Corporation plc
Ordinary shares offered:	
by us	3,500,000 ordinary shares (or 4,250,000 ordinary shares if the underwriters exercise in full their option to subscribe for additional shares)
by the selling shareholder	1,500,000 ordinary shares
Ordinary shares to be outstanding after the offering	21,179,182 ordinary shares (or 21,929,182 shares if the underwriters exercise in full their option to subscribe for additional shares)
Use of proceeds	We intend to use substantially all of the net proceeds from this offering to conduct clinical trials and the balance for working capital and general corporate purposes, including research and development. We will not receive any proceeds from the sale of ordinary shares by the selling shareholder. See Use of Proceeds on page 42 for a more complete description of the intended use of proceeds from this offering.
Risk factors	See Risk Factors beginning on page 11 and other information included in this prospectus for a discussion of factors that you should consider carefully before deciding to invest in our ordinary shares.
Symbol on The NASDAQ Global Market	PRTA

The number of ordinary shares to be outstanding after this offering is based on 17,679,182 ordinary shares outstanding as of June 30, 2013, and excludes the following:

- 1,835,500 ordinary shares issuable upon the exercise of outstanding options as of June 30, 2013 having a weighted-average exercise price of $6.57 per share; and
- 814,500 ordinary shares reserved for issuance pursuant to future awards under our 2012 Long Term Incentive Plan.

Unless otherwise indicated, all information in this prospectus assumes:

- no exercise of options outstanding as of June 30, 2013; and
- no exercise of the underwriters option to subscribe for additional ordinary shares from us.

8

Table of Contents

SUMMARY FINANCIAL DATA

The following tables set forth a summary of our historical financial data as of, and for the period ended on, the dates indicated. The Consolidated Statement of Operations data for the years ended December 31, 2012, 2011 and 2010 and the Consolidated Balance Sheet data as of December 31, 2012 and 2011 are derived from our audited Financial Statements included elsewhere in this prospectus. The Consolidated Balance Sheet data as of December 31, 2010 are derived from our audited Financial Statements not included in this prospectus. The Consolidated Statement of Operations data for the six months ended June 30, 2013 and 2012 and Consolidated Balance Sheet data as of June 30, 2013 have been derived from our unaudited Financial Statements appearing elsewhere in this prospectus. You should read this data together with our audited and unaudited Financial Statements and related notes appearing elsewhere in this prospectus and the information under the captions Selected Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations. Our historical results are not necessarily indicative of our future results, and results for the six months ended June 30, 2013 are not necessarily indicative of results to be expected for the full year ending December 31, 2013.

Our historical results of operations presented below may not be reflective of our financial position, results of operations and cash flows had we operated as a stand-alone public company during all periods presented. Prior to December 21, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. Our Combined Financial Statements prior to December 21, 2012 have been prepared on a carve-out basis from the consolidated financial statements of Elan to represent our financial position and performance as if we had existed on a stand-alone basis during each of the fiscal years presented in the Consolidated Financial Statements. Central support costs have been allocated to us for the purposes of preparing the Consolidated Financial Statements based on our estimated usage of the resources. Our estimated usage of the central support resources was determined by estimating our portion of the most appropriate driver for each category of central support costs such as headcount or labor hours, depending on the nature of the costs. We believe that such allocations have been made on a reasonable basis, but may not necessarily be indicative of all of the costs that would have been incurred if we had operated on a standalone basis.

	Years Ended December 31,			Six Months Ended June 30,	
	2012	2011	2010	2013	2012
	(in thousands, except per share data)			(unaudited)	
Consolidated Statement of Operations Data:					
Revenues related party	$ 2,658	$ 507	$ 1,243	$ 338	$ 1,139
Operating expenses:					
Research and development	34,139	24,172	9,787	14,104	16,776
General and administrative	9,929	5,579	3,618	6,393	4,885
Total operating expenses	44,068	29,751	13,405	20,497	21,661
Loss from operations	(41,410)	(29,244)	(12,162)	(20,159)	(20,522)
Interest income, net	5			36	
Loss before income taxes	(41,405)	(29,244)	(12,162)	(20,123)	(20,522)
Provision for income taxes	6	426	320	130	
Net loss	$ (41,411)	$ (29,670)	$ (12,482)	$ (20,253)	$ (20,522)
Basic and diluted net loss per share (1)	$ (2.84)	$ (2.05)	$ (0.86)	$ (1.15)	$ (1.42)
Shares used to compute basic and diluted net loss per share	14,593	14,497	14,497	17,679	14,497

Table of Contents

	December 31,			June 30,
	2012	2011	2010	2013
		(in thousands)		(unaudited)
Consolidated Balance Sheet Data:				
Cash and cash equivalents (1)	$ 124,860	$	$	$ 112,507
Total assets	129,283	3,618	3,278	117,930
Other non-current liabilities	1,055	1,650	1,384	1,618
Total liabilities	2,799	10,054	3,249	10,701
Shareholders and parent company equity	126,484	(6,436)	(30)	107,229

(1) Prior to the Separation and Distribution completed on December 20, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. As a result, Prothena did not have any ordinary shares outstanding and cash and cash equivalents prior to December 20, 2012. The calculation of basic and diluted net loss per share assumes that the 14,496,929 ordinary shares issued to Elan shareholders in connection with the separation from Elan have been outstanding for all periods presented and that the 3,182,253 ordinary shares subscribed for by a wholly owned subsidiary of Elan upon separation have been outstanding since December 20, 2012.

Table of Contents

RISK FACTORS

Investing in our ordinary shares involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this prospectus, including our Financial Statements and the related notes and Management s Discussion and Analysis of Financial Condition and Results of Operations, before deciding whether to invest in our ordinary shares. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our ordinary shares could decline, and you may lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations.

Risks Relating to Our Financial Position, Our Need for Additional Capital and Our Business

We have not generated any significant third party external revenue to date, and we anticipate that we will incur losses for the foreseeable future and we may never achieve or sustain profitability.

We may not generate the cash that is necessary to finance our operations in the foreseeable future. We have not generated any significant third party external revenues to date. We have incurred losses of $41.4 million, $29.7 million and $12.5 million for the years ended December 31, 2012, 2011 and 2010, respectively, and $20.3 million for the six months ended June 30, 2013. We expect to continue to incur substantial losses for the foreseeable future as we:

- conduct our Phase 1 clinical trial for NEOD001 and initiate additional clinical trials, if supported by the results of the Phase 1 trial;
- complete preclinical development of other product candidates and initiate clinical trials, if supported by positive preclinical data; and
- pursue our early stage research and seek to identify additional drug candidates and potentially acquire rights from third parties to drug candidates through licenses, acquisitions or other means.

We must generate significant revenue to achieve and sustain profitability. Even if we succeed in discovering, developing and commercializing one or more drug candidates, we may not be able to generate sufficient revenue and we may never be able to achieve or sustain profitability.

We will require additional capital to fund our operations, and if we are unable to obtain such capital, we will be unable to successfully develop and commercialize drug candidates.

As of June 30, 2013, we had cash and cash equivalents of $112.5 million. Although we believe, based on our current business plans, that our existing cash and cash equivalents will be sufficient to meet our obligations for at least the next twelve months, we anticipate that we will require additional capital in the future in order to continue the research and development of our drug candidates. Our future capital requirements will depend on many factors that are currently unknown to us, including, without limitation:

- the timing of initiation, progress, results and costs of our clinical trials, including our Phase 1 clinical trial for NEOD001;
- the results of our research and preclinical studies;
- the costs of clinical manufacturing and of establishing commercial manufacturing arrangements;

the costs of preparing, filing, and prosecuting patent applications and maintaining, enforcing, and defending intellectual property-related claims;

Table of Contents

our ability to establish research collaborations, strategic collaborations, licensing or other arrangements;

the costs to satisfy our obligations under potential future collaborations; and

the timing, receipt, and amount of revenues or royalties, if any, from any approved drug candidates.

We have based our expectations relating to liquidity and capital resources on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenses associated with completing the development of our current product candidates.

We are not able to provide specific estimates of the timelines or total costs to complete the ongoing Phase 1 clinical trial for NEOD001 that we initiated in April 2013. In the pharmaceutical industry, the research and development process is lengthy and involves a high degree of risk and uncertainty. This process is conducted in various stages and, during each stage, there is a substantial risk that product candidates in our research and development pipeline will experience difficulties, delays or failures. This makes it difficult to estimate the total costs to complete this ongoing Phase 1 clinical trial or any future clinical trials for NEOD001, or any potential future drug candidates, and to estimate the anticipated completion date with any degree of accuracy, and raises concerns that attempts to provide estimates of timing may be misleading by implying a greater degree of certainty than actually exists.

In order to develop and obtain regulatory approval for our product candidates we will need to raise substantial additional funds. We expect to raise any such additional funds through public or private equity or debt financings, collaborative agreements with corporate partners or other arrangements. We cannot assure you that additional funds will be available when we need them on terms that are acceptable to us, or at all. General market conditions may make it very difficult for us to seek financing from the capital markets. If we raise additional funds by issuing equity securities, substantial dilution to existing shareholders would result. If we raise additional funds by incurring debt financing, the terms of the debt may involve significant cash payment obligations as well as covenants and specific financial ratios that may restrict our ability to operate our business. We may be required to relinquish rights to our technologies or drug candidates or grant licenses on terms that are not favorable to us in order to raise additional funds through strategic alliances, joint ventures or licensing arrangements.

If adequate funds are not available on a timely basis, we may be required to:

terminate or delay clinical trials or other development for one or more of our drug candidates;

delay arrangements for activities that may be necessary to commercialize our drug candidates;

curtail or eliminate our drug research and development programs that are designed to identify new drug candidates; or

cease operations.

In addition, if we do not meet our payment obligations to third parties as they come due, we may be subject to litigation claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and distract management, and may have unfavorable results that could further adversely impact our financial condition.

Our future success depends on our ability to retain our chief executive officer and to attract, retain and motivate qualified personnel.

We are highly dependent on Dr. Dale Schenk, our President and Chief Executive Officer. We expect that we will continue to pay our key executives less cash compensation than what they were paid by Elan. There

12

Table of Contents

can be no assurance that we will be able to retain Dr. Schenk or any of our key executives. The loss of the services of Dr. Schenk or any other person on which we become highly dependent might impede the achievement of our research and development objectives. Recruiting and retaining qualified scientific personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific personnel from universities and research institutions.

Our collaborators, prospective collaborators and suppliers may need assurances that our financial resources and stability on a stand-alone basis are sufficient to satisfy their requirements for doing or continuing to do business with us.

Some of our collaborators, prospective collaborators and suppliers may need assurances that our financial resources and stability on a stand-alone basis are sufficient to satisfy their requirements for doing or continuing to do business with us. If our collaborators, prospective collaborators or suppliers are not satisfied with our financial resources and stability, it could have a material adverse effect on our ability to develop our drug candidates, enter into licenses or other agreements and on our business, financial condition or results of operations.

Risks Related to the Discovery, Development and Regulatory Approval of Drug Candidates

Our success is largely dependent on the success of our research and development programs, which are at an early stage. Our drug candidates are still in early stages of development and we have only one drug candidate in its first Phase 1 clinical trials. We may not be able to successfully discover, develop, obtain regulatory approval for or commercialize any drug candidates.

The success of our business depends substantially upon our ability to discover, develop, obtain regulatory approval for and commercialize our drug candidates successfully. Our research and development programs are prone to the significant and likely risks of failure inherent in drug development. We intend to continue to invest most of our time and financial resources in our research and development programs. Although we have initiated one Phase 1 clinical trial for NEOD001, there is no assurance that this clinical trial will support further development of this drug candidate. In addition, we currently do not, and may never, have any other drug candidates in clinical trials, and we have not identified drug candidates for many of our research programs.

Before obtaining regulatory approvals for the commercial sale of any drug candidate for a target indication, we must demonstrate with substantial evidence gathered in well-controlled clinical trials, and, with respect to approval in the United States, to the satisfaction of the United States Food and Drug Administration, or FDA, or, with respect to approval in other countries, similar regulatory authorities in those countries, that the drug candidate is safe and effective for use for that target indication. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain, and subject to unanticipated delays. Despite our efforts, our drug candidates may not:

- offer improvement over existing, comparable products;
- be proven safe and effective in clinical trials; or
- meet applicable regulatory standards.

Positive results in preclinical studies of a drug candidate may not be predictive of similar results in humans during clinical trials, and promising results from early clinical trials of a drug candidate may not be replicated in later clinical trials. Interim results of a clinical trial do not necessarily predict final results. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in early-stage development. Accordingly, the

Table of Contents

results from completed preclinical studies and clinical trials for our drug candidates may not be predictive of the results we may obtain in later stage trials or studies. Our preclinical studies or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials, or to discontinue clinical trials altogether.

Furthermore, we have not marketed, distributed or sold any products. Our success will, in addition to the factors discussed above, depend on the successful commercialization of our drug candidates, which may require:

- obtaining and maintaining commercial manufacturing arrangements with third-party manufacturers;
- collaborating with pharmaceutical companies or contract sales organizations to market and sell any approved drug; or
- acceptance of any approved drug in the medical community and by patients and third-party payors.

Many of these factors are beyond our control. We do not expect any of our drug candidates to be commercially available for several years and some or all may never become commercially available. Accordingly, we may never generate revenues through the sale of products.

If clinical trials of our drug candidates are prolonged, delayed, suspended or terminated, we may be unable to commercialize our drug candidates on a timely basis, which would require us to incur additional costs and delay our receipt of any revenue from potential product sales.

We cannot predict whether we will encounter problems with our Phase 1 clinical trial for NEOD001 or any future clinical trials that will cause us or any regulatory authority to delay or suspend those clinical trials or delay the analysis of data derived from them. For example, our current Phase 1 NEOD001 clinical trial targets patients with amyoloidosis, an orphan population with a relatively small pool of patients who may be eligible, accessible and interested in participating in clinical trials. A number of events, including any of the following, could delay the completion of our planned clinical trials and negatively impact our ability to obtain regulatory approval for, and to market and sell, a particular drug candidate:

- conditions imposed on us by the FDA or any foreign regulatory authority regarding the scope or design of our clinical trials;
- delays in obtaining, or our inability to obtain, required approvals from institutional review boards, or IRBs, or other reviewing entities at clinical sites selected for participation in our clinical trials;
- insufficient supply or deficient quality of our drug candidates or other materials necessary to conduct our clinical trials;
- delays in obtaining regulatory agency agreement for the conduct of our clinical trials;
- lower than anticipated enrollment and retention rate of subjects in clinical trials for a variety of reasons, including size of patient population, nature of trial protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;
- serious and unexpected drug-related side effects experienced by patients in clinical trials; or

failure of our third-party contractors to meet their contractual obligations to us in a timely manner.

Table of Contents

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us, the FDA, the IRBs at the sites where the IRBs are overseeing a trial, or a data safety monitoring board, or DSMB, overseeing the clinical trial at issue, or other regulatory authorities due to a number of factors, including:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities resulting in the imposition of a clinical hold;
- varying interpretation of data by the FDA or similar foreign regulatory authorities;
- failure to achieve primary or secondary endpoints or other failure to demonstrate efficacy;
- unforeseen safety issues; or
- lack of adequate funding to continue the clinical trial.

Additionally, changes in regulatory requirements and guidance may occur and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs for reexamination, which may impact the cost, timing or successful completion of a clinical trial.

We do not know whether our clinical trials will be conducted as planned, will need to be restructured or will be completed on schedule, if at all. Delays in our clinical trials will result in increased development costs for our drug candidates. In addition, if we experience delays in the completion of, or if we terminate, any of our clinical trials, the commercial prospects for our drug candidates may be harmed and our ability to generate product revenues will be jeopardized. Furthermore, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of a drug candidate.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our drug candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA and comparable foreign authorities is inherently unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a drug candidate s clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any drug candidate and it is possible that none of our existing drug candidates or any drug candidates we may seek to develop in the future will ever obtain regulatory approval.

Our drug candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a drug candidate is safe and effective for its proposed indication;

15

Table of Contents

- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;

- we may be unable to demonstrate that a drug candidate s clinical and other benefits outweigh its safety risks;

- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;

- the data collected from clinical trials of our drug candidates may not be sufficient to support the submission of a Biologics License Application, or BLA, or other submission or to obtain regulatory approval in the United States or elsewhere;

- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; or

- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market our drug candidates, which would significantly harm our business, results of operations and prospects. In addition, even if we were to obtain approval, regulatory authorities may approve any of our drug candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a drug candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that drug candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our drug candidates.

Even if our drug candidates receive regulatory approval in the United States, we may never receive approval or commercialize our products outside of the United States.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks detailed above regarding FDA approval in the United States as well as other risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval would impair our ability to develop foreign markets for our drug candidates.

Both before and after marketing approval, our drug candidates are subject to ongoing regulatory requirements and continued regulatory review, and if we fail to comply with these continuing requirements, we could be subject to a variety of sanctions and the sale of any approved products could be suspended.

Both before and after regulatory approval to market a particular drug candidate, the manufacturing, labeling, packaging, adverse event reporting, storage, advertising, promotion, distribution and record keeping related to the product are subject to extensive, ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued

Table of Contents

compliance with current good manufacturing practice, or cGMP, requirements and current good clinical practice, or cGCP, requirements for any clinical trials that we conduct post-approval. Any regulatory approvals that we receive for our drug candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials, and surveillance to monitor the safety and efficacy of the drug candidate. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with the regulatory requirements of the FDA and other applicable U.S. and foreign regulatory authorities could subject us to administrative or judicially imposed sanctions, including:

- restrictions on the marketing of our products or their manufacturing processes;
- warning letters;
- civil or criminal penalties;
- fines;
- injunctions;
- product seizures or detentions;
- import or export bans;
- voluntary or mandatory product recalls and related publicity requirements;
- suspension or withdrawal of regulatory approvals;
- total or partial suspension of production; and
- refusal to approve pending applications for marketing approval of new products or supplements to approved applications.

The FDA s policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our drug candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

If side effects are identified during the time our drug candidates are in development or after they are approved and on the market, we may choose to or be required to perform lengthy additional clinical trials, discontinue development of the affected drug candidate, change the labeling of any such products, or withdraw any such products from the market, any of which would hinder or preclude our ability to generate revenues.

Undesirable side effects caused by our drug candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. The

drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly. Even if any of our drug candidates receives marketing approval, as greater numbers of patients use a drug

Table of Contents

following its approval, an increase in the incidence of side effects or the incidence of other post-approval problems that were not seen or anticipated during pre-approval clinical trials could result in a number of potentially significant negative consequences, including:

- regulatory authorities may withdraw their approval of the product;
- regulatory authorities may require the addition of labeling statements, such as warnings or contraindications;
- we may be required to change the way the product is administered, conduct additional clinical trials or change the labeling of the product;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could substantially increase the costs and expenses of developing, commercializing and marketing any such drug candidates or could harm or prevent sales of any approved products.

We deal with hazardous materials and must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Some of our research and development activities involve the controlled storage, use, and disposal of hazardous materials. We are subject to federal, state, and local laws and regulations governing the use, manufacture, storage, handling, and disposal of these hazardous materials. Although we believe that our safety procedures for the handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state or federal authorities may curtail our use of these materials, and we could be liable for any civil damages that result, which may exceed our financial resources and may seriously harm our business. Because we believe that our laboratory and materials handling policies and practices sufficiently mitigate the likelihood of materials liability or third-party claims, we currently carry no insurance covering such claims. An accident could damage, or force us to shut down, our operations.

Risks Related to the Commercialization of Our Drug Candidates

Even if any of our drug candidates receives regulatory approval, if such approved product does not achieve broad market acceptance, the revenues that we generate from sales of the product will be limited.

Even if any drug candidates we may develop or acquire in the future obtain regulatory approval, they may not gain broad market acceptance among physicians, healthcare payors, patients and the medical community. The degree of market acceptance for any approved drug candidate will depend on a number of factors, including:

- the indication and label for the product and the timing of introduction of competitive products;
- demonstration of clinical safety and efficacy compared to other products;
- prevalence and severity of adverse side effects;

availability of reimbursement from managed care plans and other third-party payors;

convenience and ease of administration;

Table of Contents

cost-effectiveness;

other potential advantages of alternative treatment methods; and

the effectiveness of marketing and distribution support of the product.

Consequently, even if we discover, develop and commercialize a product, the product may fail to achieve broad market acceptance and we may not be able to generate significant revenue from the product.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell an approved product, we may be unable to generate product revenue.

We do not currently have an organization for the sales, marketing and distribution of pharmaceutical products. In order to market any products that may be approved by the FDA, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate product revenue and may not become profitable.

If government and third-party payors fail to provide coverage and adequate reimbursement rates for any of our drug candidates that receive regulatory approval, our revenue and prospects for profitability will be harmed.

In both domestic and foreign markets, our sales of any future products will depend in part upon the availability of reimbursement from third-party payors. Such third-party payors include government health programs such as Medicare, managed care providers, private health insurers, and other organizations. There is significant uncertainty related to the third-party coverage and reimbursement of newly approved drugs. Coverage and reimbursement may not be available for any drug that we or our collaborators commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Third-party payors are also increasingly attempting to contain healthcare costs by demanding price discounts or rebates and limiting both coverage and the amounts that they will pay for new drugs, and, as a result, they may not cover or provide adequate payment for our drug candidates. We might need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to such payors satisfaction. Such studies might require us to commit a significant amount of management time and financial and other resources. Our future products might not ultimately be considered cost-effective. Adequate third-party reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we or our collaborators may not be able to successfully commercialize any product candidates for which marketing approval is obtained.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drugs vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay commercial launch of the drug, possibly for lengthy time periods, and negatively impact our ability to generate revenue from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more drug candidates, even if our drug candidates obtain marketing approval.

Table of Contents

U.S. and foreign governments continue to propose and pass legislation designed to reduce the cost of healthcare. In the United States, we expect that there will continue to be federal and state proposals to implement similar governmental controls. In addition, recent changes in the Medicare program and increasing emphasis on managed care in the United States will continue to put pressure on pharmaceutical product pricing. For example, in 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Healthcare Reform Law, was enacted. The Healthcare Reform Law substantially changes the way healthcare is financed by both governmental and private insurers and significantly affects the pharmaceutical industry. Among the provisions of the Healthcare Reform Law of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance;
- a new Medicare Part D coverage gap discount program, under which manufacturers must agree to offer 50 percent point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer s outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level beginning in 2014, thereby potentially increasing a manufacturer s Medicaid rebate liability;
- a licensure framework for follow-on biologic products;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Open Payments program and its implementing regulations;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the Healthcare Reform Law was enacted. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. On March 1, 2013, the President signed an executive order implementing the 2% Medicare payment reductions, and on April 1, 2013, these reductions went into effect. In January 2013,

President

Table of Contents

Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, our financial operations.

We expect that the Healthcare Reform Law, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug. Legislation and regulations affecting the pricing of pharmaceuticals might change before our drug candidates are approved for marketing. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

There can be no assurance that our drug candidates, if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication, that they will be considered cost-effective by third-party payors, that coverage or an adequate level of reimbursement will be available, or that third-party payors reimbursement policies will not adversely affect our ability to sell our drug candidates profitably if they are approved for sale.

The markets for our drug candidates are subject to intense competition. If we are unable to compete effectively, our drug candidates may be rendered noncompetitive or obsolete.

The research, development and commercialization of new drugs is highly competitive. We will face competition with respect to all drug candidates we may develop or commercialize in the future from pharmaceutical and biotechnology companies worldwide. The key factors affecting the success of any approved product will be its indication, label, efficacy, safety profile, drug interactions, method of administration, pricing, reimbursement and level of promotional activity relative to those of competing drugs.

Furthermore, many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs that target the same indications we are targeting with our research and development program. We face, and expect to continue to face, intense and increasing competition as new products enter the market and advanced technologies become available. Many of our competitors have:

- significantly greater financial, technical and human resources than we have and may be better equipped to discover, develop, manufacture and commercialize drug candidates;
- more extensive experience in preclinical testing and clinical trials, obtaining regulatory approvals and manufacturing and marketing pharmaceutical products;
- drug candidates that have been approved or are in late-stage clinical development; and/or
- collaborative arrangements in our target markets with leading companies and research institutions.

Competitive products may render our research and development program obsolete or noncompetitive before we can recover the expenses of developing and commercializing our drug candidates. Furthermore, the development of new treatment methods and/or the widespread adoption or increased utilization of any vaccine or development of other products or treatments for the diseases we are targeting could render any of our drug candidates noncompetitive, obsolete or uneconomical. If we successfully develop and obtain approval for a drug candidate, we will face competition based on the safety and effectiveness of the approved product, the timing of its entry into the market in relation to competitive products in development, the availability and cost of supply,

Table of Contents

marketing and sales capabilities, reimbursement coverage, price, patent position and other factors. Even if we successfully develop drug candidates but those drug candidates do not achieve and maintain market acceptance, our business will not be successful.

Our drug candidates for which we intend to seek approval as biologic products may face competition sooner than anticipated.

Our drug candidates are regulated by the FDA as biologic products and we intend to seek approval for these products pursuant to the BLA pathway. The Biologics Price Competition and Innovation Act of 2009, or BPCIA, created an abbreviated pathway for the approval of biosimilar and interchangeable biologic products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on its similarity to an existing brand product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our biologic products.

We believe that any of our drug candidates approved as a biologic product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our drug candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biologic products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

We may be subject, directly or indirectly, to federal and state anti-kickback, fraud and abuse, false claims, physician payment transparency, health information privacy and security, and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.

If we obtain FDA approval for any of our drug candidates and begin commercializing those products in the United States, our operations may be directly, or indirectly through our customers, subject to various federal and state fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, which may constrain the business or financial arrangements and relationships through which we sell, market and distribute any drugs for which we obtain marketing approval. In addition, we may be subject to physician payment transparency laws and patient privacy regulation by both the federal government and the states and foreign jurisdictions in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, which impose criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

Table of Contents

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that impose criminal and civil liability for executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;

the federal Open Payments program, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children s Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians, which is defined to include doctors, dentists, optometrists, podiatrists and chiropractors, and teaching hospitals and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians and their immediate family members, with data collection beginning on August 1, 2013, requirements for manufacturers to submit reports to CMS by March 31, 2014 and the 90th day of each subsequent calendar year, and disclosure of such information to be made by CMS on a publicly available website beginning in September 2014;

HIPAA, as amended by the Health Information Technology and Clinical Health Act, and its implementing regulations, which impose obligations on covered healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information; and

analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to significant civil, criminal, and administrative penalties, including, without limitation, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, imprisonment, damages, fines and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which could also adversely affect our business.

If a successful product liability or clinical trial claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, we could incur substantial liability.

The use of our drug candidates in clinical trials and the sale of any products for which we obtain marketing approval will expose us to the risk of product liability and clinical trial liability claims. Product

Table of Contents

liability claims might be brought against us by consumers, health care providers or others selling or otherwise coming into contact with our products. Clinical trial liability claims may be filed against us for damages suffered by clinical trial subjects or their families. If we cannot successfully defend ourselves against product liability claims, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- decreased demand for any approved drug candidates;
- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs of related litigation;
- distraction of management s attention;
- substantial monetary awards to patients or other claimants;
- loss of revenues; and
- the inability to successfully commercialize any approved drug candidates.

We currently have clinical trial liability insurance coverage for our ongoing Phase 1 clinical trial of NEOD001 with a $5.0 million annual aggregate coverage limit; however, our insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for any of our drug candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain this product liability insurance on commercially reasonable terms. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our share price to decline and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet established deadlines for the completion of any such clinical trials.

We do not have the ability to independently conduct clinical trials for our drug candidates, and we rely on third parties, such as consultants, contract research organizations, medical institutions, and clinical investigators, to perform this function. Our reliance on these third parties for clinical development activities results in reduced control over these activities. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. Although we have and will enter into agreements with these third parties, we will be responsible for confirming that our clinical trials are conducted in accordance with their general investigational plans and protocols. Moreover, the FDA requires us to comply with regulations and standards, commonly referred to as cGCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the trial participants are adequately protected. Our reliance on third parties does not relieve us of these responsibilities and requirements. If we or any of our third party contractors fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon

24

Table of Contents

inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with cGCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

To date, we believe our consultants, contract research organizations and other similar entities with which we are working have performed well; however, if these third parties do not successfully carry out their contractual duties, meet expected deadlines, or comply with applicable regulations, we may be required to replace them. Although we believe that there are a number of other third-party contractors we could engage to continue these activities, we may not be able to enter into arrangements with alternative third-party contractors or to do so on commercially reasonable terms, which may result in a delay of our planned clinical trials. Accordingly, we may be delayed in obtaining regulatory approvals for our drug candidates and may be delayed in our efforts to successfully develop our drug candidates.

In addition, our third-party contractors are not our employees, and except for remedies available to us under our agreements with such third-party contractors, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, nonclinical and preclinical programs. If third-party contractors do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our drug candidates. As a result, our results of operations and the commercial prospects for our drug candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

If we do not establish strategic collaborations, we may have to alter our research and development plans.

Our drug research and development programs and potential commercialization of our drug candidates will require substantial additional cash to fund expenses. Our strategy includes potentially collaborating with leading pharmaceutical and biotechnology companies to assist us in furthering development and potential commercialization of some of our drug candidates, in some or all geographies. It may be difficult to enter into one or more of such collaborations in the future. We face significant competition in seeking appropriate collaborators and these collaborations are complex and time-consuming to negotiate and document. We may not be able to negotiate collaborations on acceptable terms, or at all, in which case we may have to curtail the development of a particular drug candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we will need to obtain additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds, we will not be able to bring our drug candidates to market and generate product revenue.

We have no manufacturing capacity and depend on a third-party manufacturer to produce our pre-clinical and clinical trial drug supplies.

We do not currently operate manufacturing facilities for pre-clinical or clinical production of any of our drug candidates. We have limited experience in drug manufacturing, and we lack the resources and the capabilities to manufacture any of our drug candidates on a clinical or commercial scale. As a result, we rely on a single third-party manufacturer to supply, store, and distribute pre-clinical and clinical supply of our drug candidates, and plan to continue to do so until we increase the number of manufacturers with whom we contract. Any performance failure on the part of our existing or future manufacturers could delay clinical development or regulatory approval of our drug candidates or commercialization of any approved products, producing additional losses and depriving us of potential product revenue.

Table of Contents

Our drug candidates require precise, high quality manufacturing. Failure by our contract manufacturer to achieve and maintain high manufacturing standards could result in patient injury or death, product recalls or withdrawals, delays or failures in testing or delivery, cost overruns, or other problems that could seriously hurt our business. Contract manufacturers may encounter difficulties involving production yields, quality control, and quality assurance. These manufacturers are subject to ongoing periodic and unannounced inspections by the FDA and corresponding state and foreign agencies to ensure strict compliance with cGMPs and other applicable government regulations and corresponding foreign standards; however, we do not have control over third-party manufacturers compliance with these regulations and standards.

If a contract manufacturer cannot perform as agreed, we may be required to replace it. Although we believe there are a number of potential replacements as our manufacturing processes are not manufacturer specific, we may incur added costs and delays in identifying and qualifying any such replacements because the FDA must approve any replacement manufacturer prior to manufacturing our drug candidates. Such approval would require new testing and compliance inspections. In addition, a new manufacturer would have to be educated in, or develop substantially equivalent processes for, production of our drug candidates after receipt of FDA approval.

We anticipate continued reliance on third-party manufacturers if we are successful in obtaining marketing approval from the FDA and other regulatory agencies for any of our drug candidates, and our commercialization of any of our drug candidates may be halted, delayed or made less profitable if those third parties fail to obtain such approvals, fail to provide us with sufficient quantities of drug product or fail to do so at acceptable quality levels or prices.

To date, our drug candidates have been manufactured in small quantities for preclinical and clinical testing by third-party manufacturers. If the FDA or other regulatory agencies approve any of our drug candidates for commercial sale, we expect that we would continue to rely, at least initially, on third-party manufacturers to produce commercial quantities of approved drug candidates. These manufacturers may not be able to successfully increase the manufacturing capacity for any approved drug candidates in a timely or economic manner, or at all. Significant scale-up of manufacturing may require additional validation studies, which the FDA must review and approve. If third party manufacturers are unable to successfully increase the manufacturing capacity for a drug candidate, or we are unable to establish our own manufacturing capabilities, the commercial launch of any approved products may be delayed or there may be a shortage in supply, which in turn could have a material adverse effect on our business.

In addition, the facilities used by our contract manufacturers to manufacture our drug candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit a BLA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with cGMPs, for manufacture of both active drug substances and finished drug products. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our drug candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our drug candidates, if approved.

We depend on third-party suppliers for key raw materials used in our manufacturing processes, and the loss of these third-party suppliers or their inability to supply us with adequate raw materials could harm our business.

We rely on third-party suppliers for the raw materials required for the production of our drug candidates. Our dependence on these third-party suppliers and the challenges we may face in obtaining adequate supplies of raw materials involve several risks, including limited control over pricing, availability, quality and delivery

Table of Contents

schedules. We cannot be certain that our suppliers will continue to provide us with the quantities of these raw materials that we require or satisfy our anticipated specifications and quality requirements. Any supply interruption in limited or sole sourced raw materials could materially harm our ability to manufacture our products until a new source of supply, if any, could be identified and qualified. Although we believe there are currently several other suppliers of these raw materials, we may be unable to find a sufficient alternative supply channel in a reasonable time or on commercially reasonable terms. Any performance failure on the part of our suppliers could delay the development and potential commercialization of our drug candidates, including limiting supplies necessary for clinical trials and regulatory approvals, which would have a material adverse effect on our business.

Risks Related to Our Intellectual Property

If we are unable to adequately protect or enforce the intellectual property relating to our drug candidates our ability to successfully commercialize our drug candidates will be harmed.

Our success depends in part on our ability to obtain patent protection both in the United States and in other countries for our drug candidates. Our ability to protect our drug candidates from unauthorized or infringing use by third parties depends in substantial part on our ability to obtain and maintain valid and enforceable patents. Due to evolving legal standards relating to the patentability, validity and enforceability of patents covering pharmaceutical inventions and the scope of claims made under these patents, our ability to obtain, maintain and enforce patents is uncertain and involves complex legal and factual questions. Accordingly, rights under any issued patents may not provide us with sufficient protection for our drug candidates or provide sufficient protection to afford us a commercial advantage against competitive products or processes.

In addition, we cannot guarantee that any patents will issue from any pending or future patent applications owned by or licensed to us or our affiliates. Even if patents have issued or will issue, we cannot guarantee that the claims of these patents are or will be valid or enforceable or will provide us with any significant protection against competitive products or otherwise be commercially valuable to us. Patent applications in the United States are maintained in confidence for up to 18 months after their filing. In some cases, however, patent applications remain confidential in the U.S. Patent and Trademark Office, or the USPTO, for the entire time prior to issuance as a U.S. patent. Similarly, publication of discoveries in the scientific or patent literature often lags behind actual discoveries. Consequently, we cannot be certain that we or our licensors or co-owners were the first to invent, or the first to file patent applications on, our drug candidates or their use as drugs. In the event that a third party has also filed a U.S. patent application relating to our drug candidates or a similar invention, we may have to participate in interference or derivation proceedings declared by the USPTO to determine priority of invention in the United States. The costs of these proceedings could be substantial and it is possible that our efforts would be unsuccessful, resulting in a loss of our U.S. patent position. Furthermore, we may not have identified all U.S. and foreign patents or published applications that affect our business either by blocking our ability to commercialize our drugs or by covering similar technologies.

Composition-of-matter patents on the biological or chemical active pharmaceutical ingredient are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. We cannot be certain that the claims in our patent applications covering composition-of-matter of our product candidates will be considered patentable by the USPTO and courts in the United States or by the patent offices and courts in foreign countries, nor can we be certain that the claims in our issued composition-of-matter patents will not be found invalid or unenforceable if challenged. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute.

Table of Contents

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art, may affect patent litigation, and switch the U.S. patent system from a first-to-invent system to a first-to-file system. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The U.S. Patent and Trademark Office recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first-to-file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

We may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review, or other patent office proceedings or litigation, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights.

We may not be able to protect our intellectual property rights throughout the world.

The laws of some foreign jurisdictions do not protect intellectual property rights to the same extent as in the United States and many companies have encountered significant difficulties in protecting and defending such rights in foreign jurisdictions. If we encounter such difficulties in protecting or are otherwise precluded from effectively protecting our intellectual property rights in foreign jurisdictions, our business prospects could be substantially harmed.

We license patent rights from third-party owners. Such licenses may be subject to early termination if we fail to comply with our obligations in our licenses with third parties, which could result in the loss of rights or technology that are material to our business.

We are a party to licenses that give us rights to third-party intellectual property that is necessary or useful for our business, and we may enter into additional licenses in the future. Under these license agreements we are obligated to pay the licensor fees, which may include annual license fees, milestone payments, royalties, a percentage of revenues associated with the licensed technology and a percentage of sublicensing revenue. In addition, under certain of such agreements, we are required to diligently pursue the development of products using the licensed technology. If we fail to comply with these obligations and fail to cure our breach within a specified period of time, the licensor may have the right to terminate the applicable license, in which event we could lose valuable rights and technology that are material to our business.

If the licensor retains control of prosecution of the patents and patent applications licensed to us, we may have limited or no control over the manner in which the licensor chooses to prosecute or maintain its patents and patent applications and have limited or no right to continue to prosecute any patents or patent applications that the licensor elects to abandon.

Table of Contents

We jointly own certain patent rights with third parties. Our ability to out-license these patent rights, or to prevent the third party from out-licensing these patent rights, may be limited in certain countries.

We jointly own certain patents and patent applications with third parties, and may jointly own patents and patent applications with third parties in the future. Unless we enter into an agreement with the joint owner, we will be subject to certain default rules pertaining to joint ownership. Certain countries require the consent of all joint owners to license jointly owned patents, and if we are unable to obtain such consent from the joint owner, we may not be able to license our rights under these patents and patent applications. In certain other countries, including the United States, the joint owner could license its rights under these patents and patent applications to another party without our consent and without any duty of accounting to us.

Litigation regarding patents, patent applications and other proprietary rights may be expensive and time consuming. If we are involved in such litigation, it could cause delays in bringing drug candidates to market and harm our ability to operate.

Our success will depend in part on our ability to operate without infringing the proprietary rights of third parties. Although we are not currently aware of any litigation or other proceedings or third-party claims of intellectual property infringement related to our drug candidates, the pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may hold or obtain patents in the future and allege that the use of our technologies infringes these patent claims or that we are employing their proprietary technology without authorization. Elan is involved in litigation with the Alzheimer s Institute of America, or AIA. While the lawsuit was dismissed with prejudice, AIA appealed the result and if the appeal is successful, AIA may institute suit against us related to our research activities. If we become involved in this matter it may distract our management and result in substantial costs, although Elan is contractually obligated pursuant to the terms of the Demerger Agreement to reimburse us for our expenses and indemnify us for any damages.

In addition, third parties may challenge or infringe upon our existing or future patents. Proceedings involving our patents or patent applications or those of others could result in adverse decisions regarding:

- the patentability of our inventions relating to our drug candidates; and/or
- the enforceability, validity or scope of protection offered by our patents relating to our drug candidates.

Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us.

If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, if we do not obtain a license, develop or obtain non-infringing technology, fail to defend an infringement action successfully or have infringed patents declared invalid, we may:

- incur substantial monetary damages;
- encounter significant delays in bringing our drug candidates to market; and/or
- be precluded from participating in the manufacture, use or sale of our drug candidates or methods of treatment requiring licenses.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these

29

Table of Contents

trademarks and trade names, which we need to build name recognition by potential partners or customers in our markets of interest. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected.

We may be unable to adequately prevent disclosure of trade secrets and other proprietary information.

We rely on trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable; however, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers, and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover our trade secrets and proprietary information. Costly and time consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Many of our employees were previously employed at universities, Elan or Elan subsidiaries, or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee s former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

Risks Relating to the Separation and Distribution

We may not realize some or all of the potential benefits we expect from our separation from Elan.

We may not realize the benefits we anticipate from our separation from Elan. These benefits include the following:

- greater strategic focus of financial resources and management s efforts;
- direct and differentiated access to capital resources;
- enhanced investor ability to evaluate our financial performance and strategy against our peer group; and
- improved ability to align management incentive compensation with our performance by issuing options exercisable for Prothena ordinary shares.

We may not achieve the anticipated benefits from our separation for a variety of reasons, including the following:

- the regulatory and other managerial challenges of operating as an independent public company may distract our management team from focusing on our business and strategic priorities;

Table of Contents

- we will require substantial ongoing cash investment for the foreseeable future, we will no longer be supported by the revenue and cash flows of Elan s business and we may not be able to issue debt or equity on terms acceptable to us or at all;

- our ability to differentiate our company against our peer group and attract early stage biotechnology investors is largely dependent on the success of our research and development programs, which are at an early stage; and

- we expect to continue to pay our key executives less cash compensation than what they were paid at Elan, so even if we are able to provide potential equity compensation tied specifically to our business, we may not be able to attract and retain key employees as desired.

We also may not fully realize the anticipated benefits from our separation if any of the matters identified as risks in this Risks Factors section were to occur. If we do not realize the anticipated benefits from our separation for any reason, our business may be materially adversely affected.

If we are unable to maintain effective internal controls, our business, financial position and results of operations could be adversely affected.

We are subject to the reporting and other obligations under the Securities Exchange Act of 1934, as amended, or the Exchange Act, including the requirements of Section 404 of the Sarbanes-Oxley Act of 2002, which require annual management assessments of the effectiveness of our internal control over financial reporting. However, our auditors will not be required to formally attest to the effectiveness of our internal control over financial reporting pursuant to Section 404 until we are no longer an emerging growth company as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, if we continue to take advantage of the exemptions available to us through the JOBS Act.

The rules governing the standards that must be met for management to assess our internal control over financial reporting are complex and require significant documentation, testing and possible remediation to meet the detailed standards under the rules. During the course of its testing, our management may identify material weaknesses or deficiencies which may not be remedied in time to meet the deadline imposed by the Sarbanes-Oxley Act of 2002. These reporting and other obligations place significant demands on our management and administrative and operational resources, including accounting resources.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of Financial Statements for external purposes in accordance with accounting principles generally accepted in the United States. Any failure to maintain effective internal controls could have an adverse effect on our business, financial position and results of operations.

Our historical financial information is not necessarily representative of the results we would have achieved as a separate, publicly traded company and may not be a reliable indicator of our future results.

Our financial results previously were included within the consolidated results of Elan; however, we were not directly subject to the reporting and other requirements of the Exchange Act until our separation from Elan in December 2012. The historical financial information we have included in this prospectus may not reflect what our results of operations, financial position and cash flows would have been had we been an independent, publicly traded company during the periods presented or what our results of operations, financial position and cash flows will be in the future. This is primarily because:

- our historical financial information reflects allocations for services historically provided to us by Elan, which allocations may not reflect the costs we will incur for similar services in the future as an independent company;

Table of Contents

subsequent to the completion of the Separation and Distribution, the cost of capital for our business may be higher than Elan s cost of capital prior to the Separation and Distribution because Elan s current cost of debt will likely be lower than ours; and

our historical financial information does not reflect changes that we have incurred as a result of the separation of the Prothena Business from Elan, including changes in the cost structure, personnel needs, financing and operations of the contributed business as a result of the separation from Elan and from reduced economies of scale.

We are also responsible for the additional costs associated with being an independent, public company, including costs related to corporate governance and compliance with the rules of The NASDAQ Global Market, or NASDAQ, and the SEC. Prior to the Separation and Distribution, the Prothena Business was operated by Elan as part of its broader corporate organization, rather than as an independent company. Elan or one of its affiliates performed various corporate functions for us, including, but not limited to, legal, treasury, accounting, auditing, risk management, information technology, human resources, corporate affairs, tax administration, certain governance functions and external reporting. Our historical financial results include allocations of corporate expenses from Elan for these and similar functions. These allocations of cash and non-cash expenses are less than the comparable expenses we have incurred thus far as a separate publicly traded company. Therefore, our Financial Statements may not be indicative of our future performance as an independent company. For additional information about our past financial performance and the basis of presentation of our Financial Statements, please see Selected Financial Data, Management s Discussion and Analysis of Financial Condition and Results of Operations and our Financial Statements and the notes thereto included elsewhere in this prospectus.

In addition, we incur costs and expenses, including professional fees, to comply with Irish corporate and tax laws and financial reporting requirements and costs and expenses incurred in connection with holding the meetings of our board of directors, or our Board, in Ireland. There can be no assurance that these costs will not exceed the costs historically borne by Elan and those allocated to us in connection with the separation.

The agreements we have entered into with Elan involve conflicts of interest and therefore may have materially disadvantageous terms to us.

We have entered into certain agreements with Elan, including the Demerger Agreement, Tax Matters Agreement, Transitional Services Agreement, Research and Development Services Agreement and Subscription and Registration Rights Agreement, which set forth the main terms of the separation and provide a framework for our initial relationship with Elan. These agreements may have terms that are materially disadvantageous to us or are otherwise not as favorable as those that might be negotiated between unaffiliated third parties. In addition, in July 2013, Elan announced that it had entered into a definitive agreement to be acquired by Perrigo. If this transaction is consummated, Elan may be less willing to collaborate with us in connection with these and other matters.

We believe that we will be a passive foreign investment company for U.S. federal income tax purposes, which could result in adverse U.S. federal income tax consequences to U.S. holders of our ordinary shares.

While the determination of passive foreign investment company, or PFIC, status is fact specific, and generally cannot be made until the close of the taxable year in question, based on the market price of our ordinary shares and the value and composition of our assets, we believe we will be a PFIC for U.S. federal income tax purposes for our current taxable year. A non-U.S. corporation will be considered a PFIC for any taxable year if either (1) at least 75% of its gross income for such year is passive income or (2) at least 50% of the value of its assets (based on an average of the quarterly values of the assets during such year) is attributable to assets that produce or are held for the production of passive income (the asset test). In general, the total value of our assets for purposes of the asset test will be determined based on the market price of our ordinary shares. A separate determination must be made each taxable year as to whether we are a PFIC (after the close of

Table of Contents

each taxable year). We believe we will be a PFIC for our current taxable year unless our share value increases and/or we invest a substantial amount of the cash and other passive assets we hold in assets that produce active income. Because we expect to be a PFIC for our current taxable year, certain adverse U.S. federal income tax consequences could apply to U.S. persons who acquire our ordinary shares in this offering with respect to any excess distribution received from us and any gain from a sale or other disposition of our ordinary shares. See Material United States. Federal Income Tax Consequences to U.S. Holders.

Relationships between certain of our executive officers and directors with our principal shareholder could adversely affect our other shareholders and/or present actual, potential or perceived conflicts of interest.

Certain of our executive officers and directors are former officers and employees of Elan and thus have professional relationships with Elan s executive officers and directors. Our Chairman of the Board, Dr. Lars G. Ekman, is Elan s former President of Research and Development and a former member of Elan s board of directors. Our Chief Executive Officer and director, Dr. Dale B. Schenk, has held the position of Executive Vice President and Chief Scientific Officer for Elan. Our director, Shane Cooke, is a former director of Elan and Elan s former Chief Financial Officer, Executive Vice President and Head of Elan Drug Technologies. Our director, Richard T. Collier, is Elan s former Executive Vice President and General Counsel. Our Head of Corporate and Business Development and Secretary, Dr. Tara Nickerson, has held the position of Vice President and Head of Business Development for Elan Pharmaceuticals, Inc., a subsidiary of Elan. Our Chief Scientific Officer and Head of Research and Development, Dr. Gene Kinney, has held the position of Senior Vice President, Pharmacological Sciences for Elan. In addition, certain of our other employees and directors have a meaningful financial interest in Elan as a result of their ownership of Elan ordinary shares, options and other equity awards. These relationships may create, or may create the appearance of, conflicts of interest when these directors and officers face decisions that could have different implications for Elan than for us.

For as long as we are an emerging growth company, we will be exempt from certain reporting requirements, including those relating to accounting standards and disclosure about our executive compensation, that apply to other public companies.

In April 2012, President Obama signed into law the JOBS Act. The JOBS Act contains provisions that, among other things, relax certain reporting requirements for emerging growth companies, including certain requirements relating to accounting standards and compensation disclosure. We are classified as an emerging growth company, which is defined as a company with annual gross revenues of less than $1 billion, that has been a public reporting company for a period of less than five years, and that does not have a public float of $700 million or more in securities held by non-affiliated holders. We will remain an emerging growth company until the earliest of (i) the end of the fiscal year in which the market value of our ordinary shares that are held by non-affiliates exceeds $700 million as of the end of the second fiscal quarter, (ii) the end of the fiscal year in which we have total annual gross revenues of $1 billion or more during such fiscal year, (iii) the date on which we issue more than $1 billion in non-convertible debt in a three-year period or (iv) the end of the fiscal year following the fifth anniversary of the date of the first sale of our ordinary shares pursuant to an effective registration statement filed under the Securities Act of 1933, as amended, or the Securities Act.

For as long as we are an emerging growth company, unlike other public companies, we are eligible to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. These include, but are not limited to, (i) reduced obligations with respect to the disclosure of selected financial data in registration statements filed with the Securities and Exchange Commission, (ii) reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, (iii) an exception from compliance with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, and (iv) exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and the requirement to obtain shareholder approval of any golden parachute payments not previously approved.

Table of Contents

As noted above, under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards that have different effective dates for public and private companies until such time as those standards apply to private companies. We intend to take advantage of such extended transition period. Since we would then not be required to comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies, our Financial Statements may not be comparable to the financial statements of companies that comply with public company effective dates. If we were to elect to comply with these public company effective dates, such election would be irrevocable pursuant to Section 107 of the JOBS Act.

Risks Related to Our Ordinary Shares and this Offering

A trading market may not develop to provide you with adequate liquidity for our ordinary shares. In addition, the market price of our shares may fluctuate widely.

Our ordinary shares have been traded on The NASDAQ Global Market since December 21, 2012; however, there can be no assurance that an active trading market for our ordinary shares will develop or be sustained in the future. We cannot predict the prices at which our ordinary shares may trade at. The market price of our ordinary shares may fluctuate widely, depending upon many factors, some of which may be beyond our control, including:

our ability to obtain financing as needed;

progress in and results from our clinical trials, including our Phase 1 clinical trial of NEOD001;

failure or delays in advancing our preclinical drug candidates or other drug candidates we may develop in the future, into clinical trials;

results of clinical trials conducted by others on drugs that would compete with our drug candidates;

issues in manufacturing our drug candidates;

regulatory developments or enforcement in the United States and foreign countries;

developments or disputes concerning patents or other proprietary rights;

introduction of technological innovations or new commercial products by our competitors;

changes in estimates or recommendations by securities analysts, if any, who cover our company;

public concern over our drug candidates;

litigation;

future sales of our ordinary shares;

general market conditions;

changes in the structure of healthcare payment systems;

failure of any of our drug candidates, if approved, to achieve commercial success;

economic and other external factors or other disasters or crises;

Table of Contents

period-to-period fluctuations in our financial results;

overall fluctuations in U.S. equity markets;

the sale of our shares by some shareholders, who received shares through the separation, because our business profile and market capitalization may not fit their investment objectives;

our quarterly or annual results, or those of other companies in our industry;

announcements by us or our competitors of significant acquisitions or dispositions;

the operating and share price performance of other comparable companies;

investor perception of our company and the drug development industry;

natural or environmental disasters that investors believe may affect us; or

fluctuations in the budget of federal, state and local governmental entities around the world.

These and other external factors may cause the market price and demand for our ordinary shares to fluctuate substantially, which may limit or prevent investors from readily selling their ordinary shares and may otherwise negatively affect the liquidity of our ordinary shares. In particular, stock markets in general have experienced volatility that has often been unrelated to the operating performance of a particular company. These broad market fluctuations may adversely affect the trading price of our ordinary shares. In the past, when the market price of a stock has been volatile, some holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our shareholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit. Such a lawsuit could also divert the time and attention of our management.

We rely on permitted exemptions from certain SEC and NASDAQ corporate governance standards, which may afford less protection to the holders of our ordinary shares.

NASDAQ and SEC rules and regulations generally require all members of the audit committee of a listed company to be independent directors as defined thereunder; furthermore, NASDAQ rules also generally require that the compensation committee and the nominating committee of listed companies consist solely of independent directors, and that the majority of a listed company s board of directors be independent directors as defined thereunder. However, these rules are subject to certain phase-in periods for newly listed companies. We rely on the phase-in periods for the audit committee, compensation committee and nominating committee that allows each of our committees to include (i) a minimum of one independent director at the time of our NASDAQ listing, (ii) a majority of independent directors within 90 days of our NASDAQ listing and (iii) all independent directors within one year of our NASDAQ listing. Furthermore, we rely on the phase-in period for our Board to include a majority of independent directors within 12 months of our NASDAQ listing. Our reliance on these phase-in periods may adversely affect the level of independent oversight over the management of our company and therefore afford less protection to the holders of our ordinary shares.

We do not anticipate paying cash dividends, and accordingly, shareholders must rely on share appreciation for any return on their investment.

We anticipate losing money for the foreseeable future and, even if we do ever turn a profit, we intend to retain future earnings, if any, for the development, operation and expansion of our business. Thus, we do not anticipate declaring or paying any cash dividends for the foreseeable future. Therefore, the success of an

35

Table of Contents

investment in our ordinary shares will depend upon appreciation in their value and in order to receive any income or realize a return on your investment, you will need to sell your Prothena ordinary shares. There can be no assurance that our ordinary shares will maintain their price or appreciate in value.

Your percentage ownership in Prothena may be diluted in the future.

As with any publicly traded company, your percentage ownership in us may be diluted in the future because of equity issuances for acquisitions, capital market transactions or otherwise. We may need to raise additional capital in the future. If we are able to raise additional capital, we may issue equity or convertible debt instruments, which may severely dilute your ownership interest in us. In addition, we intend to continue to grant option awards to our directors, officers and employees, which would dilute your ownership stake in us. As of June 30, 2013, the number of ordinary shares authorized under our equity plan is 2,650,000.

Future sales of our ordinary shares could adversely affect the trading price of our ordinary shares.

All of our ordinary shares will be freely tradable without restriction or further registration under the Securities Act unless the shares are restricted securities under the Securities Act or are owned by our affiliates as those terms are defined in the rules under the Securities Act. Restricted securities and shares held by affiliates may be sold in the public market if registered or if they qualify for an exemption from registration under Rule 144. Further, we have filed a registration statement to cover the shares issuable under our equity-based benefit plans.

In addition, at August 31, 2013, a wholly-owned subsidiary of Elan held approximately 18% of our outstanding ordinary shares. The ordinary shares held by a wholly-owned subsidiary of Elan are restricted securities, and Elan has agreed to cause the disposition of our ordinary shares as soon as a disposition is warranted consistent with the business purposes for Elan s retention of our ordinary shares. We have agreed that, upon the request of Elan, we will use our reasonable best efforts to effect a registration under applicable federal and state securities laws of any of our ordinary shares issued to Elan. The sales of significant amounts of our ordinary shares or the perception in the market that this will occur may result in the lowering of the market price of our ordinary shares.

Elan has agreed not to dispose of or hedge any shares or any securities convertible into or exchangeable for our ordinary shares for a period of 90 days from the date of this prospectus. Please see Shares Eligible for Future Sale Lock-Up Agreements.

Irish law differs from the laws in effect in the United States and may afford less protection to holders of our ordinary shares.

It may not be possible to enforce court judgments obtained in the United States against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is uncertainty as to whether the courts of Ireland would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liabilities provisions of the U.S. federal or state securities laws or hear actions against us or those persons based on those laws. We have been advised that the United States currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Acts, which differ in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are owed to the company only. Shareholders of Irish

Table of Contents

companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our ordinary shares may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a jurisdiction of the United States.

Irish law differs from the laws in effect in the United States with respect to defending unwanted takeover proposals and may give our board of directors less ability to control negotiations with hostile offerors.

We are subject to the Irish Takeover Rules. Under the Irish Takeover Rules, our Board is not permitted to take any action that might frustrate an offer for our shares once our Board has received an approach that may lead to an offer or has reason to believe that such an offer is or may be imminent, subject to certain exceptions. Potentially frustrating actions such as (i) the issue of shares, options or convertible securities, (ii) material acquisitions or disposals, (iii) entering into contracts other than in the ordinary course of business or (iv) any action, other than seeking alternative offers, which may result in frustration of an offer, are prohibited during the course of an offer or at any earlier time during which our Board has reason to believe an offer is or may be imminent. These provisions may give our Board less ability to control negotiations with hostile offerors and protect the interests of holders of ordinary shares than would be the case for a corporation incorporated in a jurisdiction of the United States.

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

Our management will have broad discretion to use the net proceeds to us from this offering, and you will be relying on the judgment of our management regarding the application of these proceeds. Our management might not apply the net proceeds from this offering in ways that increase the value of your investment. We expect to use the net proceeds to us from this offering to conduct clinical trials and the balance for working capital and general corporate purposes, including research and development. We may also use a portion of the net proceeds for the acquisition of technologies, solutions or businesses that we believe are complementary to our own, although we have no agreements or understandings with respect to any acquisition at this time. We have not allocated the net proceeds from this offering for any specific purposes. Until we use the net proceeds to us from this offering, we plan to invest them, and these investments may not yield a favorable rate of return. If we do not invest or apply the net proceeds from this offering in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause our share price to decline.

Transfers of our ordinary shares may be subject to Irish stamp duty.

Transfers of our shares effected by means of the transfer of book entry interests in DTC will not be subject to Irish stamp duty. However, if a shareholder holds our ordinary shares directly rather than beneficially through DTC any transfer of those shares could be subject to Irish stamp duty (currently at the rate of 1% of the higher of the price paid or the market value of the shares acquired). Payment of Irish stamp duty is generally a legal obligation of the transferee. The potential for stamp duty could adversely affect the price of your shares. Please see Certain Irish Tax Consequences Relating to the Holding of our Ordinary Shares.

In certain limited circumstances, dividends paid by us may be subject to Irish dividend withholding tax.

In certain limited circumstances, dividend withholding tax (currently at a rate of 20%) may arise to the extent we decide to pay dividends in the future. A number of exemptions from dividend withholding tax exist such that shareholders resident in the U.S. and shareholders resident in other countries that have entered into a double taxation treaty with Ireland may be entitled to exemptions from dividend withholding tax subject to the completion of certain dividend withholding tax declaration forms.

Dividends received by Irish residents and certain other shareholders may be subject to Irish income tax.

Shareholders entitled to an exemption from Irish dividend withholding tax on any dividends received from us will not be subject to Irish income tax in respect of those dividends, unless they have some connection

Table of Contents

with Ireland other than their shareholding (for example, they are resident in Ireland). Shareholders who receive dividends subject to Irish dividend withholding tax will generally have no further liability to Irish income tax on those dividends.

Prothena shares, received by means of a gift or inheritance could be subject to Irish capital acquisitions tax.

Irish capital acquisitions tax, or CAT, could apply to a gift or inheritance of our shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our shares will be regarded as property situated in Ireland. The person who receives the gift or inheritance has primary liability for CAT. Gifts and inheritances passing between spouses are exempt from CAT. At the date hereof, children have a tax-free threshold of 225,000 in respect of taxable gifts or inheritances received from their parents. Please see Certain Irish Tax Consequences Relating to the Holding of our Ordinary Shares. It is recommended that each shareholder consult his or her own tax advisor as to the tax consequences of holding our shares or receiving dividends from us.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements concerning our business, operations and financial performance and condition, as well as our plans, objectives and expectations for our business operations and financial performance and condition. Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as aim, anticipate, assume, believe, contemplate, continue, could, due, estimate, expect, goa objective, plan, predict, potential, positioned, seek, should, target, will, would, and other similar expressions that are predictio future events and future trends, or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our ability to obtain additional financing in this or future offerings;
- our history of operating losses;
- our ability to successfully complete research and development of our drug candidates and the growth of the markets for those drug candidates;
- our ability to develop and commercialize products before competitors that are superior to the alternatives developed by such competitors;
- our ability to protect our patents and other intellectual property;
- loss of key employees;
- tax treatment of our separation from Elan and subsequent distribution of our ordinary shares;
- restrictions on our taking certain actions due to tax rules and covenants with Elan;
- the impact of our separation from Elan and risks relating to our ability to operate effectively as a stand-alone, publicly traded company, including, without limitation:
  - our ability to achieve benefits from our separation;
  - changes in our cost structure, management, financing and business operations;
  - growth in costs and expenses;

our ability to maintain financial flexibility and sufficient cash, cash equivalents, and investments and other assets capable of being monetized to meet our liquidity requirements;

disruptions in the U.S. and global capital and credit markets;

fluctuations in foreign currency exchange rates;

extensive government regulation;

the volatility of our share price;

general changes in U.S. Generally Accepted Accounting Principles;

Table of Contents

business disruptions caused by information technology failures;

our use of proceeds from this offering; and

the other risks and uncertainties described in Risk Factors above.

These forward-looking statements are based on management s current expectations, estimates, forecasts, and projections about our business and the industry in which we operate and management s beliefs and assumptions and are not guarantees of future performance or development and involve known and unknown risks, uncertainties, and other factors that are in some cases beyond our control. As a result, any or all of our forward-looking statements in this prospectus may turn out to be inaccurate. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Risk Factors and elsewhere in this prospectus. Potential investors are urged to consider these factors carefully in evaluating the forward-looking statements. These forward-looking statements speak only as of the date of this prospectus. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future. You should, however, review the factors and risks we describe in the reports we will file from time to time with the SEC after the date of this prospectus. See Where You Can Find More Information.

Table of Contents

MARKET, INDUSTRY AND OTHER DATA

This prospectus also contains estimates, projections and other information concerning our industry, our business, and the markets for our product candidates, including data regarding the estimated size of those markets, their projected growth rates, the perceptions and preferences of patients and physicians regarding certain therapies and other prescription, prescriber and patient data, as well as data regarding market research, estimates and forecasts prepared by our management. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

Table of Contents

USE OF PROCEEDS

We estimate that the net proceeds from the issue by us of 3,500,000 ordinary shares in this offering will be approximately $65.1 million at an assumed public offering price of $20.24 per share, which was the closing price of our ordinary shares as reported on NASDAQ on September 27, 2013, after deducting the underwriting discount and estimated offering expenses payable by us. If the underwriters exercise their option to subscribe for additional shares in full, we estimate that net proceeds will be approximately $79.2 million after deducting the underwriting discount and estimated offering expenses payable by us.

We currently expect to use substantially all of the net proceeds from this offering to conduct clinical trials and the balance for working capital and general corporate purposes, including research and development.

Our management will have broad discretion over the use of the net proceeds from this offering. The amounts and timing of our expenditures will depend upon numerous factors, including: the results of our Phase I clinical trial for NEOD001; the scope of research and development efforts; the timing and success of preclinical studies or clinical trials we may commence in the future; and the timing of regulatory submissions.

Pending the use of the proceeds from this offering, we intend to invest the net proceeds in short-term, interest-bearing, investment-grade securities, certificates of deposit or government securities.

We will not receive any proceeds from the ordinary shares to be offered by the selling shareholder, although we will pay certain of the expenses, other than underwriting discount, associated with the registration and sale of those shares.

PRICE RANGE OF OUR ORDINARY SHARES AND DIVIDEND POLICY

Our ordinary shares have been traded on The NASDAQ Global Market, or NASDAQ, under the symbol PRTA since December 21, 2012. The following table sets forth, for the periods indicated, the high and low intraday prices per share of our ordinary shares as reported by NASDAQ.

Year Ended December 31, 2012	**High**	**Low**
Fourth quarter (beginning December 21, 2012)	$ 8.10	$ 6.60

Year Ending December 31, 2013	**High**	**Low**
First quarter	$ 7.50	$ 5.64
Second quarter	14.00	6.49
Third quarter (through September 27, 2013)	22.48	12.14

On September 27, 2013, the last sale price of our ordinary shares as reported on NASDAQ was $20.24 per share. As of June 30, 2013, there were approximately 1,552 holders of record of our ordinary shares. Because many of our shares are held by brokers and other institutions on behalf of shareholders, we are unable to estimate the total number of shareholders represented by these recordholders.

We have never declared or paid cash dividends on our ordinary shares. We intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our Board.

Table of Contents

CAPITALIZATION

The following table sets forth our capitalization as of June 30, 2013:

- on an actual basis;
- on an as adjusted basis to give effect to the issuance and sale by us of 3,500,000 ordinary shares in this offering at an assumed public offering price of $20.24 per share, which was the closing price of our ordinary shares as reported on NASDAQ on September 27, 2013, after deducting the underwriting discount and estimated offering expenses payable by us.

You should read this information together with our Financial Statements and related notes appearing elsewhere in this prospectus and the information set forth under the headings Selected Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations.

	June 30, 2013	
	Actual	As Adjusted
	(unaudited, in thousands)	
Cash and cash equivalents	$ 112,507	$ 177,588
Shareholders equity:		
Euro deferred shares, 22 nominal value:		
10,000 shares authorized and none issued and outstanding, actual and as adjusted	$	$
Ordinary shares, $0.01 par value:		
100,000,000 shares authorized; 17,679,182 and 21,179,182 shares issued and outstanding, actual and as adjusted, respectively	177	212
Additional paid-in capital	127,650	192,696
Accumulated deficit	(20,598)	(20,598)
Total shareholders equity	107,229	172,310
Total capitalization	$ 107,229	$ 172,310

The outstanding share information in the capitalization table above is based on the number of ordinary shares outstanding as of June 30, 2013, and excludes the following:

- 1,835,500 ordinary shares issuable upon the exercise of outstanding options as of June 30, 2013 having a weighted-average exercise price of $6.57 per share; and
- 814,500 ordinary shares reserved for issuance pursuant to future awards under our 2012 Long Term Incentive Plan.

Table of Contents

DILUTION

If you invest in our ordinary shares, your interest will be diluted to the extent of the difference between the public offering price per share of our ordinary shares in this offering and the net tangible book value per share of our ordinary shares after this offering. As of June 30, 2013, we had a historical net tangible book value of $107.2 million, or $6.07 per ordinary share. Our net tangible book value represents total tangible assets less total liabilities, all divided by the number of ordinary shares outstanding on June 30, 2013.

After giving effect to the issue by us of ordinary shares in this offering at an assumed public offering price of $20.24 per share, which was the closing price of our ordinary shares as reported on NASDAQ on September 27, 2013, and after deducting the underwriting discount and estimated offering expenses, our as adjusted net tangible book value at June 30, 2013 would have been approximately $172.3 million, or $8.14 per share. This represents an immediate increase in as adjusted net tangible book value of $2.07 per share to existing shareholders and an immediate dilution of $12.10 per share to new investors. The following table illustrates this per share dilution:

Assumed public offering price per share		$ 20.24
Historical net tangible book value per share as of June 30, 2013	$ 6.07	
Increase in as adjusted net tangible book value per share attributable to new investors	2.07	
As adjusted net tangible book value per share after this offering		8.14
Dilution per share to new investors participating in this offering		$ 12.10

If the underwriters fully exercise their option to subscribe for additional shares, as adjusted net tangible book value after this offering would increase to approximately $8.50 per share, and there would be an immediate dilution of approximately $11.74 per share to new investors.

To the extent that outstanding options with an exercise price per share that is less than the as adjusted net tangible book value per share, before giving effect to the issuance and sale of shares in this offering, are exercised, new investors will experience further dilution. If all of our outstanding options described above were exercised, our net tangible book value as of June 30, 2013, before giving effect to the issuance and sale of shares in this offering, would have been approximately $110.0 million, or approximately $6.06 per share, and our as adjusted net tangible book value as of June 30, 2013 after this offering at an assumed public offering price of $20.24 per share, which was the closing price of our ordinary shares as reported on NASDAQ on September 27, 2013, would have been approximately $175.1 million, or approximately $8.09 per share, causing dilution to new investors of approximately $12.15 per share.

In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our shareholders.

The following table shows, as of June 30, 2013, on an as adjusted basis, the number of ordinary shares subscribed for from us, the total consideration paid to us and the average price paid per share by existing shareholders and by new investors purchasing ordinary shares in this offering at an assumed public offering price of $20.24 per share, which was the closing price of our ordinary shares as reported on NASDAQ on September 27, 2013, before deducting the estimated underwriting discount and estimated offering expenses payable by us.

	Shares Purchased		Total Consideration		Average Price Per Share
	Number	Percent	Amount	Percent	
Existing shareholders	17,679,182	83%	$ 126,745,000	64%	$ 7.17
Investors participating in this offering	3,500,000	17%	70,840,000	36%	20.24
	21,179,182	100%	$ 197,585,000	100%	9.33

Table of Contents

The number of ordinary shares to be outstanding after this offering is based on the number of shares outstanding as of June 30, 2013 and excludes the following:

- 1,835,500 ordinary shares issuable upon the exercise of outstanding options as of June 30, 2013 having a weighted-average exercise price of $6.57 per share; and

- 814,500 ordinary shares reserved for issuance pursuant to future awards under our 2012 Long Term Incentive Plan.

Table of Contents

SELECTED FINANCIAL DATA

You should read the following selected financial data together with our audited and unaudited Financial Statements, the related notes appearing at the end of this prospectus and the information under the caption Management s Discussion and Analysis of Financial Condition and Results of Operations. The selected financial data included in this section are not intended to replace the Financial Statements and the related notes included elsewhere in this prospectus.

We derived the selected Consolidated Statement of Operations data for the years ended December 31, 2012, 2011 and 2010 and the Consolidated Balance Sheet data as of December 31, 2012 and 2011 from our audited Financial Statements appearing elsewhere in this prospectus. The selected Consolidated Statement of Operations data for the year ended December 31, 2009 and the Consolidated Balance Sheet data as of December 31, 2010 are derived from our audited Financial Statements not included in this prospectus. The Consolidated Statement of Operations data for the six months ended June 30, 2013 and 2012 and Consolidated Balance Sheet data as of June 30, 2013 have been derived from our unaudited Financial Statements appearing elsewhere in this prospectus. Our historical results are not necessarily indicative of the results that may be expected in the future, and results for the six months ended June 30, 2013 are not necessarily indicative of results to be expected for the full year ending December 31, 2013.

Our historical results of operations presented below may not be reflective of our financial position, results of operations and cash flows had we operated as a stand-alone public company during all periods presented. Prior to December 21, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. Our Combined Financial Statements prior to December 21, 2012 have been prepared on a carve-out basis from the consolidated financial statements of Elan to represent our financial position and performance as if we had existed on a stand-alone basis during each of the fiscal years presented in the Consolidated Financial Statements. Central support costs have been allocated to us for the purposes of preparing the Consolidated Financial Statements based on our estimated usage of the resources. Our estimated usage of the central support resources was determined by estimating our portion of the most appropriate driver for each category of central support costs such as headcount or labor hours, depending on the nature of the costs. We believe that such allocations have been made on a reasonable basis, but may not necessarily be indicative of all of the costs that would have been incurred if we had operated on a standalone basis.

	Years Ended December 31,				Six Months Ended June 30,	
	2012	2011	2010	2009	2013	2012
	(in thousands, except per share data)					
					(unaudited)	
Consolidated Statement of Operations Data:						
Revenues related party	$ 2,658	$ 507	$ 1,243	$ 2,505	$ 338	$ 1,139
Operating expenses:						
Research and development	34,139	24,172	9,787	2,933	14,104	16,776
General and administrative	9,929	5,579	3,618	683	6,393	4,885
Total operating expenses	44,068	29,751	13,405	3,616	20,497	21,661
Loss from operations	(41,410)	(29,244)	(12,162)	(1,111)	(20,159)	(20,522)
Interest income, net	5				36	
Loss before income taxes	(41,405)	(29,244)	(12,162)	(1,111)	(20,123)	(20,522)
Provision for income taxes	6	426	320	47	130	
Net loss	$ (41,411)	$ (29,670)	$ (12,482)	$ (1,158)	$ (20,253)	$ (20,522)
Basic and diluted net loss per share (1)	$ (2.84)	$ (2.05)	$ (0.86)	$ (0.08)	$ (1.15)	$ (1.42)
Shares used to compute basic and diluted net loss per share	14,593	14,497	14,497	14,497	17,679	14,497

46

Table of Contents

	December 31,			June 30,
	2012	2011	2010	2013
		(in thousands)		(unaudited)
Consolidated Balance Sheet Data:				
Cash and cash equivalents (1)	$ 124,860	$	$	$ 112,507
Total assets	129,283	3,618	3,278	117,930
Other non-current liabilities	1,055	1,650	1,384	1,618
Total liabilities	2,799	10,054	3,249	10,701
Shareholders and parent company equity	126,484	(6,436)	(30)	107,229

(1) Prior to the Separation and Distribution completed on December 20, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. As a result, Prothena did not have any ordinary shares outstanding and cash and cash equivalents prior to December 20, 2012. The calculation of basic and diluted net loss per share assumes that the 14,496,929 ordinary shares issued to Elan shareholders in connection with the separation of the Prothena Business from Elan have been outstanding for all periods presented and that the 3,182,253 ordinary shares subscribed for by a wholly owned subsidiary of Elan upon separation have been outstanding since December 20, 2012.

Table of Contents

MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of financial condition and results of operations together with the section entitled Selected Financial Data and our Financial Statements and related notes included elsewhere in this prospectus. This discussion and other parts of this prospectus contain forward-looking statements that involve risk and uncertainties, such as statements of our plans, objectives, expectations and intentions. Our actual results could differ materially from those discussed in these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the Risk Factors section.

Overview

We are a clinical stage biotechnology company focused on the discovery, development and commercialization of novel antibodies for the treatment of a broad range of diseases that involve protein misfolding or cell adhesion. We focus on the discovery, development and commercialization of therapeutic monoclonal antibodies directed specifically to disease causing proteins. Our antibody-based product candidates target a broad range of potential indications including AL and AA forms of amyloidosis (NEOD001), Parkinson s disease and other synucleinopathies (PRX002) and inflammatory diseases and cancers (PRX003). We initiated a Phase 1 clinical trial for NEOD001, with the first patient dosing in April 2013. The Phase 1 clinical trial of NEOD001 is evaluating its safety and tolerability in AL amyloidosis patients. 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 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. Our business consists of a substantial portion of Elan s former drug discovery business platform, including Neotope Biosciences Limited and its wholly owned subsidiaries Onclave Therapeutics Limited and Prothena Biosciences Inc (which for the period prior to separation and distribution we refer to herein as the Prothena Business). Our Financial Statements for the periods prior to December 21, 2012 have been derived from Elan s historical accounting records and reflect significant allocations of direct costs and expenses. All of the allocations and estimates in these Financial Statements are based on assumptions that we believe are reasonable. However, the Financial Statements do not necessarily represent our financial position or results of operations had we been operating as a separate independent entity. See Critical Accounting Policies and Estimates below as well as Note 2 to the audited Financial Statements included in this prospectus.

The Separation and Distribution

On August 13, 2012, Elan announced that its board of directors had approved the separation of Elan and its drug discovery business into two independent, publicly traded companies: Elan and Prothena. On December 7, 2012, the Elan board of directors approved a deemed *in specie* distribution by Prothena issuing directly to the holders of Elan ordinary shares and Elan American Depository Shares, or ADS, on a pro rata basis, Prothena ordinary shares representing 99.99% of Prothena s outstanding shares (with the remaining 0.01% of Prothena s outstanding shares, which were previously issued to the original incorporators of Prothena and which we refer to as the incorporator shares, being mandatorily redeemed by Prothena after the related demerger). On December 12, 2012, shareholders of Elan voted to approve the *in specie* distribution as required by Elan s Articles of Association. On December 20, 2012, each holder of Elan ordinary shares or ADSs received 1 Prothena ordinary share for every 41 Elan ordinary shares or Elan ADSs held at the close of business on the record date for the distribution, subject to certain conditions.

Immediately after the Separation and Distribution, a wholly-owned subsidiary of Elan subscribed for ordinary shares of Prothena, representing 18% of the outstanding ordinary shares of Prothena (as calculated

Table of Contents

immediately following the acquisition), for a cash payment to Prothena of $26.0 million. Immediately after the consummation of this subscription, the incorporator shares were mandatorily redeemed by Prothena pursuant to their terms for their initial subscription price, and cancelled. Immediately following the Separation and Distribution and Elan s subscription for Prothena ordinary shares, Elan shareholders owned directly 82% of the outstanding ordinary shares of Prothena, and Elan owned the remaining 18%.

Basis of Presentation and Preparation of the Financial Statements

Our business consists of a substantial portion of Elan s former drug discovery business platform, including Neotope Biosciences Limited and its wholly owned subsidiaries Onclave Therapeutics Limited and Prothena Biosciences Inc, and related tangible assets and liabilities.

Prior to December 21, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. Our Consolidated Financial Statements for the periods prior to December 21, 2012 have been prepared on a carve-out basis from the consolidated financial statements of Elan to represent our financial performance as if we had existed on a stand-alone basis during those periods.

Prior to the Separation and Distribution on December 20, 2012, centralized support costs were allocated to us for the purposes of preparing the Consolidated Financial Statements based on our estimated usage of the resources. Our estimated usage of the centralized support resources was determined by estimating our portion of the most appropriate driver for each category of centralized support costs such as headcount or labor hours, depending on the nature of the costs. We believe that such allocations were made on a reasonable basis, but may not necessarily be indicative of the costs that would have been incurred if we had operated on a standalone basis. For additional information regarding the basis of preparation, refer to Note 2 to the audited Financial Statements included in this prospectus.

Critical Accounting Policies and Estimates

Management s discussion and analysis of our financial condition and results of operations is based on our Consolidated Financial Statements, which have been prepared in accordance with U.S. GAAP. The preparation of these Consolidated Financial Statements requires us to make estimates and assumptions for the reported amounts of assets, liabilities, revenues, expenses and related disclosures. We believe the following policies to be critical to the judgments and estimates used in the preparation of our financial statements.

Carve-out of the Results of Operations, Financial Condition and Cash Flows of the Prothena Business

Prior to December 21, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. Our Consolidated Financial Statements have been prepared on a carve-out basis from the consolidated financial statements of Elan to represent the financial position and performance of Prothena as if we had existed on a stand-alone basis during the years ended December 31, 2012, 2011 and 2010 and six months ended June 30, 2012, and as if Financial Accounting Standards Board, or FASB, Accounting Standard Codification, or ASC, Topic 810, *Consolidation*, or ASC 810, had been applied throughout. The Consolidated Financial Statements have been prepared in conformity with U.S. GAAP, by aggregating financial information from the components of Prothena described in Note 2 to the Consolidated Financial Statements included with this prospectus.

The accompanying Consolidated Financial Statements include allocations of direct costs and indirect costs attributable to our operations. Indirect costs relate to certain support functions that were provided on a centralized basis within Elan. The support functions provided to us by Elan included, but were not limited to: accounting, information technology, taxation, legal, corporate strategy, investor relations, corporate governance and other professional services, employee benefit administration, including equity award and pension services, and cash and treasury management. Central support costs of our business for the years ended December 31, 2012,

Table of Contents

2011 and 2010 were $7.7 million, $4.0 million and $2.8 million, respectively and for the six months ended June 30, 2012 was $4.1 million. These costs have been allocated to us for the purposes of preparing the Consolidated Financial Statements based on our estimated usage of the resources. Our estimated usage of the central support resources was determined by estimating our portion of the most appropriate driver for each category of central support costs such as headcount or labor hours, depending on the nature of the costs. We believe that such allocations have been made on a reasonable basis, but may not necessarily be indicative of the costs that would have been incurred if we had operated on a standalone basis.

Share-Based Compensation

We account for our share-based compensation in accordance with the fair value recognition provisions of current authoritative guidance. Share-based awards, including stock options, are measured at fair value as of the grant date and recognized to expense over the requisite service period (generally the vesting period), which we have elected to amortize on a straight-line basis. Since share-based compensation expense is based on awards ultimately expected to vest, it has been reduced by an estimate for future forfeitures. We estimate forfeitures at the time of grant and revise our estimate, if necessary, in subsequent periods. We estimate the fair value of options granted using the Black-Scholes option valuation model. Significant judgment is required in determining the proper assumptions used in these models. The assumptions used include the risk free interest rate, expected term, expected volatility and expected dividend yield. We base our assumptions on historical data when available or when not available, on a peer group of companies. However, these assumptions consist of estimates of future market conditions, which are inherently uncertain, and therefore subject to our judgment. Share-based compensation expense for restricted stock units is measured based on the closing fair market value of Elan s ordinary shares on the date of grant.

Total share-based compensation expense for the years ended December 31, 2012, 2011 and 2010 was $7.5 million, $3.6 million and $1.9 million, respectively and for the six months ended June 30, 2013 and 2012 was $1.1 million and $6.1 million, respectively. The expense for periods prior to December 31, 2012 was allocated to us based on awards from Elan equity plans granted to Elan employees who have, directly or indirectly, provided services to Prothena. We will not recognize any expense going forward in relation to the existing Elan equity-based awards as our employees are not required to provide service after the Separation and Distribution in order to receive the awards.

Recent Accounting Pronouncements

In May 2011, the FASB issued ASU No. 2011-04, Fair Value Measurement: Amendments to Achieve Common Fair Value Measurement and Disclosure Requirements in U.S. GAAP and IFRSs, which results in common fair value measurement and disclosure requirements in U.S. GAAP and IFRS. The amendments change the wording used to describe many of the requirements in U.S. GAAP for measuring fair value and for disclosing information about fair value measurements. Some of the amendments clarify the FASB s intent about the application of existing fair value measurement requirements while other amendments change a particular principle or requirement for measuring fair value or for disclosing information about fair value measurements. The adoption of ASU 2011-04 impacts our disclosures but did not have a material impact on its financial position, results of operations or cash flows. We adopted this standard during the year ended December 31, 2011.

As an emerging growth company under the JOBS Act, unlike many other public companies, we are eligible to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. We have an extended transition period for adopting new or revised accounting standards that have different effective dates for public and private companies until such time as those standards apply to private companies.

Table of Contents

Results of Operations

Results for the Years Ended December 31, 2012, 2011 and 2010 and the Six Months Ended June 30, 2013 and 2012

	Years Ended December 31,			Six Months Ended June 30,	
	2012	2011	2010	2013	2012
			(in thousands)		
Revenues related party	$ 2,658	$ 507	$ 1,243	$ 338	$ 1,139
Operating expenses:					
Research and development	34,139	24,172	9,787	14,104	16,776
General and administrative	9,929	5,579	3,618	6,393	4,885
Total operating expenses	44,068	29,751	13,405	20,497	21,661
Loss from operations	(41,410)	(29,244)	(12,162)	(20,159)	(20,522)
Interest income, net	5			36	
Loss before income taxes	(41,405)	(29,244)	(12,162)	(20,123)	(20,522)
Provision for income taxes	6	426	320	130	
Net loss	$ (41,411)	$ (29,670)	$ (12,482)	$ (20,253)	$ (20,522)

Six Months Ended June 30, 2013 and 2012

Revenue

Revenue consists of fees earned from the provision of R&D services to Elan.

During the six months ended June 30, 2013, total revenues decreased $0.8 million, or 70%, compared to the six months ended June 30, 2012. The decrease was primarily due to a reduction in the scope of the R&D services provided to Elan.

Operating Expenses

Total operating expenses consist of R&D expenses and general and administrative, or G&A, expenses. Operating expenses for the six months ended June 30, 2013 was $20.5 million, compared to $21.7 million for the six months ended June 30, 2012. R&D expenses primarily consist of employee and related expenses, costs associated with preclinical activities and regulatory operations, share-based compensation and other research costs we incurred in providing research services to Elan s ELND005 program. G&A expenses primarily consist of professional services expenses, management compensation expenses and, for the six months ended June 30, 2012, certain centralized support costs that had been allocated to us by Elan based on our estimated usage of the resources. Share-based compensation expense during the six months ended June 30, 2012 was allocated to us by Elan. For additional information regarding the allocation of centralized G&A expenses, please refer to Note 2 to the Financial Statements included in this prospectus.

Research and Development Expenses

For the six months ended June 30, 2013, R&D expenses decreased by $2.7 million, or 16%, as compared to the six months ended June 30, 2012. The decrease for the six months ended June 30, 2013 as compared to the prior year period was primarily due to decreases in share-based compensation expense, personnel costs attributable to Prothena programs and external expenses related to our NEOD001 development program, partially offset by increases in costs related to our PRX002 and PRX003 programs.

51

Table of Contents

Our research activities are aimed at developing new drug products. Our development activities involve the translation of our research into potential new drugs. R&D expenses include personnel, materials, equipment and facilities costs that are allocated to clearly related R&D activities.

The successful development of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete development of our product candidates. This is due to the numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- the scope, rate of progress and expense of our drug discovery efforts and other R&D activities;
- the potential benefits of our product candidates over other therapies;
- clinical trial results; and
- the terms and timing of regulatory approvals.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA or other regulatory authority were to require us to conduct clinical trials beyond those which we currently anticipate will be required for the completion of clinical development of a product candidate or if we experience significant delays in enrollment in any clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development.

The following table sets forth the R&D expenses for our major program (specifically, any program where an Investigational New Drug Application has been filed with the FDA), NEOD001, and other R&D expenses for the six months ended June 30, 2013 and 2012, and the cumulative amounts to date (in thousands):

	Six Months Ended June 30,		Cumulative to Date
	2013	2012	
NEOD001 (1)	$ 1,491	$ 3,841	$ 24,930
Other R&D (2)	12,613	12,935	
	$ 14,104	$ 16,776	

(1) Cumulative R&D costs to date for NEOD001 include the costs incurred from the date when the program has been separately tracked in preclinical development. Expenditures in early discovery stage are not tracked by program and accordingly have been excluded from this cumulative amount.

(2) Other R&D is comprised of preclinical development and discovery programs that have not yet resulted in an Investigational New Drug Application filing with the FDA, including PRX002 and PRX003, and research costs we incurred in providing research services to Elan s ELND005 program.

General and Administrative Expenses

For the six months ended June 30, 2013, G&A expenses increased by $1.5 million, or 31%, compared to the six months ended June 30, 2012. G&A expenses consisted primarily of professional services fees (including payments to Elan under the Transitional Services Agreement), internal personnel costs and share-based compensation expense of $0.8 million for the six months ended June 30, 2013. For the six months ended June 30, 2012, G&A expenses was presented on a carve-out basis as the Prothena Business consisted of a substantial portion of Elan s former drug discovery business platform, therefore the G&A expenses during the six months ended June 30, 2012 consisted of $0.8 million of

direct expense incurred by the Prothena Business and $4.1 million of indirect expenses which was based on an allocation to the Prothena Business by Elan.

Table of Contents

Taxation

Our operations were historically included in Elan s consolidated U.S. federal and state income tax returns and in returns of certain Elan foreign subsidiaries. The current and deferred tax provision calculations have been prepared as if we were a separate taxable entity during the six months ended June 30, 2012 and are consistent with the asset and liability method prescribed by ASC 740. The current and deferred tax provision and the related tax disclosures are not necessarily representative of the tax provision (benefit) that may arise for the Company in the future.

The tax provision for the six months ended June 30, 2013 was $0.1 million compared to $Nil for the six months ended June 30, 2012. The tax provision reflects U.S. federal and state taxes and the availability of Irish tax losses.

Years Ended December 31, 2012, 2011 and 2010

Revenue

Total revenues increased $2.2 million, or 424%, from 2011 to 2012, primarily by an expansion of the scope of the research and development services provided to Elan.

Total revenues decreased by $0.7 million, or 59%, from 2010 to 2011, primarily by a reduction of the scope of the research and development services provided to Elan.

Operating Expenses

For the years ended December 31, 2012, 2011 and 2010, total operating expenses were $44.1 million, $29.8 million and $13.4 million, respectively. R&D expenses primarily consist of expenses for the early discovery efforts on pathology-biology based misfolding protein targets in chronic degenerative diseases, and research costs we incurred in providing research services to Elan s ELND005 program. These expenses primarily consist of employee and related costs, and spending associated with external research. G&A expense primarily consists of professional services expenses, management compensation expenses and certain central support costs that had been allocated to us by Elan based on our estimated usage of the resources.

Research and Development Expenses

R&D expenses increased by $10.0 million, or 41%, in 2012 compared to 2011 and by $14.4 million, or 147%, in 2011 compared to 2010. The increases were primarily due to increases in share-based compensation expense, headcount attributable to Prothena programs and external expenses related to PRX002 and PRX003, offset by decreases in NEOD001 related costs.

The following table sets forth the R&D expenses for our major program (specifically, any program where an Investigational New Drug Application has been filed with the FDA), NEOD001, and other R&D expenses for the years ended December 31, 2012, 2011 and 2010 (in thousands):

	Years Ended December 31,		
	2012	2011	2010
NEOD001 (1)	$ 7,995	$ 11,322	$ 2,281
Other R&D (2)	26,144	12,850	7,506
	$ 34,139	$ 24,172	$ 9,787

(1) Expenditures in early discovery stage are not tracked by program and accordingly have been excluded from this cumulative amount.

Table of Contents

(2) Other R&D is comprised of preclinical development and discovery programs that have not yet resulted in an Investigational New Drug Application filing with the FDA, and research costs we incurred in providing research services to Elan s ELND005 program.

General and Administrative Expenses

G&A expenses increased by $4.4 million, or 78% in 2012 compared to 2011 and by $2.0 million, or 54%, in 2011 compared to 2010. The increases were primarily due to increases in support costs allocated to the Prothena business by Elan.

Taxation

Our operations were historically included in Elan s consolidated U.S. federal and state income tax returns and in returns of certain Elan foreign subsidiaries. The current and deferred tax provision calculations have been prepared as if we were a separate taxable entity and consistent with the asset and liability method prescribed by ASC 740.

The tax provision for the years ended December 31, 2012, 2011 and 2010 was $6,000, $426,000 and $320,000, respectively. The tax provision reflects U.S. Federal and State taxes and the availability of Irish tax losses.

Liquidity and Capital Resources

Overview

Prior to the separation of the Prothena Business from Elan, our operating and capital resource requirements were funded by Elan. As part of the Separation and Distribution, Elan made a cash investment in us of $99.0 million, which we expect to be used to fund working capital expenses and for other general corporate purposes. Additionally, a wholly-owned subsidiary of Elan made a cash payment of $26.0 million to subscribe for 18% of our outstanding ordinary shares (as calculated immediately following the subscription). As of June 30, 2013, we had $112.5 million in cash and cash equivalents. Based on our current business plan, we believe such cash and cash equivalents will be sufficient to meet our obligations for at least the next twelve months.

We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenses associated with completing the development of our product candidates. Our future capital requirements will depend on numerous factors, including, without limitation, the timing of initiation, progress, results and costs of our clinical trials; the results of our research and preclinical studies; the costs of clinical manufacturing and of establishing commercial manufacturing arrangements; the costs of preparing, filing, and prosecuting patent applications and maintaining, enforcing, and defending intellectual property-related claims; the costs and timing of capital asset purchases; our ability to establish research collaborations, strategic collaborations, licensing or other arrangements; the costs to satisfy our obligations under potential future collaborations; and the timing, receipt, and amount of revenues or royalties, if any, from any approved drug candidates. In order to develop and obtain regulatory approval for our potential products we may need to raise substantial additional funds. We expect to raise any such additional funds through public or private equity or debt financings, collaborative agreements with corporate partners or other arrangements. We cannot assume that such additional financings will be available on acceptable terms, if at all, and such financings may only be available on terms dilutive to our shareholders.

Table of Contents

The following table summarizes, for the periods indicated, selected items in our Consolidated Statements of Cash Flows (in thousands):

	Years Ended December 31,			Six Months Ended June 30,	
	2012	2011	2010	2013	2012
Net cash used in operating activities	$ (42,072)	$ (19,697)	$ (9,083)	$ (11,958)	$ (18,988)
Net cash used in investing activities	(1,301)	(595)	(2,607)	(311)	(171)
Net cash provided by (used in) financing activities	168,233	20,292	11,690	(84)	19,159
Net decrease in cash and cash equivalents	$ 124,860	$	$	$ (12,353)	$

Cash Flows for the Six Months Ended June 30, 2013 and 2012

Cash Used in Operating Activities

Net cash used in operating activities was $12.0 million and $19.0 million during the six months ended June 30, 2013 and 2012, respectively, in each case consisting primarily of net losses (adjusted to exclude non-cash charges) and changes in working capital accounts. The decrease was primarily due to an increase in current liabilities.

Cash Used in Investing Activities

Net cash used in investing activities was $0.3 million and $0.2 million during the six months ended June 30, 2013 and 2012, respectively, consisting primarily of purchases of property and equipment.

Cash (Used in) Provided by Financing Activities

Net cash used in financing activities was $0.1 million during the six months ended June 30, 2013, consisting of the final settlement of liabilities as a result of our separation from Elan. Net cash provided by financing activities was $19.2 million during the six months ended June 30, 2012, reflecting funding provided by Elan.

Cash Flows for the Years Ended December 31, 2012, 2011 and 2010

Cash Used in Operating Activities

Net cash used in operating activities was $42.1 million, $19.7 million and $9.1 million in 2012, 2011 and 2010, respectively, in each case consisting primarily of net losses (adjusted to exclude non-cash charges) and changes in working capital accounts.

Cash Used in Investing Activities

Net cash used in investing activities was $1.3 million in 2012, consisting of purchases of property and equipment. Net cash used in investing activities was $0.6 million in 2011, consisting of purchases of property and equipment and computer software. Net cash used in investing activities was $2.6 million in 2010, primarily consisting of purchases of property and equipment.

Cash Provided by Financing Activities

Net cash provided by financing activities was $168.2 million in 2012, primarily consisting of funding provided by Elan and the issue of ordinary shares to a wholly owned subsidiary of Elan. Net cash provided by financing activities was $20.3 million and $11.7 million in 2011 and 2010, respectively, reflecting funding provided by Elan.

Table of Contents

Off-Balance Sheet Arrangements

At June 30, 2013, we were not a party to any off-balance sheet arrangements that have, or are reasonably likely to have, a current or future effect on our financial condition, changes in financial condition, revenue or expenses, results of operations, liquidity, capital expenditures or capital resources.

Contractual Obligations

The following table sets out, at December 31, 2012 and June 30, 2013, our main contractual obligations due by period. This represents our future minimum rental commitments under our operating lease. The table does not include items such as future investments in financial assets.

Years Ending December 31,	December 31, 2012	June 30, 2013 (unaudited)
2013 (remaining)	$ 1,155	$ 587
2014	1,261	1,261
2015	1,342	1,342
2016	1,396	1,396
2017	1,452	1,452
Thereafter	4,569	4,569
	$11,175	$10,607

We had commitments to suppliers for purchases totaling $1.3 million and $Nil at December 31, 2012 and June 30, 2013, respectively.

Table of Contents

BUSINESS

Overview

We are a clinical stage biotechnology company focused on the discovery, development and commercialization of novel antibodies for the treatment of a broad range of diseases that involve protein misfolding or cell adhesion. Our team has a track record of discovering and developing immunotherapy products including a beta immunotherapy platform and Tysabri. We focus on the discovery, development and commercialization of therapeutic monoclonal antibodies directed specifically to disease causing proteins. Our antibody-based product candidates target a broad range of potential indications including AL and AA forms of amyloidosis (NEOD001), Parkinson s disease and other synucleinopathies (PRX002) and inflammatory diseases and cancers (PRX003). We initiated a Phase 1 clinical trial for NEOD001, with the first patient dosing in April 2013. The Phase 1 clinical trial of NEOD001 is evaluating its safety and tolerability in AL amyloidosis patients. 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 by applying our extensive expertise in generating novel therapeutic antibodies and working with collaborators having expertise in specific animal models of disease.

We were formed under the laws of Ireland as a private limited company under the name Neotope Corporation Limited on September 26, 2012. We subsequently re-registered as a public limited company and changed our name to Neotope Corporation plc. On November 1, 2012, our shareholders resolved to change our name to Prothena Corporation plc, and this was approved by the Irish Registrar of Companies on November 7, 2012.

Our business consists of a substantial portion of Elan s former drug discovery business platform, including Neotope Biosciences Limited and its wholly owned subsidiaries Onclave Therapeutics Limited and Prothena Biosciences Inc (which for the period prior to separation and distribution we refer to herein as the Prothena Business). Prior to December 21, 2012, the Prothena Business operated as part of Elan and not as a separate stand-alone entity. After the separation from Elan, and the related distribution of our ordinary shares to Elan s shareholders (which we refer to as the Separation and Distribution), our ordinary shares began trading on The NASDAQ Global Market under the symbol PRTA on December 21, 2012.

In connection with the Separation and Distribution, Elan invested total cash in us of $125.0 million, which includes 18% of our outstanding ordinary shares (as calculated immediately following the consummation of such subscription) that a wholly-owned subsidiary of Elan subscribed for immediately following the Separation and Distribution.

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 broad range of potential indications including AL (primary) and AA (secondary) forms of amyloidosis, Parkinson s disease and other synucleinopathies, and novel cell adhesion targets involved in inflammatory diseases and cancers. 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.

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 against neo-epitope targets for the potential treatment of patients having a disease associated with the neo-epitope.

Table of Contents

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

Table of Contents

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 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

We are developing NEOD001, a monoclonal antibody targeting AL and AA amyloid for the potential treatment of 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 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 transplant 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 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 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.

Table of Contents

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). Preclinical data has demonstrated survival benefits and selectivity of NEOD001 for amyloid deposits in a mouse model of AA amyloidosis. This approach has the potential to be a first-in-class agent for this orphan disease with a significant unmet medical need. 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 patient dosed in April 2013. The primary objective of the Phase 1 clinical trial is evaluating the safety and tolerability of NEOD001 in AL Amyloidosis patients and determining a recommended dose for testing in Phase 2 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 trial of NEOD001 in 2014 assuming a Phase 2 recommended dose is identified prior to that date.

PRX002 for Parkinson s Disease

We are developing PRX002, a monoclonal antibody targeting synuclein for the potential treatment of Parkinson s disease and other synucleinopathies. Together with scientists at the University of California, San Diego, or UCSD, under various laboratory services agreements pursuant to which such scientists performed research pursuant to statements of work established by UCSD and Neotope Biosciences, Prothena scientists have published a number of scientific papers describing effects of these antibodies in preclinical models resembling Parkinson s disease.

Alpha-synuclein is a protein that is a prominent component of Lewy bodies and neurites which are pathological hallmarks of Parkinson s disease, dementia with Lewy bodies, multiple system atrophy and certain other neurological disorders, collectively known as 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 insoluble fibrils that contribute to the pathology of the disease.

Parkinson s disease is a degenerative disorder of the central nervous system. The motor symptoms of Parkinson s disease result from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain.

Early in the course of the disease, the most obvious symptoms are movement-related and include shaking, rigidity, slowness of movement and difficulty with walking and gait. Later, cognitive and behavioral problems may arise, with dementia commonly occurring in the advanced stages of the disease. Other symptoms include sensory, sleep and emotional problems. Parkinson s disease is more common in the elderly, with most cases occurring after the age of 50.

Parkinson s disease is the second most common neurodegenerative disorder after Alzheimer s disease. There are an estimated seven to 10 million Parkinson patients worldwide. 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 ineffective at treating the symptoms. The goal of our approach is to slow down the progressive neurodegenerative consequences of disease, a current unmet need.

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.

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, a 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 filing an IND and initiating a Phase 1 trial of PRX002 for Parkinson s disease in 2014.

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 travelling 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 and migrate into tissues to initiate 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. Inflammatory disease arises 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 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 animal models of inflammatory diseases and cancers. Based on early results from these studies, we have identified a lead clinical

Table of Contents

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 late 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 and 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 discovery, development and commercialization of novel antibodies for the treatment of a broad range 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 and 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 amyloidosis patients 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 and 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.
We intend to seek to collaborate or license certain potentially therapeutic antibody products to biotechnology or pharmaceutical companies for preclinical and clinical development and commercialization. For certain product opportunities, we may choose to proceed with further clinical development independently in order to create long term value. We intend to seek strategic alliances in which we would provide our research and development services for our collaborators as part of our plan to generate revenue.

Table of Contents

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.

Table of Contents

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

64

Table of Contents

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;

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.

Table of Contents

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.

Table of Contents

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 aggressively strive 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 and any other inventions that may be commercially important to the development