

Prothena Corp plc
 Form 424B5
 March 06, 2017
Table of Contents

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-203258

Title of Securities Being Registered	Amount to be Registered	Proposed Maximum Offering Price Per Share	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee(1)
Ordinary Shares, par value \$0.01 per share	3,105,000 shares(2)	\$57.50	\$178,537,500	\$20,692.50

- (1) Calculated in accordance with Rule 457(r) under the Securities Act of 1933, as amended (the Securities Act). The fee payable in connection with the offering of ordinary shares pursuant to this prospectus supplement has been paid in accordance with Rule 456(b) and Rule 457(r) under the Securities Act.
- (2) Equals the aggregate number of ordinary shares to be registered hereunder and includes 405,000 ordinary shares that may be offered and sold pursuant to the exercise in full of the underwriter's option to subscribe for additional ordinary shares.

Table of Contents

2,700,000 Shares

Ordinary Shares

Prothena Corporation plc is offering 2,700,000 of its ordinary shares.

Our ordinary shares are listed on The NASDAQ Global Select Market under the symbol PRTA. The closing price of our ordinary shares on The NASDAQ Global Select Market on March 2, 2017 was \$60.07 per ordinary share.

The underwriter has a thirty-day option to subscribe for up to an aggregate of 405,000 additional ordinary shares.

Investing in our ordinary shares involves a high degree of risk. See the risks set forth under the heading Risk Factors section beginning on page S-7 of this prospectus supplement.

	Price to Public	Underwriting Discounts and Commissions(1)	Proceeds to Prothena
Per Share	\$ 57.50	\$ 1.75	\$ 55.75
Total	\$ 155,250,000	\$ 4,725,000	\$ 150,525,000

(1) See Underwriting in this prospectus supplement for a description of the compensation payable to the underwriter. If all of the shares are not sold at the public offering price, the underwriter may change the offering price and may offer shares from time to time for sale in negotiated transactions or otherwise, at market prices prevailing at the time of sale, at prices related to such prevailing market prices or otherwise.

Delivery of the ordinary shares will be made on or about March 8, 2017.

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

Cantor Fitzgerald & Co.

The date of this prospectus supplement is March 2, 2017.

Table of Contents

TABLE OF CONTENTS

Prospectus Supplement

	Page
<u>PROSPECTUS SUPPLEMENT SUMMARY</u>	S-1
<u>THE OFFERING</u>	S-6
<u>RISK FACTORS</u>	S-7
<u>SPECIAL NOTE REGARDING FORWARD -LOOKING STATEMENTS</u>	S-11
<u>MARKET, INDUSTRY AND OTHER DATA</u>	S-12
<u>USE OF PROCEEDS</u>	S-13
<u>PRICE RANGE OF OUR ORDINARY SHARES AND DIVIDEND POLICY</u>	S-14
<u>DILUTION</u>	S-15
<u>MATERIAL UNITED STATES FEDERAL INCOME TAX CONSEQUENCES TO U.S. HOLDERS</u>	S-16
<u>CERTAIN IRISH TAX CONSEQUENCES RELATING TO THE HOLDING OF OUR ORDINARY SHARES</u>	S-21
<u>DESCRIPTION OF SHARE CAPITAL</u>	S-23
<u>UNDERWRITING</u>	S-35
<u>LEGAL MATTERS</u>	S-42
<u>EXPERTS</u>	S-42
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	S-42
<u>INCORPORATION BY REFERENCE</u>	S-43

Prospectus

	Page
<u>ABOUT THIS PROSPECTUS</u>	1
<u>WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE</u>	2
<u>SPECIAL NOTE REGARDING FORWARD -LOOKING STATEMENTS</u>	4
<u>THE COMPANY</u>	6
<u>RISK FACTORS</u>	7
<u>USE OF PROCEEDS</u>	8
<u>DESCRIPTION OF SHARE CAPITAL</u>	9
<u>GLOBAL SECURITIES</u>	22
<u>PLAN OF DISTRIBUTION</u>	25
<u>LEGAL MATTERS</u>	26
<u>EXPERTS</u>	26

Neither we nor the underwriter have authorized anyone to provide you with information that is different from that contained or incorporated by reference in this prospectus supplement, the accompanying 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 and the underwriter 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 or incorporated by reference in this prospectus supplement and the accompanying prospectus is accurate only as of the date on the front of this prospectus supplement, regardless of the time of delivery of this prospectus supplement or any sale of our ordinary shares.

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT AND THE PROSPECTUS

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of ordinary shares and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated April 6, 2015, provides more general information about our ordinary shares. To the extent the information contained in this prospectus supplement differs or varies from the information contained in the accompanying prospectus or the documents incorporated by reference herein or therein, you should rely on the information in this prospectus supplement. Generally, when we refer to the prospectus, we are referring to this prospectus supplement and the accompanying prospectus combined.

Prothena and our logo are our trademarks and are used in this prospectus supplement and the accompanying prospectus. This prospectus supplement and the accompanying prospectus also include trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, our trademarks and tradenames referred to in this prospectus supplement and the accompanying 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 the underwriter have taken any action that would permit this offering or possession or distribution of this prospectus supplement and the accompanying 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 supplement and the accompanying 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 supplement and the accompanying prospectus.

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

The items in the following summary are described in more detail later or incorporated by reference in this prospectus supplement and the accompanying 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 supplement and the accompanying prospectus carefully (including the documents incorporated by reference herein), especially the Risk Factors section beginning on page S-7 and our consolidated financial statements (which we refer to as our Financial Statements) and the related notes incorporated by reference in this prospectus supplement and the accompanying prospectus, before deciding to invest in our ordinary shares. In this prospectus supplement and the accompanying prospectus, unless the context otherwise requires, references to we, us, our or Prothena refer to Prothena Corporation plc.

Overview

We are a global, late-stage clinical biotechnology company establishing fully-integrated research, development and commercial capabilities. Fueled by our deep scientific understanding built over decades of research in protein misfolding and cell adhesion the root causes of many serious or currently untreatable amyloid and inflammatory diseases we are seeking to fundamentally change the course of progressive diseases associated with this biology. We have advanced several drug candidates into clinical studies while pursuing discovery of additional novel therapies.

We are developing antibody-based product candidates that target a number of potential indications including AL amyloidosis (NEOD001), Parkinson's disease and other related synucleinopathies (PRX002), inflammatory diseases including psoriasis and psoriatic arthritis (PRX003) and ATTR amyloidosis (PRX004). Our lead programs consist of three clinical development programs and one late-stage preclinical development program:

NEOD001 is a monoclonal antibody that specifically targets the amyloid that accumulates in both the AL and AA forms of amyloidosis. NEOD001 was granted orphan drug designation for the treatment of AL amyloidosis by the U.S. Food and Drug Administration, or FDA, in 2012 and by the European Medicines Agency, or EMA, in 2013. NEOD001 for the treatment of systemic amyloidosis received Fast Track designation from the FDA in December 2014. The Fast Track designation is designed to accelerate the development of drugs to treat serious conditions and fill an unmet medical need in an effort to make important new drugs available to patients earlier.

AL amyloidosis is a rare disease caused by an accumulation of misfolded proteins (amyloid) resulting in vital organ (e.g. heart or kidney) dysfunction. AL amyloidosis represents the majority of systemic amyloidosis (including AA and ATTR) and it is estimated that there are between 30,000 and 45,000 patients with AL amyloidosis in the U.S. and Europe. There are currently no approved therapies for AL amyloidosis; existing approaches reduce light chain production, but do not address resident amyloid in vital organs. Safe and well tolerated therapies are needed to improve organ function. We are building our commercial capabilities and, upon a successful regulatory review, we intend to commercialize NEOD001 in the U.S. and Europe. We may also seek a commercial partner or partners in other markets.

In our Phase 1/2 study of NEOD001, we enrolled AL amyloidosis patients with persistent organ dysfunction who had been previously treated with standard-of-care plasma cell directed therapy. The Phase 1/2 study consisted of a dose escalation phase (n=27) and expansion phase (n=42) which evaluated safety, tolerability, pharmacokinetics and immunogenicity of NEOD001 as well as the specific clinical activity against cardiac and renal endpoints. The expansion phase of this study also

S-1

Table of Contents

evaluated clinical activity against neuropathy endpoints. The 42 patients in the expansion phase of the study were enrolled into three prospectively-defined cohorts as follows: 15 patients with predominantly cardiac dysfunction, 16 patients with renal dysfunction and 11 patients with peripheral neuropathy. All patients received 24 mg/kg of NEOD001 by intravenous infusion every 28 days.

In December 2016, results from the completed Phase 1/2 study of NEOD001 in previously treated patients with persistent organ dysfunction were presented in an oral session at the American Society of Hematology (ASH) Annual Meeting. Results of the Phase 1/2 study demonstrated monthly infusions (every 28 days) of NEOD001 were safe and well-tolerated in patients with AL amyloidosis and persistent organ dysfunction. A total of 69 patients received more than 990 infusions, of up to 24 mg/kg, with a mean treatment duration of 12.8 months. In this study, clinical assessments demonstrated improvements in three organ systems in previously treated patients with AL amyloidosis. In a best response analysis of patients in the Phase 1/2 study who received NEOD001, 53% or 19 of 36 total cardiac-evaluable patients demonstrated a cardiac response, defined as more than 30% and 300 pg/mL decrease in levels of NT-proBNP. These cardiac best response rates compared favorably to cardiac response rates of 0% to 15% from available published historical data in patients previously treated with plasma cell directed therapy, and were consistent with the best response rate reported in the interim analysis of the dose escalation phase (n=27) of the NEOD001 Phase 1/2 study published in the *Journal of Clinical Oncology* in February 2016. In a best response analysis of patients in the Phase 1/2 study who received NEOD001, 64%, or 23 of 36 total renal-evaluable patients, demonstrated a renal response, defined as a 30% decrease in proteinuria in the absence of estimated glomerular filtration rate (eGFR) worsening. These renal best response rates compared favorably to renal response rates of 17% to 29% from published historical data in patients previously treated with plasma cell directed therapy, and were consistent with the best response rate reported in the interim analysis of the dose-escalation phase (n=27) of the NEOD001 Phase 1/2 study published in the *Journal of Clinical Oncology* in February 2016. In addition, an improvement in peripheral neuropathy in patients in the prospectively defined peripheral neuropathy expansion cohort was demonstrated by a mean 35% (median 23%) decrease in NIS-LL measured at month 10, indicating improvement to a third organ system in NEOD001-treated patients. Complete resolution of peripheral neuropathy, as measured by NIS-LL, was achieved in two patients in this cohort. Improvements in patient NIS-LL scores resulted in a response rate of 82% or nine of 11 patients in the peripheral neuropathy expansion cohort of the Phase 1/2 study. A response on the NIS-LL is defined as a less than 2-point increase on the 88-point scale.

Consistent with a commitment to developing a disease-modifying therapy for patients with AL amyloidosis, Prothena is currently conducting two global, multi-center, randomized, double-blind, placebo-controlled clinical studies for NEOD001, which are described below.

Phase 2b PRONTO Registration-Directed Study

In October 2015, Prothena announced the PRONTO study, which is enrolling patients with AL amyloidosis and persistent cardiac dysfunction who have been previously treated with plasma cell directed therapy. PRONTO is a global, Phase 2b multi-center, randomized, double-blind, placebo-controlled, registration-directed study. The study is designed to enroll approximately 100 patients who will be randomized on a 1:1 basis to receive 24 mg/kg of NEOD001 or placebo via intravenous infusion every 28 days. The primary endpoint is best response over 12 months of the cardiac functional biomarker NT-proBNP, defined by the consensus criteria of NT-proBNP change. Secondary endpoints include evaluations of Short-Form 36 (SF-36, a quality of life measure), Six-Minute Walk Test, proteinuria and NIS-LL. The study was designed with 80% power to detect an absolute difference of 26.5% in NT-proBNP best response rate between the treatment and placebo groups with a two-sided alpha of 0.05. The PRONTO study was designed to align with feedback from the EMA related to The VITAL Amyloidosis Study. When combined with data from the NEOD001 Phase 1/2 study, the PRONTO study has the potential to expedite patient access.

S-2

Table of Contents**Phase 3 VITAL Registrational Study**

In December 2014, Prothena announced The VITAL Amyloidosis Study, which is enrolling newly-diagnosed, treatment-naïve patients with AL amyloidosis and cardiac dysfunction. VITAL is a global, Phase 3 multi-center, randomized, double-blind, placebo-controlled, registrational study. The study is designed to enroll approximately 230 patients who will be randomized on a 1:1 basis to receive 24 mg/kg of NEOD001 or placebo via intravenous infusion every 28 days, with both arms receiving concurrent standard-of-care therapy. The composite primary endpoint is event-based, with all-cause mortality or cardiac hospitalizations as qualifying events. Secondary endpoints of the study include evaluation of the cardiac biomarker NT-proBNP, proteinuria, SF-36, Six-Minute Walk Test and NIS-LL. The study was designed with 90% power to detect as little as a 30% change in the event rate between the treatment and placebo groups with a two-sided alpha of 0.05. The VITAL Amyloidosis Study is designed to support full global registration.

PRX002 is a monoclonal antibody targeting alpha-synuclein designed to slow the progressive neurodegeneration associated with synuclein misfolding and/or the cell-to-cell transmission of the pathogenic forms of synuclein in Parkinson's disease and other synucleinopathies.

In December 2013, we entered into a License, Development, and Commercialization Agreement, or the License Agreement, with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or collectively, Roche, to develop and commercialize, and in the United States, co-develop and potentially co-promote certain anti-alpha-synuclein antibodies, including PRX002, for the treatment of Parkinson's disease and other related synucleinopathies, which are referred to in this prospectus supplement collectively as the Licensed Products. Under the terms of the License Agreement, upon the satisfaction of certain milestones, we may receive up to an aggregate of \$600 million in upfront and milestone payments, of which we have already received \$45 million. In the United States, Prothena and Roche will share all development and commercialization costs, as well as profits, on a 70/30 basis (70% Roche and 30% Prothena) for PRX002 in the Parkinson's disease indication, as well as any other Licensed Products and/or indications for which we opt in to co-develop and co-fund. Outside the United States, Roche will have sole responsibility for developing and commercializing PRX002 and will pay us up to double-digit royalties on net sales.

In November 2016, we announced data from a Phase 1b multiple ascending dose study of PRX002 in patients with Parkinson's disease that was designed to assess the safety, tolerability, pharmacokinetics and immunogenicity of PRX002. The 80 patients with Parkinson's disease in this Phase 1b double-blind, placebo-controlled, multiple ascending dose study were randomized into six escalating dose cohorts to receive PRX002 or placebo (2:1 randomization for 0.3, 1, 3 or 10 mg/kg, and 3:1 randomization for 30 or 60 mg/kg). All dose levels of PRX002 were found to have an acceptable safety and tolerability profile in patients with Parkinson's disease, meeting the primary objective of the study. Central nervous system (CNS) penetration was demonstrated by a dose-dependent increase in PRX002 levels in cerebrospinal fluid (CSF), and a mean concentration of PRX002 in CSF of 0.3% relative to serum across all dose levels, which exceeded our expectations based on our preclinical experience. Data from the study also demonstrated rapid, dose- and time-dependent mean reduction in levels of free serum alpha-synuclein of up to 97% after a single dose, which were statistically significant ($p < 0.0001$), and maintained following two additional monthly doses. The data from the Phase 1b multiple ascending dose study supports advancing PRX002 into a Phase 2 clinical study.

PRX003 is a monoclonal antibody targeting CD146, also known as melanoma cell adhesion molecule (MCAM) for the potential treatment of inflammatory diseases including psoriasis and psoriatic arthritis.

In June 2016, we announced data from a Phase 1 single ascending dose study of PRX003 in healthy volunteers, that was designed to assess the safety, tolerability, pharmacokinetics and immunogenicity of PRX003. The 40 healthy volunteers in this Phase 1 double-blind, placebo-controlled, single

S-3

Table of Contents

ascending dose study were randomized 3:1 into five escalating dose cohorts (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg) to receive either PRX003 or placebo. The data from this study demonstrated that PRX003 was well-tolerated with an acceptable safety profile following a single infusion, up to and including the highest dose level tested of 30 mg/kg. Data from the study also demonstrated that administration of PRX003 led to greater than 95 percent neutralization of CD146 at saturating drug exposures. The data showed a statistically significant ($p < 0.0001$) dose-dependent duration of downregulation of CD146 on Th17 cells.

In the second quarter of 2016, we initiated a randomized, double-blind, placebo-controlled, Phase 1b multiple ascending dose proof-of-biology study of PRX003 designed to further assess the safety, tolerability, pharmacokinetics and immunogenicity of PRX003 in patients with psoriasis. Our strategy is to advance PRX003 into a Phase 2 clinical study in psoriatic arthritis, based on certain pre-specified criteria being met in the Phase 1b proof-of-biology study in patients with psoriasis. We may elect to license or partner PRX003 for disease areas that would require larger clinical trials and investment.

PRX004 is a monoclonal antibody in preclinical development targeting the misfolded forms of transthyretin protein that are found to accumulate in ATTR amyloidosis.

We are a public limited company formed under the laws of Ireland. On December 20, 2012, we separated from Elan Corporation Limited (formerly Elan Corporation, plc), or Elan. Our ordinary shares trade on The NASDAQ Global Select Market under the symbol PRTA. Our principal executive offices are located at Adelphi Plaza, Upper George's Street, Dún Laoghaire, Co. Dublin, A96 T927, Ireland, and our telephone number is 011-353-1-236-2500.

Upcoming Milestones

NEOD001 for the potential treatment of AL Amyloidosis

Complete enrollment in the Phase 3 VITAL Amyloidosis Study expected in the second quarter of 2017.

Topline results in the Phase 2b PRONTO study expected in the second quarter of 2018.

PRX002 for the potential treatment of Parkinson's disease and other related synucleinopathies (worldwide collaboration with Roche)

Phase 2 clinical study expected to begin in 2017.

PRX003 for the potential treatment of inflammatory diseases including psoriasis and psoriatic arthritis

Topline results from the Phase 1b multiple ascending dose, proof-of-biology study in patients with psoriasis expected in the third quarter of 2017.

PRX004 for the potential treatment of ATTR amyloidosis

Clinical development expected to begin in early 2018.

S-4

Table of Contents

Research and Development Pipeline

Lead Programs

Our research and development pipeline includes four therapeutic antibody programs that we intend to advance: NEOD001 for the potential treatment of AL amyloidosis; PRX002, in collaboration with Roche, for the potential treatment of Parkinson's disease and other related synucleinopathies; PRX003 for the potential treatment of inflammatory diseases including psoriasis and psoriatic arthritis; and PRX004 for the potential treatment of ATTR amyloidosis.

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

Discovery Programs

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

Table of Contents

THE OFFERING

Ordinary shares we are offering 2,700,000 ordinary shares (or 3,105,000 ordinary shares if the underwriter exercises in full its option to subscribe for additional shares)

Ordinary shares to be outstanding after the offering 37,452,116 ordinary shares (or 37,857,116 ordinary shares if the underwriter exercises in full its option to subscribe for additional shares)

Use of proceeds We currently intend to use the net proceeds from this offering to conduct our ongoing clinical trials, for drug discovery activities, including preclinical and clinical trials for other potential product candidates targeting misfolded proteins and for activities relating to the potential commercial launch of NEOD001, if approved. Net proceeds not used for these activities may be used for working capital and other general corporate purposes. Our management will have broad discretion over the use of the net proceeds from this offering. See **Use of Proceeds** for a more complete description of the intended use of proceeds from this offering.

Risk factors See **Risk Factors** beginning on page S-7 and other information included and incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors that you should consider carefully before deciding to invest in our ordinary shares.

Symbol on The NASDAQ Global Select Market **PRTA**

The number of ordinary shares to be outstanding after this offering is based on 34,752,116 ordinary shares outstanding as of December 31, 2016, and excludes the following, in each case as of such date:

4,064,207 ordinary shares issuable upon the exercise of outstanding options having a weighted-average exercise price of approximately \$27.19 per share; and

2,284,938 ordinary shares reserved for issuance pursuant to future awards under our Amended and Restated 2012 Long Term Incentive Plan.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of the underwriter's option to subscribe for additional ordinary shares from us.

S-6

Table of Contents

RISK FACTORS

Investing in our ordinary shares involves significant risks, some of which are described below. You should carefully consider the following risks, the risks described in our Annual Report on Form 10-K for the year ended December 31, 2016, as well as other information in this prospectus supplement and the accompanying prospectus, including information incorporated by reference herein and therein, and any free writing prospectus that we have authorized for use in connection with this offering, before deciding whether to invest in our ordinary shares. The occurrence of any of the events or developments described below could materially and adversely affect 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 in our ordinary shares. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations. Some statements in this prospectus supplement, including statements in the following risk factors, constitute forward-looking statements. See Special Note Regarding Forward-Looking Statements.

Risks Related to Our Ordinary Shares and this Offering

The market price of our ordinary shares may fluctuate widely.

Our ordinary shares commenced trading on The NASDAQ Global Market on December 21, 2012 and currently trade on The NASDAQ Global Select Market. We cannot predict the prices at which our ordinary shares may trade. 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 ongoing or future clinical trials;

our collaboration with Roche pursuant to the License Agreement to develop and commercialize PRX002, as well as any future licensed products targeting alpha-synuclein;

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 U.S. 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;

period-to-period fluctuations in our financial results;

S-7

Table of Contents

overall fluctuations in U.S. equity markets;

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 ordinary 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 budgets 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.

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 from this offering, and you will be relying on the judgment of our management regarding the application of such proceeds. Our management might not apply the net proceeds from this offering in ways that increase the value of your investment. We currently intend to use the net proceeds from this offering to conduct our ongoing clinical trials, for drug discovery activities, including preclinical and clinical trials for other potential product candidates targeting misfolded proteins, and for activities relating to the potential commercial launch of NEOD001, if approved. Net proceeds not used for these activities may be used for working capital and other general corporate 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. The failure by our management to invest and apply the net proceeds from this offering effectively could harm our business.

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 raising 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 December 31, 2016, the

number of ordinary shares available for issuance pursuant to outstanding and future equity awards under our equity plan was 6,349,145.

If we are a passive foreign investment company for U.S. federal income tax purposes, it could result in adverse U.S. federal income tax consequences to United States holders of our ordinary shares.

Significant potential adverse U.S. federal income tax implications generally apply to U.S. investors owning shares of a passive foreign investment company (PFIC), directly or indirectly. In general, we would be a PFIC for a taxable year if either (i) 75% or more of our gross income constitutes passive income (the income test) or (ii) 50% or more of our assets produce passive income (the asset test). Changes in the composition of our active or passive income, passive assets or fair market value may cause us to become a PFIC. A separate determination must be made each taxable year as to whether we are a PFIC (after the close of each taxable year).

Table of Contents

We do not believe we were a PFIC for U.S. federal income tax purposes for our taxable years ended December 31, 2015 and 2016 and we don't expect to be a PFIC for our current taxable year ended December 31, 2017. However, the application of the PFIC rules is subject to uncertainties in a number of respects, and we cannot assure that the U.S. Internal Revenue Service (the IRS) will not take a contrary position. We also cannot assure that we will not be a PFIC for U.S. federal income tax purposes for any future taxable year.

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 U.S. 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 U.S. 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 federal or state securities laws, would not automatically be enforceable in Ireland.

As an Irish incorporated company, we are governed by the Irish Companies Act 2014, 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 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 U.S.

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 Panel Act, 1997, Takeover Rules, 2013. Under those Irish Takeover Rules, our board of directors is not permitted to take any action that might frustrate an offer for our ordinary shares once our board of directors 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 ordinary 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 U.S.

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

Transfers of our ordinary shares effected by means of the transfer of book entry interests in DTC should 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 ordinary 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 ordinary 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 ordinary shares.

Table of Contents

We do not anticipate paying cash dividends, and accordingly, shareholders must rely on ordinary 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 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. Please see *Certain Irish Tax Consequences Relating to the Holding of our Ordinary Shares* in this prospectus supplement.

Dividends paid by us may be subject to Irish dividend withholding tax.

Although we do not currently anticipate paying cash dividends, if we were to do so in the future, a dividend withholding tax (currently at a rate of 20%) may arise. 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.

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

Irish capital acquisitions tax (CAT) could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary 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. Please see *Certain Irish Tax Consequences Relating to the Holding of our Ordinary Shares* in this prospectus supplement. It is recommended that each shareholder consult his or her own tax advisor as to the tax consequences of holding our ordinary shares or receiving dividends from us.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus contain 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, expect, goal, intend, may, objective, plan, predict, potential, positioned, seek, should, target, similar expressions that are predictions of or indicate 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 operating losses;

our ability to successfully complete research and development of our drug candidates;

our ability to develop, manufacture and commercialize products;

our collaboration with Roche pursuant to the License Agreement;

our ability to protect our patents and other intellectual property;

our ability to hire and retain key employees;

tax treatment of our separation from Elan and subsequent distribution of our ordinary shares;

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;

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

government regulation of our industry;

the volatility of our ordinary share price;

business disruptions;

our use of proceeds from this offering; and

the other risks and uncertainties described in Risk Factors.

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. They 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 supplement and the accompanying 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, including the risks incorporated therein from our Annual Report on Form 10-K for the year ended December 31, 2016, and elsewhere in or incorporated by reference in this prospectus supplement and the accompanying 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 supplement and the accompanying 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 Securities and Exchange Commission, or the SEC, after the date of this prospectus supplement. See Where You Can Find More Information in this prospectus supplement.

S-11

Table of Contents

MARKET, INDUSTRY AND OTHER DATA

This prospectus supplement and the accompanying prospectus may contain 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 other similar sources.

S-12

Table of Contents

USE OF PROCEEDS

We estimate that the net proceeds from the issue by us of the ordinary shares in this offering will be approximately \$150.2 million after deducting the underwriting discount and estimated offering expenses payable by us. If the underwriter exercises its option to subscribe for additional ordinary shares in full, we estimate that the net proceeds will be approximately \$172.8 million after deducting the underwriting discount and estimated offering expenses payable by us.

We currently intend to use the net proceeds from this offering to conduct our ongoing clinical trials for drug discovery activities, including preclinical and clinical trials for other potential product candidates targeting misfolded proteins and for activities relating to the potential commercial launch of NEOD001, if approved. Net proceeds not used for these activities may be used for working capital and other general corporate purposes. 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 clinical trials; the timing and success of preclinical studies or clinical trials we may commence in the future; and the timing of regulatory submissions. The amounts and timing of our actual expenditures for each purpose may vary significantly depending upon numerous factors, including the status of our product development and clinical trial efforts; the scope of research and development efforts; regulatory approvals; competition; and our evaluation of strategic opportunities to further the development efforts for our product candidates. We reserve the right to change the use of proceeds as a result of certain contingencies such as competitive developments, clinical trial results, opportunities to acquire technologies or products, any unanticipated cash expenses and other factors.

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

Table of Contents**PRICE RANGE OF OUR ORDINARY SHARES AND DIVIDEND POLICY**

Our ordinary shares began trading on The NASDAQ Global Market under the symbol **PRTA** on December 21, 2012 and currently trade on The NASDAQ Global Select Market. The following table sets forth, for the periods indicated, the high and low intraday prices per share of our ordinary shares as reported by The NASDAQ Global Select Market.

Year Ended December 31, 2014	High	Low
First quarter	\$ 49.24	\$ 24.42
Second quarter	41.33	18.52
Third quarter	24.31	16.71
Fourth quarter	24.67	17.00
Year Ended December 31, 2015	High	Low
First quarter	\$ 45.00	\$ 18.76
Second quarter	55.97	30.14
Third quarter	70.52	42.20
Fourth quarter	76.42	40.47
Year Ended December 31, 2016	High	Low
First quarter	\$ 67.32	\$ 28.20
Second quarter	51.45	33.53
Third quarter	64.50	35.04
Fourth quarter	68.18	40.58
Year Ending December 31, 2017	High	Low
First quarter (through March 2, 2017)	\$ 63.14	\$ 45.13

On March 2, 2017, the last sale price of our ordinary shares as reported on The NASDAQ Global Select Market was \$60.07 per share. As of December 31, 2016, there were approximately 1,297 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 record holders.

We have never declared or paid cash dividends on our ordinary shares. We intend to retain all available funds and 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 of directors.

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 December 31, 2016, we had a historical net tangible book value of \$365.4 million, or \$10.51 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 December 31, 2016.

After giving effect to the issue of 2,700,000 ordinary shares in this offering at a public offering price of \$57.50 per share, and after deducting the underwriting discount and estimated offering expenses, our as adjusted net tangible book value as of December 31, 2016 would have been \$515.6 million, or \$13.77 per share. This represents an immediate increase in as adjusted net tangible book value of \$3.26 per share to existing shareholders and an immediate dilution of \$43.73 per share to new investors. The following table illustrates this per share dilution:

Public offering price per share	\$ 57.50
Historical net tangible book value per share as of December 31, 2016	\$ 10.51
Increase in as adjusted net tangible book value per share attributable to new investors	3.26
As adjusted net tangible book value per share after this offering	13.77
Dilution per share to new investors participating in this offering	\$ 43.73

If the underwriter fully exercises its option to subscribe for additional shares, as adjusted net tangible book value after this offering would increase to \$14.22 per share, and there would be an immediate dilution of \$43.28 per share to new investors.

To the extent that outstanding options are exercised, new investors will experience further dilution. 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 outstanding share information in the table above is based on the number of ordinary shares outstanding as of December 31, 2016 and excludes the following, in each case as of such date:

4,064,207 ordinary shares issuable upon the exercise of outstanding options having a weighted-average exercise price of approximately \$27.19 per share; and

2,284,938 ordinary shares reserved for issuance pursuant to future awards under our Amended and Restated 2012 Long Term Incentive Plan.

Table of Contents

MATERIAL UNITED STATES FEDERAL INCOME TAX CONSEQUENCES TO U.S. HOLDERS

The following discussion describes the material U.S. federal income tax consequences to U.S. Holders (as defined below) under present law of an investment in our ordinary shares. The effects of any applicable state or local laws, or other U.S. federal tax laws such as estate and gift tax laws, or the Medicare contribution tax, are not discussed. This summary applies only to investors who hold our ordinary shares as capital assets (generally, property held for investment) and who have the U.S. dollar as their functional currency. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended, or the Code, U.S. Treasury regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the IRS in effect as of the date of this offering. All of the foregoing authorities are subject to change, which change could apply retroactively and could affect the tax consequences described below.

The following discussion does not address all U.S. federal income tax consequences relevant to a holder's particular circumstances or to holders subject to particular rules, including:

U.S. expatriates and certain former citizens or long-term residents of the United States;

persons subject to the alternative minimum tax;

persons holding our ordinary shares as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;

banks, insurance companies, and other financial institutions;

real estate investment trusts or regulated investment companies;

brokers, dealers or traders in securities, commodities or currencies;

partnerships, S corporations, or other entities or arrangements treated as partnerships for U.S. federal income tax purposes;

tax-exempt organizations or governmental organizations;

persons who acquired our ordinary shares pursuant to the exercise of any employee share option or otherwise as compensation;

persons deemed to sell our ordinary shares under the constructive sale provisions of the Code; and

persons that own or are deemed to own ten percent (10%) or more of our ordinary shares.

U.S. HOLDERS ARE URGED TO CONSULT THEIR TAX ADVISORS ABOUT THE APPLICATION OF THE U.S. FEDERAL TAX RULES TO THEIR PARTICULAR CIRCUMSTANCES AS WELL AS THE U.S. STATE AND LOCAL AND FOREIGN TAX CONSEQUENCES TO THEM OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR ORDINARY SHARES.

For purposes of this discussion, a U.S. Holder is a beneficial owner of our ordinary shares who is for U.S. federal income tax purposes:

an individual who is a citizen or resident of the United States;

a corporation (or other entity treated as a corporation for U.S. federal income tax purposes) organized under the laws of the United States, any State or the District of Columbia;

an estate, the income of which is subject to U.S. federal income tax regardless of its source; or

a trust that (1) is subject to the supervision of a U.S. court and the control of one or more U.S. persons (within the meaning of Section 7701(a)(30) of the Code), or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

If you are a partner in a partnership (or other entity taxable as a partnership for U.S. federal income tax purposes) that holds our ordinary shares, your tax treatment generally will depend on your status and the

Table of Contents

activities of the partnership. Partnerships holding our ordinary shares and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences applicable to them.

Taxation of Dividends and Other Distributions on our Ordinary Shares

Subject to the PFIC rules discussed below, distributions to you with respect to our ordinary shares will be included in your gross income as a dividend when actually or constructively received to the extent that the distribution is paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). To the extent the amount of the distribution exceeds our current and accumulated earnings and profits, it will be treated first as a tax-free return of your tax basis in the ordinary shares, and to the extent the amount of the distribution exceeds your tax basis, the excess will be taxed as capital gain. We do not intend to calculate our earnings and profits under U.S. federal income tax principles. Therefore, a U.S. Holder should expect a distribution will generally be treated as a dividend even if that distribution would otherwise be treated as a non-taxable return of capital or as capital gain under the rules described above. The dividends will not be eligible for the dividends-received deduction allowed to corporations in respect of dividends received from other U.S. corporations.

Subject to certain limitations, including minimum holding period requirements, and provided we are not a PFIC in the taxable year in which a dividend is paid or in the preceding taxable year, dividends paid to non-corporate U.S. Holders may be qualified dividend income taxable at a maximum rate of 20%. As discussed below in Passive Foreign Investment Company, we do not believe we will be a PFIC for our current taxable year. You should consult your tax advisor regarding the availability of this preferential tax rate under your particular circumstances.

Dividends will generally constitute foreign source income for foreign tax credit limitation purposes. If the dividends are qualified dividend income (as discussed above), the amount of the dividend taken into account for purposes of calculating the foreign tax credit limitation will be limited to the gross amount of the dividend, multiplied by the reduced rate divided by the highest rate of tax normally applicable to dividends. The limitation on foreign taxes eligible for credit is calculated separately with respect to specific classes of income. For this purpose, dividends distributed by us with respect to our ordinary shares generally will constitute passive category income but could, in the case of certain U.S. Holders, constitute general category income. The rules with respect to the foreign tax credit are complex and you are urged to consult your tax advisor regarding the availability of the foreign tax credit under your particular circumstances.

Taxation of Disposition of our Ordinary Shares

Subject to the PFIC rules discussed below, you will recognize taxable gain or loss on any sale, exchange or other taxable disposition of an ordinary share equal to the difference between the amount realized (in U.S. dollars) on the disposition of the ordinary share and your tax basis (in U.S. dollars) in the ordinary share. The gain or loss will be capital gain or loss. If you are a non-corporate U.S. Holder, including an individual, who has held the ordinary share for more than one year, you generally will be eligible for reduced tax rates on a long-term capital gain. The deductibility of a capital loss is subject to limitations. Any such gain or loss you recognize generally will be treated as U.S. source income or loss.

Passive Foreign Investment Company

Based on the composition of our active and passive income, the value of our passive assets and the fair market value of the Company, we do not expect to be a PFIC for U.S. federal income tax purposes for our current taxable year ending on December 31, 2017. However, the application of the PFIC rules is subject to uncertainty in several respects, and we cannot assure you that the IRS will not take a contrary position. We also cannot assure holders that we will not

be a PFIC for U.S. federal income tax purposes for any future taxable year. A non-U.S. corporation is considered a PFIC for any taxable year if either:

at least 75% of its gross income for such taxable year is passive income (the gross income test), or

S-17

Table of Contents

at least 50% of the value of its assets (based on an average of the quarterly values of the assets during a taxable year) is attributable to assets that produce or are held for the production of passive income (the asset test).

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation in which we own, directly or indirectly, at least 25% (by value) of the stock of such corporation. Passive income generally includes dividends, interest, rents, royalties and capital gains, but generally excludes rents and royalties which are derived in the active conduct of a trade or business and which are received from a person other than a related person.

A separate determination must be made each taxable year as to whether we are a PFIC (after the close of each such taxable year). If we are a PFIC for any year during which you hold our ordinary shares, we generally will continue to be treated as a PFIC with respect to you for all succeeding years during which you hold our ordinary shares. However, if we cease to be a PFIC, you may avoid some of the adverse effects of the PFIC regime by making a deemed sale election with respect to our ordinary shares. If such election is made, you will be deemed to have sold our ordinary shares you hold at their fair market value, and any gain from such deemed sale would be subject to the excess distribution regime described in the following paragraph. After the deemed sale election, your ordinary shares with respect to which the deemed sale election was made would not be treated as shares in a PFIC and you would not be subject to the rules described below with respect to any excess distribution you receive from us or any gain from an actual sale or other disposition of the ordinary shares. **The rules dealing with deemed sale elections are very complex. You are strongly encouraged to consult your tax advisor as to the possibility and consequences of making a deemed sale election if such election becomes available to you.**

For each taxable year we are treated as a PFIC with respect to you, you will be subject to special tax rules with respect to any excess distribution you receive and any gain you realize from a sale or other disposition (including a pledge) of our ordinary shares, unless you make a mark-to-market election as discussed below. Distributions you receive in a taxable year that are greater than 125% of the average annual distributions you received during the shorter of the three preceding taxable years or your holding period for the ordinary shares will be treated as an excess distribution. Under these special tax rules, if you receive any excess distribution or realize any gain from a sale or other disposition of our ordinary shares:

the excess distribution or gain will be allocated ratably over your holding period for the ordinary shares,

the amount allocated to the current taxable year, and any taxable year before the first taxable year in which we were a PFIC, will be treated as ordinary income, and

the amount allocated to each other year will be subject to the highest tax rate in effect for that year and the interest charge generally applicable to underpayments of tax will be imposed on the resulting tax attributable to each such year.

The tax liability for amounts allocated to years before the year of disposition or excess distribution cannot be offset by any net operating losses for such years, and gains (but not losses) realized on the sale of our ordinary shares cannot be treated as capital, even if you hold the ordinary shares as capital assets.

If we are treated as a PFIC with respect to you for any taxable year, to the extent any of our subsidiaries are also PFICs, you will be deemed to own shares in such lower-tier PFICs that are directly or indirectly owned by us in the

proportion that the value of the ordinary shares you own bears to the value of all of our ordinary shares, and you may be subject to the excess distribution regime described in the preceding two paragraphs with respect to the shares of such lower-tier PFICs you would be deemed to own. You should consult your tax advisor regarding the application of the PFIC rules to any of our subsidiaries.

Alternatively, a U.S. Holder of marketable stock (as defined below) in a PFIC may make a mark-to-market election for such stock to elect out of the tax treatment discussed above. If you make a mark-to-market

Table of Contents

election for our ordinary shares, you will include in income for each year we are a PFIC, (*i.e.*, for each taxable year in which we meet the gross income test or asset test), an amount equal to the excess, if any, of the fair market value of our ordinary shares as of the close of your taxable year over your adjusted basis in such ordinary shares. You are allowed a deduction for the excess, if any, of the adjusted basis of the ordinary shares over their fair market value as of the close of the taxable year. However, deductions are allowable only to the extent of any net mark-to-market gains on the ordinary shares included in your income for prior taxable years. Amounts included in your income under a mark-to-market election, as well as gain on the actual sale or other disposition of the ordinary shares are treated as ordinary income. Ordinary loss treatment also applies to the deductible portion of any mark-to-market loss on the ordinary shares, as well as to any loss realized on the actual sale or disposition of the ordinary shares to the extent the amount of such loss does not exceed the net mark-to-market gains previously included for such ordinary shares. Your basis in the ordinary shares will be adjusted to reflect any such income or loss amounts. If you make a valid mark-to-market election, the tax rules that apply to distributions by corporations which are not PFICs would apply to distributions by us, except the lower applicable tax rate for qualified dividend income would not apply. If we cease to be a PFIC when you have a mark-to-market election in effect, gain or loss realized by you on the sale of our ordinary shares will be a capital gain or loss and taxed in the manner described above under Taxation of Dispositions of our Ordinary Shares.

The mark-to-market election is available only for marketable stock, which is stock that is traded in other than *de minimis* quantities on at least 15 days during each calendar quarter (regularly traded) on a qualified exchange or other market, as defined in applicable U.S. Treasury regulations. We expect our ordinary shares will continue to be listed on the NASDAQ and, accordingly, provided the ordinary shares are regularly traded, if you are a holder of ordinary shares, the mark-to-market election would be available to you if we are a PFIC. If any of our subsidiaries are or become PFICs, the mark-to-market election will not be available with respect to the shares of such subsidiaries that are treated as owned by you. Consequently, you could be subject to the PFIC rules with respect to income of the lower-tier PFICs the value of which already had been taken into account indirectly via mark-to-market adjustments.

In certain circumstances, a U.S. Holder of stock in a PFIC can make a qualified electing fund election to mitigate some of the adverse tax consequences of holding stock in a PFIC by including in income its share of the corporation's income on a current basis. However, we do not currently intend to prepare or provide the information that would enable you to make a qualified electing fund election.

Unless otherwise provided by the U.S. Treasury, each U.S. shareholder of a PFIC is required to file an annual report on IRS Form 8621 containing such information as the U.S. Treasury may require.

YOU ARE STRONGLY URGED TO CONSULT YOUR TAX ADVISOR REGARDING THE APPLICATION OF THE PFIC RULES TO YOUR INVESTMENT IN OUR ORDINARY SHARES.

Information Reporting and Backup Withholding

Dividend payments with respect to our ordinary shares and proceeds from the sale, exchange or redemption of ordinary shares may be subject to information reporting to the IRS and possible U.S. backup withholding. Backup withholding will not apply, however, to a U.S. Holder who furnishes a correct taxpayer identification number and makes any other required certification or who is otherwise exempt from backup withholding. U.S. Holders who are required to establish their exempt status generally must provide such certification on IRS Form W-9. U.S. Holders should consult their tax advisors regarding the application of the U.S. information reporting and backup withholding rules.

Backup withholding is not an additional tax. Amounts withheld as backup withholding may be credited against your U.S. federal income tax liability, and you may obtain a refund of any excess amounts withheld under the backup withholding rules by filing the appropriate claim for refund with the IRS and furnishing any required information.

Table of Contents

Additional Reporting Requirements

Certain U.S. Holders who are individuals are required to report information relating to an interest in our ordinary shares, subject to certain exceptions (including an exception for ordinary shares held in accounts maintained by certain financial institutions). U.S. Holders should consult their tax advisors regarding the effect, if any, of these rules on their ownership and disposition of our ordinary shares.

S-20

Table of Contents

CERTAIN IRISH TAX CONSEQUENCES RELATING TO THE HOLDING OF OUR ORDINARY SHARES

The information set out in these paragraphs is intended as a brief and general guide only based on current legislation and the current published practice of the Revenue Commissioners of Ireland. Legislative, administrative or judicial changes may modify the tax consequences described below. The statements do not constitute tax advice and are intended only as a general guide. This information relates only to the certain limited aspects of the Irish taxation treatment for the holders of our ordinary shares. It is intended to apply only to persons who are absolute beneficial holders of our ordinary shares and who hold them as investments (and not as securities to be realized in the course of a trade). The information set out below may not apply to certain holders of our ordinary shares such as dealers in securities, insurance companies and those holders who have (or are deemed to have) acquired their ordinary shares by virtue of an office or employment. Such persons may be subject to special rules. This summary is not exhaustive and shareholders should consult their own tax advisers as to the tax consequences in Ireland, or other relevant jurisdictions where we operate, including the acquisition, ownership and disposition of ordinary shares.

Stamp Duty

Irish stamp duty may be payable in respect of transfers of our ordinary shares at the rate of 1% of the higher of the price paid or the market value of the shares acquired.

Shares Held Through DTC

Transfers of our ordinary shares from a seller who holds shares through DTC to a buyer who holds the acquired shares through DTC should not be subject to Irish stamp duty.

Shares Held Outside of DTC or Transferred Into or Out of DTC

A transfer of our ordinary shares (i) by a seller who holds shares outside of DTC to any buyer, or (ii) by a seller who holds the shares through DTC to a buyer who holds the acquired shares outside of DTC, may be subject to Irish stamp duty (currently at the rate of 1% of the price paid or the market value of the shares acquired, if higher) payable by the buyer.

A shareholder who holds our ordinary shares outside of DTC may transfer those shares into DTC (or vice versa) without giving rise to Irish stamp duty provided there is no change in the ultimate beneficial ownership of the shares as a result of the transfer and, at the time of the transfer into DTC (or out of DTC), there is no agreement in place for the sale of the shares to a third party by a beneficial owner. In order to benefit from this exemption from Irish stamp duty, the seller must confirm to us that there is no change in the ultimate beneficial ownership of the shares as a result of the transfer and there is no agreement in place for the sale of the shares by the beneficial owner to a third party.

Payment of Stamp Duty

A written instrument of transfer is required under Irish law in order for a transfer of the legal ownership of shares to be registered on our official share register. Such instruments of transfer may be subject to Irish stamp duty, which must be paid prior to the official share register being updated. A holder of ordinary shares who holds shares through DTC is not the legal owner of such shares (instead, the depository (for example, Cede & Co., as nominee for DTC) is holder of record of such shares). Accordingly, a transfer of shares from a person who holds such shares through DTC to a person who also holds such shares through DTC will not be registered in our official share register, i.e., the nominee of the depository will remain the record holder of such shares.

To the extent that stamp duty is due but has not been paid, we may, in our absolute discretion, pay (or cause one of our subsidiaries to pay) the outstanding stamp duty in respect of a transfer of shares. Our Articles of Association provide that, in the event of any such payment, we (i) may seek reimbursement from the transferee, (ii) may set-off the amount of the stamp duty against future dividends payable to the transferee, and (iii) will have a lien against the ordinary shares on which we (or one of our subsidiaries) have paid stamp duty.

S-21

Table of Contents

Irish Tax on Capital Gains

Disposal of Prothena ordinary shares.

A liability to Irish tax on capital gains on a disposal of our ordinary shares depends on the individual circumstances of each shareholder.

(i) Non-Irish resident / ordinarily resident shareholders:

Shareholders (individual or corporate) should not be subject to Irish tax on capital gains on a disposal of our ordinary shares if such holders are neither resident nor, in the case of individuals only, ordinarily resident in Ireland and do not hold such shares in connection with a trade carried on by such holder in Ireland through a branch or agency.

(ii) Irish resident shareholders:

Shareholders who are resident or, in the case of individuals only, ordinarily resident in Ireland for tax purposes, may be subject to Irish tax on capital gains at the rate of 33% if they dispose of our ordinary shares. Shareholders falling into this category should consult their own tax advisers as to the tax consequences of such a disposal.

Dividends

We do not currently intend to pay dividends to our shareholders. A payment of a dividend by an Irish resident entity is subject to dividend withholding tax at the current rate of 20% (subject to applicable exemptions).

Capital Acquisitions Tax

Irish capital acquisitions tax, or CAT, is comprised of gift tax and inheritance tax. CAT could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares are regarded as property situated in Ireland as our share register must be held in Ireland. The person who receives the gift or inheritance has primary liability for CAT. CAT is levied at a rate of 33% above certain tax-free thresholds. The appropriate tax-free threshold is dependent upon (i) the relationship between the donor and the donee and (ii) the aggregation of the values of previous gifts and inheritances received by the donee from persons within the same category of relationship for CAT purposes. Gifts and inheritances passing between spouses are exempt from CAT.

Table of Contents

DESCRIPTION OF SHARE CAPITAL

The following description of our share capital is not complete and may not contain all the information you should consider before investing in our share capital. This description is summarized from, and qualified in its entirety by reference to, our Memorandum and Articles of Association, which has been publicly filed with the SEC. See [Where You Can Find More Information](#).

The following description of our ordinary shares and Euro Deferred Shares is a summary. This summary does not purport to be complete and is qualified in its entirety by reference to the Irish Companies Act 2014, or the Companies Act, and the complete text of our Memorandum and Articles of Association. You should read those laws and documents carefully.

For the avoidance of any doubt, the ordinary shares are the subject of this registration statement. The Euro Deferred Shares are not listed on any stock exchange and are not the subject of any registration.

Capital Structure

Issued Share Capital

As of December 31, 2016, our issued share capital was 34,752,116 ordinary shares. We have no Euro Deferred Shares in issue. Our ordinary shares are listed on The NASDAQ Global Select Market, or NASDAQ, under the symbol PRTA.

Authorized Share Capital

The authorized share capital of the Company is \$1,000,000 and 220,000 consisting of 100,000,000 ordinary shares with a par value of \$0.01 per share and 10,000 Euro Deferred Shares with a par value of 22 per share. We may issue shares subject to the maximum authorized share capital contained in our Articles of Association. The authorized share capital may be increased or reduced by a resolution approved by a simple majority of the votes cast at a general meeting of our shareholders (referred to under Irish law as an ordinary resolution). The shares comprising our authorized share capital may be divided into shares of such nominal value as the resolution shall prescribe. As a matter of Irish law, the directors of a company may issue new ordinary shares or Euro Deferred Shares without shareholder approval once authorized to do so by the Articles of Association or by an ordinary resolution adopted by the shareholders at a general meeting. The authorization may be granted for a maximum period of five years, at which point it must be renewed by the shareholders by an ordinary resolution.

Our Articles of Association authorize our board of directors, or our Board, to issue new ordinary shares and Euro Deferred Shares for cash without shareholder approval for a period of five years from the date of adoption of our Articles of Association, which adoption was on September 26, 2012. As a result, our shareholders must renew this authorization by an ordinary resolution by September 26, 2017.

The rights and restrictions to which our ordinary shares and Euro Deferred Shares are subject are prescribed in our Articles of Association. We may, by ordinary resolution and without obtaining any vote or consent of the holders of any class or series of shares, unless expressly provided by the terms of that class or series of shares, provide from time to time for the issuance of other classes or series of shares and to establish the characteristics of each class or series, including the number of shares, designations, relative voting rights, dividend rights, liquidation and other rights, redemption, repurchase or exchange rights and any other preferences and relative, participating, optional or other rights and limitations not inconsistent with applicable law.

Irish law does not recognize fractional shares held of record. Accordingly, our Articles of Association do not provide for the issuance of fractional shares of the Company, and the official Irish share register of the Company will not reflect any fractional shares. Whenever as a result of an issuance, alteration, reorganization,

S-23

Table of Contents

consolidation, division, or subdivision of the share capital of the Company would result in any shareholder becoming entitled to fractions of a share, no such fractions shall be issued or delivered to any shareholder. All such fractions of a share will be aggregated into whole shares and sold in the open market at prevailing market prices and the aggregate cash proceeds from such sale (net of tax, commissions, costs and other expenses) shall be distributed on a pro rata basis, rounding down to the nearest cent, to each shareholder who would otherwise have been entitled to receive fractions of a share.

Preemption Rights, Share Warrants and Share Options

Under Irish law, certain statutory preemption rights apply automatically in favor of shareholders where shares are to be issued for cash. However, we have opted out of these preemption rights in our Articles of Association as permitted under Irish law. Because Irish law requires this opt-out to be renewed every five years by a resolution approved by not less than 75% of the votes cast at a general meeting of our shareholders (referred to under Irish law as a special resolution), our Articles of Association provide that this opt-out must be so renewed. As a result, our shareholders must renew this authorization by a special resolution by September 26, 2017.

If the opt-out is not renewed, shares issued for cash must be offered to existing shareholders of the Company on a *pro rata* basis to their existing shareholding before the shares may be issued to any new shareholders. The statutory preemption rights do not apply (i) where shares are issued for non-cash consideration (such as in a share-for-share acquisition), (ii) to the issue of non-equity shares (that is, shares that have the right to participate only up to a specified amount in any income or capital distribution) or (iii) where shares are issued pursuant to an employee share option or similar equity plan.

Our Articles of Association provide that, subject to any shareholder approval requirement under any laws, regulations or the rules of any stock exchange to which we are subject, our Board is authorized, from time to time, in its discretion, to grant such persons, for such periods and upon such terms as it deems advisable, options to purchase such number of shares of any class or classes or of any series of any class as our Board may deem advisable, and to cause warrants or other appropriate instruments evidencing such options to be issued. The Companies Act provide that directors may issue share warrants or options without shareholder approval once authorized to do so by the Articles of Association or an ordinary resolution of shareholders. We are subject to the rules of NASDAQ and the U.S. Internal Revenue Code of 1986, as amended, which require shareholder approval of certain equity plans and share issuances. Our Board may issue shares upon exercise of warrants or options without shareholder approval or authorization (up to the relevant authorized share capital limit).

Dividends

Under Irish law, dividends and distributions may only be made from distributable reserves. Distributable reserves generally means accumulated, realized profits, so far as not previously utilized by distribution or capitalization, less accumulated, realized losses, so far as not previously written off in a reduction or re-organization of capital duly made. In addition, no distribution or dividend may be made unless our net assets are equal to, or in excess of, the aggregate of our called up share capital plus undistributable reserves and the distribution does not reduce our net assets below such aggregate. Undistributable reserves include the undenominated capital, the share premium account, the capital redemption reserve fund and the amount by which our accumulated unrealized profits, so far as not previously utilized by any capitalization, exceed the Company's accumulated unrealized losses, so far as not previously written off in a reduction or reorganization of capital.

The determination as to whether or not we have sufficient distributable reserves to fund a dividend must be made by reference to the relevant financial statements of the Company. The relevant financial statements are either the last set

of unconsolidated annual audited financial statements or other financial statements properly prepared in accordance with the Companies Act, which give a true and fair view of our unconsolidated financial position and accord with accepted accounting practice. The relevant financial statements must be filed in the Companies Registration Office (the official public registry for companies in Ireland).

S-24

Table of Contents

Our Articles of Association authorize the Board to declare dividends without shareholder approval to the extent they appear justified by profits lawfully available for distribution. Our Board may also recommend a dividend to be approved and declared by the shareholders at a general meeting. Our Board may direct that the payment be made by distribution of assets, shares or cash, and no dividend issued may exceed the amount recommended by the directors. Dividends may be declared and paid in the form of cash or non-cash assets and may be paid in dollars or any other currency.

Our Board may deduct from any dividend payable to any shareholder any amounts payable by such shareholder to the Company in relation to the shares of the Company.

The Board may also authorize the Company to issue shares with preferred rights to participate in dividends declared by the Company from time to time, as determined by ordinary resolution. The holders of preferred shares may, depending on their terms, rank senior to our ordinary shares in terms of dividend rights and or be entitled to claim arrears of a declared dividend out of subsequently declared dividends in priority to ordinary shareholders.

Share Repurchases, Redemptions and Conversions

Overview

Our Articles of Association provide that any ordinary share that we have agreed to acquire shall be deemed to be a redeemable share. Accordingly, for Irish law purposes, the repurchase of ordinary shares by us may technically be effected as a redemption of those shares as described below under *Description of Share Capital Repurchases and Redemptions by Prothena*. If our Articles of Association did not contain such provision, repurchases by us would be subject to many of the same rules that apply to purchases of our ordinary shares by subsidiaries described below under *Description of Share Capital Purchases by Subsidiaries of Prothena*, including the shareholder approval requirements described below, and the requirement that any overseas market purchases be effected on a recognized stock exchange, which, for purposes of the Companies Act, includes NASDAQ. Neither Irish law nor any of our constituent documents places limitations on the right of non-resident or foreign owners to vote or hold our ordinary shares. Except where otherwise noted, references in this Prospectus Supplement to repurchasing or buying back our ordinary shares refer to the redemption of ordinary shares by us or the purchase of our ordinary shares by one of our subsidiaries, in each case in accordance with our Articles of Association and Irish company law as described below.

Repurchases and Redemptions by Prothena

Under Irish law, a company may issue redeemable shares and redeem them out of distributable reserves or the proceeds of a new issue of shares for that purpose. Please see also *Description of Share Capital Dividends*. We may only issue redeemable shares if the nominal value of the issued share capital that is not redeemable is not less than 10% of the nominal value of our total issued share capital. All redeemable shares must also be fully-paid and the terms of redemption of the shares must provide for payment on redemption. Redeemable shares may, upon redemption, be cancelled or held in treasury. Based on the provisions of our Articles of Association, shareholder approval will not be required to redeem our shares.

We may also be given an additional general authority for overseas market purchases of our ordinary shares by way of ordinary resolution, which would take effect on the same terms and be subject to the same conditions as applicable to purchases by our subsidiaries as described below.

Repurchased and redeemed shares may be cancelled or held as treasury shares. The nominal value of treasury shares held by us at any time must not exceed 10% of the nominal value of our issued share capital. We may not exercise any

voting rights in respect of any shares held as treasury shares. Treasury shares may be cancelled by us or re-issued subject to certain conditions.

S-25

Table of Contents

Purchases by Subsidiaries of Prothena

Under Irish law, an Irish or non-Irish subsidiary of the Company may purchase our shares by way of an: (i) overseas market purchase; or (ii) off-market purchase. For one of our subsidiaries to make overseas market purchases of our ordinary shares, our shareholders must provide general authorization for such purchase by way of ordinary resolution. However, as long as this general authority has been granted, no specific shareholder authority for a particular overseas market purchase by a subsidiary of our ordinary shares is required. For a purchase by one of our subsidiaries off-market, the proposed purchase contract must be authorized by special resolution of our shareholders before the contract is entered into. The person whose ordinary shares are to be bought back cannot vote in favor of the special resolution and, for at least 21 days prior to the special resolution being passed, the purchase contract must be on display or must be available for inspection by our shareholders at our registered office.

In order for one of our subsidiaries to make overseas market purchases of our shares, such shares must be purchased on a recognized stock exchange. NASDAQ, on which our ordinary shares are listed, is specified as a recognized stock exchange for this purpose in accordance with Irish law.

The number of shares held by our subsidiaries at any time will count as treasury shares and will be included in any calculation of the permitted treasury share threshold of 10% of the nominal value of our issued share capital. While a subsidiary holds our shares, it cannot exercise any voting rights in respect of those shares. The acquisition of our ordinary shares by a subsidiary must be funded out of distributable reserves of the subsidiary.

Lien on Shares, Calls on Shares and Forfeiture of Shares

Our Articles of Association provide that we have a first and paramount lien on every share that is not a fully paid up share for all amounts payable at a fixed time or called in respect of that share. Subject to the terms of their allotment, directors may call for any unpaid amounts in respect of any shares to be paid, and if payment is not made, the shares may be forfeited. These provisions are standard inclusions in the Articles of Association of an Irish public company limited by shares such as Prothena and are only applicable to our shares that have not been fully paid up. Irish stamp duty may be payable in respect of transfers of our ordinary shares at the rate of 1%.

Consolidation and Division; Subdivision

Under our Articles of Association, we may, by ordinary resolution, consolidate and divide all or any of our share capital into shares of larger nominal value than our existing shares or subdivide our shares into smaller amounts than are fixed by our Articles of Association.

Reduction of Share Capital

We may, by ordinary resolution, reduce our authorized share capital in any way. We also may, by special resolution and subject to confirmation by the Irish High Court, reduce or cancel our issued share capital in any manner permitted by the Companies Act.

Annual Meetings of Shareholders

Under Irish company law, we are required to hold annual general meetings at intervals of no more than 15 months from the previous annual general meeting, provided that an annual general meeting is held in each calendar year following the first annual general meeting and no more than nine months after our fiscal year-end. Subject to compliance with the Companies Act, any of our annual general meetings may be held outside Ireland. Notice of an

annual general meeting must be given to all of our shareholders and to our auditors. Our Articles of Association provide for a minimum notice period of 21 days notice, which is the minimum permitted by the Companies Act.

S-26

Table of Contents

The only matters which must, as a matter of Irish company law, be transacted at the Company's annual general meeting are the consideration of the statutory financial statements and report of the directors, the report of the auditors on those statements and that report, the review by the shareholders of the Company's affairs, the election and re-election of directors in accordance with the Company's Articles of Association, the declaration of a dividend (if any), the appointment or reappointment of the auditors and the fixing of the auditor's remuneration (or delegation of same). If no resolution is made in respect of the reappointment of an existing auditor at an annual general meeting, the existing auditor will be deemed to have continued in office.

Extraordinary General Meetings of Shareholders

Extraordinary general meetings of the Company may be convened by (i) our Board, (ii) on requisition of our shareholders holding not less than 10% of the paid up share capital of our carrying voting rights, (iii) shareholders of the Company holding not less than 50% of the paid up share capital, (iv) on requisition of our auditors or (v) in exceptional cases, by order of the Irish High Court. Extraordinary general meetings are generally held for the purpose of approving shareholder resolutions as may be required from time to time. At any extraordinary general meeting only such business shall be conducted as is set forth in the notice thereof.

Notice of an extraordinary general meeting must be given to all of our shareholders and to our auditors. Under Irish law and our Articles of Association, the minimum notice periods are 21 days' notice in writing for an extraordinary general meeting to approve a special resolution and 14 days' notice in writing for any other extraordinary general meeting.

In the case of an extraordinary general meeting convened by the requisition of our shareholders under part (ii) above, the proposed purpose of the meeting must be set out in the requisition notice. Upon receipt of any such valid requisition notice, our Board has 21 days to convene a meeting of our shareholders to vote on the matters set out in the requisition notice. This meeting must be held within two months of the receipt of the requisition notice. If our Board does not convene the meeting within such 21-day period, the requisitioning shareholders, or any of them representing more than one half of the total voting rights of all of them, may themselves convene a meeting, which meeting must be held within three months of our receipt of the requisition notice.

In the case of an extraordinary general meeting convened by our shareholders under part (iii) above, the meeting must be convened in the same manner as near as possible as that in which meetings are convened by the Board.

If our Board becomes aware that our net assets are not greater than half of the amount of our called-up share capital, it must convene an extraordinary general meeting of our shareholders not later than 28 days from the date that they learn of this fact to consider how to address the situation.

Quorum for General Meetings

Our Articles of Association provide that no business shall be transacted at any general meeting unless a quorum is present. One or more of our shareholders present in person or by proxy holding not less than one-half of our issued and outstanding shares entitled to vote at the meeting in question constitute a quorum.

Voting

Our Articles of Association provide that our Board or chairman may determine the manner in which the poll is to be taken and the manner in which the votes are to be counted.

Each Company shareholder is entitled to one vote for each ordinary share that he or she holds as of the record date for the meeting. Voting rights may be exercised by shareholders registered in our share register as of the record date for the meeting or by a duly appointed proxy, which proxy need not be a Company shareholder. Where interests in shares are held by a nominee trust company, such company may exercise the rights of the beneficial holders on their behalf as their proxy. All proxies must be appointed in the manner prescribed by our Articles of Association, which permit shareholders to notify us of their proxy appointments electronically in such manner as may be approved by our Board.

S-27

Table of Contents

In accordance with our Articles of Association, we may from time to time be authorized by ordinary resolution to issue preferred shares. These preferred shares may have such voting rights as may be specified in the terms of such preferred shares (e.g., they may carry more votes per share than ordinary shares or may entitle their holders to a class vote on such matters as may be specified in the terms of the preferred shares). Treasury shares or our shares that are held by our subsidiaries are not entitled to be voted at general meetings of shareholders.

Irish law requires special resolutions of our shareholders at a general meeting to approve certain matters. Examples of matters requiring special resolutions include:

amending the objects or our Memorandum of Association;

amending our Articles of Association;

approving a change of name of Prothena;

authorizing the entering into of a guarantee or provision of security in connection with a loan, quasi loan or credit transaction to a director or connected person;

opting out of preemption rights on the issuance of new shares;

re-registration of Prothena from a public limited company to a private company;

variation of class rights attaching to classes of shares (where the Articles of Association do not provide otherwise);

purchase of our shares off-market;

reduction of issued share capital;

sanctioning a compromise/scheme of arrangement with creditors or shareholders;

resolving that we be wound up by the Irish courts;

resolving in favor of a shareholders voluntary winding-up; and

setting the re-issue price of treasury shares.

Variation of Rights Attaching to a Class or Series of Shares

Under our Articles of Association and the Companies Act, any variation of class rights attaching to our issued shares must be approved by a special resolution of our shareholders of the affected class or with the consent in writing of the holders of three-quarters of all the votes of that class of shares.

The provisions of our Articles of Association relating to general meetings apply to general meetings of the holders of any class of our shares except that the necessary quorum is determined in reference to the shares of the holders of the class. Accordingly, for general meetings of holders of a particular class of our shares, a quorum consists of the holders present in person or by proxy representing at least one-half of the issued shares of the class.

Inspection of Books and Records

Under Irish law, shareholders have the right to: (i) receive a copy of our Memorandum and Articles of Association; (ii) inspect and obtain copies of the minutes of our general meetings and resolutions; (iii) inspect and receive a copy of the register of shareholders, register of directors and secretaries, register of directors' interests; (iv) inspect copies of directors' service contracts; (v) inspect copies of instruments creating charge; (vi) receive copies of the statutory financial statements and directors' and auditors' reports which have previously been sent to shareholders prior to an annual general meeting; and (vii) receive copies of the statutory financial statements and directors' and auditors' reports of any of our subsidiaries which have previously been

Table of Contents

sent to the shareholders of the subsidiaries prior to an annual general meeting for the preceding ten years. Our auditors also have the right of access, at all reasonable times, to the accounting records of the Company. The auditors' report must be circulated to the shareholders with our financial statements prepared in accordance with Irish law 21 days (not including the day of mailing or the day of the meeting) before the annual general meeting and must be laid before the shareholders at our annual general meeting.

Acquisitions

The Company may be acquired in a number of ways, including:

a court-approved scheme of arrangement under the Companies Act. A scheme of arrangement with shareholders requires a court order from the Irish High Court and the approval of a majority in number representing 75% in value of the shareholders present and voting in person or by proxy at a meeting called to approve the scheme;

through a tender or takeover offer by a third party for all of our shares. Where the holders of 80% or more of our shares have accepted an offer for their shares in Prothena, the remaining shareholders may also be statutorily required to transfer their shares. If the bidder does not exercise its squeeze out right, then the non-accepting shareholders also have a statutory right to require the bidder to acquire their shares on the same terms; and

by way of a merger with an EU-incorporated company under the EU Cross-Border Mergers Directive 2005/56/EC. Such a merger must be approved by a special resolution. If we are being merged with another EU company under the EU Cross-Border Mergers Directive 2005/56/EC and the consideration payable to our shareholders is not all in the form of cash, our shareholders may be entitled to require their shares to be acquired at fair value.

Irish law does not generally require shareholder approval for a sale, lease or exchange of all or substantially all of a company's property and assets.

Appraisal Rights

Generally, under Irish law, shareholders of an Irish company do not have dissenters' or appraisal rights. Under the European Communities (Cross-Border Mergers) Regulations 2008 governing the merger of an Irish company limited by shares, such as Prothena, and a company incorporated in the European Economic Area (the European Economic Area includes all member states of the European Union and Norway, Iceland and Liechtenstein), a shareholder (i) who voted against the special resolution approving the merger, or (ii) of a company in which 90% of the shares are held by the other party to the merger, has the right to request that the company acquire its shares for cash at a price determined in accordance with the share exchange ratio set out in the merger agreement.

Disclosure of Interests in Shares

Under the Companies Act, our shareholders must notify us if, as a result of a transaction, the shareholder will become interested in three percent or more of the Prothena voting shares, or if as a result of a transaction a shareholder who was interested in more than three percent of Prothena voting shares ceases to be so interested. Where a shareholder is

interested in more than three percent of Prothena voting shares, the shareholder must notify us of any alteration of his or her interest that brings his or her total holding through the nearest whole percentage number, whether an increase or a reduction. The relevant percentage figure is calculated by reference to the aggregate nominal value of the voting shares in which the shareholder is interested as a proportion of the entire nominal value of our issued share capital (or any such class of share capital in issue). Where the percentage level of the shareholder's interest does not amount to a whole percentage, this figure may be rounded down to the next whole number. We must be notified within five business days of the transaction or alteration of the shareholder's interests that gave rise to the notification requirement. If a shareholder fails to comply with these notification requirements, the shareholder's rights in respect of any our shares it holds will not be enforceable, either directly or indirectly. However, such person may apply to the court to have the rights attaching to such shares reinstated.

S-29

Table of Contents

In addition to these disclosure requirements, we, under the Companies Act, may, by notice in writing, require a person whom we know or have reasonable cause to believe to be, or at any time during the three years immediately preceding the date on which such notice is issued to have been, interested in shares comprised in our relevant share capital: (i) to indicate whether or not it is the case; and (ii) where such person holds or has during that time held an interest in our shares, to provide additional information, including the person's own past or present interests in our shares. If the recipient of the notice fails to respond within the reasonable time period specified in the notice, we may apply to court for an order directing that the affected shares be subject to certain restrictions, as prescribed by the Companies Act, as follows:

any transfer of those shares or, in the case of unissued shares, any transfer of the right to be issued with shares and any issue of shares, shall be void;

no voting rights shall be exercisable in respect of those shares;

no further shares shall be issued in right of those shares or in pursuance of any offer made to the holder of those shares; and

no payment shall be made of any sums due from Prothena on those shares, whether in respect of capital or otherwise.

The court may also order that shares subject to any of these restrictions be sold with the restrictions terminating upon the completion of the sale.

In the event we are in an offer period pursuant to the Irish Takeover Rules (as defined below), accelerated disclosure provisions apply for persons holding an interest in our securities of one percent or more.

Anti-Takeover Provisions

Irish Takeover Rules and Substantial Acquisition Rules

A transaction in which a third party seeks to acquire 30% or more of Prothena voting rights and any other acquisitions of our securities are governed by the Irish Takeover Panel Act 1997 and the Irish Takeover Rules made thereunder, which are referred to in this Prospectus Supplement as the Irish Takeover Rules, and are regulated by the Irish Takeover Panel. The General Principles of the Irish Takeover Rules and certain important aspects of the Irish Takeover Rules are described below.

General Principles

The Irish Takeover Rules are built on the following General Principles which will apply to any transaction regulated by the Irish Takeover Panel:

in the event of an offer, all holders of securities of the target company must be afforded equivalent treatment and, if a person acquires control of a company, the other holders of securities must be protected;

the holders of securities in the target company must have sufficient time and information to enable them to reach a properly informed decision on the offer; where it advises the holders of securities, the board of directors of the target company must give its views on the effects of the implementation of the offer on employment, employment conditions and the locations of the target company's place of business;

a target company's board of directors must act in the interests of the company as a whole and must not deny the holders of securities the opportunity to decide on the merits of the offer;

false markets must not be created in the securities of the target company, the bidder or any other company concerned by the offer in such a way that the rise or fall of the prices of the securities becomes artificial and the normal functioning of the markets is distorted;

S-30

Table of Contents

a bidder can only announce an offer after ensuring that he or she can fulfill in full any cash consideration, if such is offered, and after taking all reasonable measures to secure the implementation of any other type of consideration;

a target company may not be hindered in the conduct of its affairs for longer than is reasonable by an offer for its securities; and

a substantial acquisition of securities (whether such acquisition is to be effected by one transaction or a series of transactions) shall take place only at an acceptable speed and shall be subject to adequate and timely disclosure.

Mandatory Bid

Under certain circumstances, a person who acquires our shares, or other voting securities, may be required under the Irish Takeover Rules to make a mandatory cash offer for remaining outstanding Prothena voting securities at a price not less than the highest price paid for the securities by the acquiror, or any parties acting in concert with the acquiror, during the previous 12 months. This mandatory bid requirement is triggered if an acquisition of securities would increase the aggregate holding of an acquiror, including the holdings of any parties acting in concert with the acquiror, to securities representing 30% or more of Prothena voting rights, unless the Irish Takeover Panel otherwise consents. An acquisition of securities by a person holding, together with its concert parties, securities representing between 30% and 50% of Prothena voting rights would also trigger the mandatory bid requirement if, after giving effect to the acquisition, the percentage of the voting rights held by that person (together with its concert parties) would increase by 0.05% within a 12-month period. Any person (excluding any parties acting in concert with the holder) holding securities representing more than 50% of the voting rights of a company is not subject to these mandatory offer requirements in purchasing additional securities.

Voluntary Bid; Requirements to Make a Cash Offer and Minimum Price Requirements

If a person makes a voluntary offer to acquire our outstanding ordinary shares, the offer price must not be less than the highest price paid for our ordinary shares by the bidder or its concert parties during the three-month period prior to the commencement of the offer period. The Irish Takeover Panel has the power to extend the look back period to 12 months if the Irish Takeover Panel, taking into account the General Principles, believes it is appropriate to do so.

If the bidder or any of its concert parties has acquired our ordinary shares (i) during the period of 12 months prior to the commencement of the offer period that represent more than 10% of our total ordinary shares or (ii) at any time after the commencement of the offer period, the offer must be in cash (or accompanied by a full cash alternative) and the price per our ordinary shares must not be less than the highest price paid by the bidder or its concert parties during, in the case of (i), the 12-month period prior to the commencement of the offer period or, in the case of (ii), the offer period. The Irish Takeover Panel may apply this rule to a bidder who, together with its concert parties, has acquired less than 10% of our total ordinary shares in the 12-month period prior to the commencement of the offer period if the Irish Takeover Panel, taking into account the General Principles, considers it just and proper to do so. An offer period will generally commence from the date of the first announcement of the offer or proposed offer.

Substantial Acquisition Rules

The Irish Takeover Rules also contain rules governing substantial acquisitions of shares and other voting securities which restrict the speed at which a person may increase his or her holding of shares and rights over shares to an

aggregate of between 15% and 30% of the Prothena voting rights. Except in certain circumstances, an acquisition or series of acquisitions of shares or rights over shares representing 10% or more of the Prothena voting rights is prohibited, if such acquisition(s), when aggregated with shares or rights already held, would result in the acquirer holding 15% or more but less than 30% of the Prothena voting rights and such acquisitions are made within a period of seven days. These rules also require accelerated disclosure of acquisitions of shares or rights over shares relating to such holdings.

S-31

Table of Contents

Frustrating Action

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. Exceptions to this prohibition are available where:

the action is approved by our shareholders at a general meeting; or

the Irish Takeover Panel has given its consent, where:

it is satisfied the action would not constitute frustrating action;

our shareholders holding more than 50% of the voting rights state in writing that they approve the proposed action and would vote in favor of it at a general meeting;

the action is taken in accordance with a contract entered into prior to the announcement of the offer (or any earlier time at which our Board considered the offer to be imminent); or

the decision to take such action was made before the announcement of the offer and either has been at least partially implemented or is in the ordinary course of business.

Certain other provisions of Irish law or our Articles of Association may be considered to have antitakeover effects, including advance notice requirements for director nominations and other shareholder proposals, as well those described under the following captions: Description of Share Capital Capital Structure Authorized Share Capital (regarding issuance of preferred shares) Description of Share Capital Preemption Rights, Share Warrants and Share Options, Description of Share Capital Disclosure of Interests in Shares and Description of Share Capital Capital Corporate Governance.

Corporate Governance

Our Articles of Association allocate authority over the day-to-day management of Prothena to our Board. Our Board may then delegate the management of Prothena to committees of the Board (consisting of one or more members of the Board) or executives, but regardless, our Board remains responsible, as a matter of Irish law, for the proper management of the affairs of Prothena. Committees may meet and adjourn as they determine proper. A vote at any committee meeting will be determined by a majority of votes of the members present.

The Board has a standing audit committee, a compensation committee and a nominating and corporate governance committee, with each committee comprised solely of independent directors, as prescribed by the NASDAQ listing

standards and SEC rules and regulations. We have adopted corporate governance guidelines, as well as a code of conduct and other compliance policies.

The Companies Act provide for a minimum of two directors. Our Articles of Association provide that the Board may determine the size of the Board from time to time.

Our Articles of Association provide that at least one-third of the directors serving on the Board shall come up for re-election at a given annual general meeting, and that directors must come up for re-election at the third annual general meeting subsequent to their appointment or reappointment to the Board. Except as otherwise provided by law, vacancies on the Board may be filled only by ordinary resolution or the affirmative vote of a majority of the remaining directors. A director elected by the Board to fill a vacancy shall serve until the subsequent annual general meeting and until such director's successor is elected and qualified. At each annual general meeting of shareholders, the successors to directors whose terms will then expire will be elected to serve from the time of election and qualification until the third subsequent annual general meeting of shareholders.

Table of Contents

Under the Companies Act and notwithstanding anything contained in the Articles of Association or in any agreement between us and a director, the shareholders may, by an ordinary resolution, remove a director from office before the expiration of his or her term at a meeting held on no less than 28 days' notice and at which the director is entitled to be heard. The power of removal is without prejudice to any claim for damages for breach of contract (e.g. employment contract) that the director may have against us in respect of his removal.

Our Articles of Association provide that the Board may fill any vacancy occurring on the Board. If the Board fills a vacancy, the director's term expires at the next annual general meeting. A vacancy on the Board created by the removal of a director may be filled by the shareholders at the meeting at which such director is removed and, in the absence of such election or appointment, the remaining directors may fill the vacancy.

Legal Name; Formation; Fiscal Year; Registered Office

Prothena Corporation plc was formed under the laws of Ireland on September 26, 2012 as a private limited company, under the name Neotope Corporation Limited (registration number 518146), and reregistered as a public limited company and changed its name to Neotope Corporation plc on October 25, 2012. On November 1, 2012, our shareholders resolved, by way of special resolution, to change the name of the company to Prothena Corporation plc, and this was approved by the Irish Registrar of Companies on November 7, 2012. Our fiscal year ends on December 31st and our registered address is Adelphi Plaza, Upper George's Street, Dún Laoghaire, Co. Dublin, A96 T927, Ireland.

Duration; Dissolution; Rights upon Liquidation

Our duration is unlimited. We may be dissolved and wound up at any time by way of a shareholders' voluntary winding up or a creditors' winding up. In the case of a shareholders' voluntary winding up, a special resolution of shareholders is required. We may also be dissolved by way of court order on the application of a creditor, or by the Companies Registration Office as an enforcement measure where we have failed to file certain returns.

If our Articles of Association contain no specific provisions in respect of a dissolution or winding up, then, subject to the priorities of any creditors, the assets will be distributed to our shareholders in proportion to the paid-up nominal value of the shares held. Our Articles of Association provide that our ordinary shareholders are entitled to participate *pro rata* in a winding up.

Uncertificated Shares

Holders of our ordinary shares that hold their ordinary shares electronically have the right to require us to issue certificates for their shares.

Stock Exchange Listing

Our ordinary shares are listed on The NASDAQ Global Select Market under the symbol PRTA.

No Sinking Fund

Our ordinary shares have no sinking fund provisions.

Transfer and Registration of Shares

The transfer agent for our ordinary shares is Computershare Trust Company, N.A. Its address is 250 Royall Street, Canton, MA 02021. An Irish based affiliate of the transfer agent, Computershare Investor Services (Ireland) Limited, maintains our share register, registration in which is determinative of ownership of our ordinary shares. This affiliate provides an inspection facility in Ireland for inspection and copying of our register

S-33

Table of Contents

in accordance with the Companies Act. A shareholder who holds shares beneficially is not the holder of record of such shares. Instead, the depository (for example, Cede & Co. as nominee for The Depository Trust Company, or DTC) or other nominee is the holder of record of those shares. Accordingly, a transfer of shares from a person who holds such shares beneficially to a person who also holds such shares beneficially through a depository or other nominee will not be registered in our official share register, as the depository or other nominee will remain the record holder of any such shares.

A written instrument of transfer is required under Irish law in order to register on our official share register any transfer of shares (i) from a person who holds such shares directly to any other person, (ii) from a person who holds such shares beneficially to a person who holds such shares directly, or (iii) from a person who holds such shares beneficially to another person who holds such shares beneficially where the transfer involves a change in the depository or other nominee that is the record owner of the transferred shares. An instrument of transfer is also required for a shareholder who directly holds shares to transfer those shares into his or her own broker account (or vice versa). Such instruments of transfer may give rise to Irish stamp duty, which must be paid prior to registration of the transfer on our official Irish share register. However, a shareholder who directly holds shares may transfer those shares into his or her own broker account (or vice versa) without giving rise to Irish stamp duty provided there is no change in the ultimate beneficial ownership of the shares as a result of the transfer and the transfer is not made in contemplation of a sale of the shares.

Any transfer of our ordinary shares that is subject to Irish stamp duty will not be registered in the name of the buyer unless an instrument of transfer is duly stamped and provided to the transfer agent. We, in our absolute discretion and insofar as the Companies Act or any other applicable law permit, may provide that one of our subsidiaries will, pay Irish stamp duty arising on a transfer of our ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of our ordinary shares which would otherwise be payable by the transferee is paid by us or any of our subsidiaries on behalf of the transferee, then in those circumstances, we will, on our behalf or on behalf of our subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those ordinary shares and (iii) claim a first and permanent lien on our ordinary shares on which stamp duty has been paid by us or our subsidiary for the amount of stamp duty paid. Our lien shall extend to all dividends paid on those ordinary shares. Parties to a share transfer may assume that any stamp duty arising in respect of a transaction in our ordinary shares has been paid unless one or both of such parties is otherwise notified by us or the transfer agent.

Our Articles of Association delegate to any director, the secretary or any of our assistant secretaries duly appointed (or such other person as may be appointed by the secretary for this purpose) the authority, on our behalf, to execute an instrument of transfer on behalf of a transferring party.

The directors may suspend registration of transfers from time to time, not exceeding 30 days in aggregate each year.

Table of Contents**UNDERWRITING**

Cantor Fitzgerald & Co. is acting as the sole underwriter. Subject to the terms and conditions set forth in an underwriting agreement among us and the underwriter, we have agreed to issue to the underwriter, and the underwriter has agreed to subscribe from us the number of ordinary shares set forth opposite its name below.

Underwriter	Number of Ordinary Shares
Cantor Fitzgerald & Co.	2,700,000
Total	2,700,000

Subject to the terms and conditions set forth in the underwriting agreement, the underwriter has agreed to purchase all of the ordinary shares sold under the underwriting agreement if any of these ordinary shares are purchased.

We have agreed to indemnify the underwriter against certain liabilities, including liabilities under the Securities Act or to contribute to payments the underwriter may be required to make in respect of those liabilities.

The underwriter is offering the ordinary shares, subject to prior sale, when, as and if issued to and accepted by it, subject to approval of legal matters by its counsel, including the validity of the ordinary shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriter of officer's certificates and legal opinions. The underwriter reserves the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part. If all the shares are not sold at the public offering price, the underwriter may change the offering price and may offer shares from time to time for sale in negotiated transactions or otherwise, at market prices prevailing at the time of sale, at prices related to such prevailing market prices or at negotiated prices, subject to receipt and acceptance by them and subject to their right to reject any order in whole or in part.

Commissions and Discounts

The underwriter has advised us that it proposes initially to offer the ordinary shares to the public at the public offering price set forth on the cover page of this prospectus supplement. After the initial offering, the public offering price or any other term of the offering may be changed.

The following table shows the public offering price, underwriting discount and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriter of its option to subscribe for additional ordinary shares.

	Per Ordinary Share	Without Option	With Option
Public Offering Price	\$ 57.50	\$ 155,250,000	\$ 178,537,500
Underwriting Discount	\$ 1.75	\$ 4,725,000	\$ 5,433,750
Proceeds, Before Expenses, to Us	\$ 55.75	\$ 150,525,000	\$ 173,103,750

Our portion of the expenses of the offering is estimated at \$300,000, which includes an amount not to exceed \$20,000 that we have agreed to reimburse the underwriter for certain FINRA-related expenses incurred by them in connection with this offering.

Option to Subscribe for Additional Ordinary Shares

We have granted an option to the underwriter, exercisable for 30 days after the date of this prospectus supplement, to subscribe for up to an aggregate of 405,000 additional ordinary shares at the public offering price, less the underwriting discount.

S-35

Table of Contents

No Sales of Similar Securities

We and our executive officers and directors have agreed not to sell or transfer any ordinary shares or securities convertible into or exchangeable or exercisable for ordinary shares, for 90 days after the date of this prospectus supplement without first obtaining the written consent of the underwriter. Specifically, we and these other persons have agreed, with certain limited exceptions, not to directly or indirectly:

offer, pledge, sell or contract to sell any ordinary shares,

sell any option or contract to purchase any ordinary shares,

purchase any option or contract to sell any ordinary shares,

grant any option, right or warrant for the sale of any ordinary shares,

otherwise dispose of or transfer any ordinary shares,

request or demand that we file a registration statement related to the ordinary shares, or

enter into any swap or any other agreement or any transaction that transfers, in whole or in part, directly or indirectly, the economic consequence of ownership of any ordinary shares, whether any such swap or transaction is to be settled by delivery of ordinary shares or other securities, in cash or otherwise.

This lock-up provision applies to ordinary shares and to securities convertible into or exchangeable or exercisable for ordinary shares. It also applies to ordinary shares owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition. It does not apply to an aggregate of up to 420,631 shares that may be sold by our executive officers or directors pursuant to Rule 10b5-1 trading plans in place as of the date of this prospectus supplement.

The NASDAQ Global Select Market Listing

The ordinary shares are listed on The NASDAQ Global Select Market under the symbol PRTA.

Price Stabilization, Short Positions

Until the distribution of the ordinary shares is completed, SEC rules may limit the underwriter and selling group members from bidding for and purchasing our ordinary shares. However, the underwriter may engage in transactions that stabilize the price of the ordinary shares, such as bids or purchases to peg, fix or maintain that price.

In connection with the offering, the underwriter may purchase and sell our ordinary shares in the open market. These transactions may include short sales, purchases on the open market to cover positions created by short sales and

stabilizing transactions. Short sales involve the sale by the underwriter of a greater number of ordinary shares than they are required to purchase in the offering. Covered short sales are sales made in an amount not greater than the underwriter's option to subscribe for additional ordinary shares described above. The underwriter may close out any covered short position by either exercising its option to subscribe for additional ordinary shares or purchasing ordinary shares in the open market. In determining the source of ordinary shares to close out the covered short position, the underwriter will consider, among other things, the price of ordinary shares available for purchase in the open market as compared to the price at which they may purchase ordinary shares through the option granted to them. Naked short sales are sales in excess of such option. The underwriter must close out any naked short position by purchasing ordinary shares in the open market. A naked short position is more likely to be created if the underwriter is concerned that there may be downward pressure on the price of our ordinary shares in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of ordinary shares made by the underwriter in the open market prior to the completion of the offering.

Table of Contents

Similar to other purchase transactions, the underwriter's purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our ordinary shares or preventing or retarding a decline in the market price of our ordinary shares. As a result, the price of our ordinary shares will be higher than the price that might otherwise exist in the open market. The underwriter may conduct these transactions on The NASDAQ Global Select Market, in the over-the-counter market or otherwise.

Neither we nor the underwriter may make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our ordinary shares. In addition, neither we nor the underwriter may make any representation that the underwriter will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

Electronic Distribution

In connection with the offering, the underwriter or securities dealers may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

The underwriter and its affiliates may have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us or our affiliates. The underwriter has received, or may in the future receive, customary fees and commissions for these transactions.

In addition, in the ordinary course of its business activities, the underwriter and its affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for its own account and for the accounts of its customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriter and its affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant Member State), no offer of ordinary shares may be made to the public in that Relevant Member State other than:

- A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- B. to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the underwriter; or
- C. in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of ordinary shares shall require the Company or the underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any ordinary shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a qualified investor within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any ordinary shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and

S-37

Table of Contents

agreed that the ordinary shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any ordinary shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the underwriter has been obtained to each such proposed offer or resale.

The Company, the underwriter and its affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus supplement has been prepared on the basis that any offer of ordinary shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of ordinary shares. Accordingly any person making or intending to make an offer in that Relevant Member State of ordinary shares which are the subject of the offering contemplated in this prospectus supplement may only do so in circumstances in which no obligation arises for the Company or the underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the Company nor the underwriter have authorized, nor do they authorize, the making of any offer of ordinary shares in circumstances in which an obligation arises for the Company or the underwriter to publish a prospectus for such offer.

For the purpose of the above provisions, the expression an offer to the public in relation to any ordinary shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the ordinary shares to be offered so as to enable an investor to decide to purchase or subscribe for the ordinary shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression Prospectus Directive means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

Notice to Prospective Investors in the United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are qualified investors (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19 (5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as relevant persons). This document must not be acted on or relied on in the United Kingdom by persons who are not relevant persons. In the United Kingdom, any investment or investment activity to which this document relates is only available to, and will be engaged in with, relevant persons.

Notice to Prospective Investors in Canada

The ordinary shares may be sold only to purchasers purchasing or subscribing, or deemed to be purchasing or subscribing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of the securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the

S-38

Table of Contents

time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriter is not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in Switzerland

The ordinary shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the ordinary shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company, the ordinary shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of ordinary shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of ordinary shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of ordinary shares.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus supplement relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus supplement is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus supplement nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The ordinary shares to which this prospectus supplement relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the ordinary shares offered should conduct their own due diligence on the ordinary shares. If you do not understand the contents of this prospectus supplement you should consult an authorized financial advisor.

Notice to Prospective Investors in Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission, or ASIC, in relation to the offering. This prospectus supplement does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001, or the Corporations Act, and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the ordinary shares may only be made to persons, or the Exempt Investors, who are sophisticated investors (within the meaning of section 708(8) of the Corporations Act), professional investors (within

the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the ordinary shares without disclosure to investors under Chapter 6D of the Corporations Act.

S-39

Table of Contents

The ordinary shares applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring ordinary shares must observe such Australian on-sale restrictions.

This prospectus supplement contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus supplement is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

Notice to Prospective Investors in Hong Kong

The securities have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to professional investors as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a prospectus as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the securities has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

Notice to Prospective Investors in Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) and, accordingly, will not be offered or sold, directly or indirectly, in Japan, or for the benefit of any Japanese Person or to others for re-offering or resale, directly or indirectly, in Japan or to any Japanese Person, except in compliance with all applicable laws, regulations and ministerial guidelines promulgated by relevant Japanese governmental or regulatory authorities in effect at the relevant time. For the purposes of this paragraph, Japanese Person shall mean any person resident in Japan, including any corporation or other entity organized under the laws of Japan.

Notice to Prospective Investors in Singapore

This prospectus supplement and the accompanying prospectus have not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement, the accompanying prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of ordinary shares may not be circulated or distributed, nor may the ordinary shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

S-40

Table of Contents

Where the ordinary shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- (a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire ordinary share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,
securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the ordinary shares pursuant to an offer made under Section 275 of the SFA except:
 - (a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;
 - (b) where no consideration is or will be given for the transfer;
 - (c) where the transfer is by operation of law;
 - (d) as specified in Section 276(7) of the SFA; or
 - (e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Ordinary shares and Debentures) Regulations 2005 of Singapore.

Table of Contents

LEGAL MATTERS

A&L Goodbody, Dublin, Ireland will pass upon certain legal matters relating to the issuance of the ordinary shares offered hereby on behalf of Prothena Corporation plc. Latham & Watkins LLP is acting as special U.S. counsel for us. Cooley LLP is acting as counsel for the underwriter in connection with this offering.

EXPERTS

The consolidated financial statements of Prothena Corporation plc as of December 31, 2016, 2015 and 2014, and for each of the years in the three-year period ended December 31, 2016, have been incorporated by reference herein and in the registration statement of which this prospectus supplement and the accompanying prospectus are a part in reliance upon the reports of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and other reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. You may also read and copy any document we file at the SEC's Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. Please call the SEC at (800) 732-0330 for further information on the Public Reference Room. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, including any amendments to those reports, and other information that we file with or furnish to the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act can also be accessed free of charge on the Investor Relations section of our website, which is located at <http://ir.prothena.com>. These filings will be available as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information contained on our website is not, and should not be deemed to be, a part of this prospectus supplement.

Table of Contents

INCORPORATION BY REFERENCE

The SEC's rules allow us to incorporate by reference information into this prospectus supplement and the accompanying prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement and the accompanying prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus supplement and the accompanying prospectus to the extent that a statement contained in this prospectus supplement modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, between the date of this prospectus supplement and the termination of the offering of the securities described in this prospectus supplement. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed filed with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

This prospectus supplement and the accompanying prospectus incorporate by reference the documents set forth below that have previously been filed with the SEC:

Our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on February 27, 2017.

The description of our ordinary shares contained in our Registration Statement on Form 10, dated December 17, 2012 and filed with the SEC on December 17, 2012, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus supplement and the accompanying prospectus and deemed to be part of this prospectus supplement from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference in this prospectus supplement and the accompanying prospectus (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Prothena Corporation plc
c/o Prothena Biosciences Inc
331 Oyster Point Boulevard
South San Francisco, CA 94080

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus supplement and the accompanying prospectus.

S-43

Table of Contents

PROSPECTUS

Prothena Corporation plc

Ordinary Shares

We may offer and issue ordinary shares from time to time in one or more offerings. This prospectus provides you with a general description of our ordinary shares.

Each time we offer and issue ordinary shares, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the ordinary shares. The supplement may also add, update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement before you invest in our ordinary shares.

We may offer and issue the ordinary shares described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If any underwriters, dealers or agents are involved in the sale of any ordinary shares, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus titled About this Prospectus and Plan of Distribution for more information. No ordinary shares may be issued without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such ordinary shares.

Investing in our ordinary shares involves risks. See the Risk Factors on page 7 of this prospectus and any similar section contained in the applicable prospectus supplement concerning factors you should consider before investing in our ordinary shares.

Our ordinary shares are listed on The NASDAQ Global Select Market under the symbol PRTA. On April 2, 2015, the last reported sale price of our ordinary shares on The NASDAQ Global Select Market was \$38.28 per ordinary share.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is April 6, 2015.

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	1
<u>WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE</u>	2
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	4
<u>THE COMPANY</u>	6
<u>RISK FACTORS</u>	7
<u>USE OF PROCEEDS</u>	8
<u>DESCRIPTION OF SHARE CAPITAL</u>	9
<u>GLOBAL SECURITIES</u>	22
<u>PLAN OF DISTRIBUTION</u>	25
<u>LEGAL MATTERS</u>	26
<u>EXPERTS</u>	26

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, as a well-known seasoned issuer as defined in Rule 405 under the Securities Act of 1933, as amended, using a shelf registration process. By using a shelf registration statement, we may issue ordinary shares from time to time and in one or more offerings as described in this prospectus. Each time that we offer and issue ordinary shares, we will provide a prospectus supplement to this prospectus that contains specific information about the securities being offered and issued and the specific terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you should rely on the prospectus supplement. Before subscribing for any ordinary shares, you should carefully read both this prospectus and the applicable prospectus supplement, together with the additional information described under the heading *Where You Can Find More Information; Incorporation by Reference*.

We have not authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We will not make an offer to issue these securities in any jurisdiction where the offer or issue is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate as of the date on its respective cover, and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates.

When we refer to *Prothena*, *we*, *our*, *us* and the *Company* in this prospectus, we mean Prothena Corporation plc and its consolidated subsidiaries unless otherwise specified. When we refer to *you*, we mean the holders and potential subscribers 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.

Table of Contents

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Section of the SEC at prescribed rates. Further information on the operation of the SEC's Public Reference Room in Washington, D.C. can be obtained by calling the SEC at (800) 732-0330. The SEC also maintains a website that contains reports, proxy and registration statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is <http://www.sec.gov>.

Our website address is <http://www.prothena.com>. The information on our website, however, is not, and should not be deemed to be, a part of this prospectus.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement at the SEC's Public Reference Room in Washington, D.C. or through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to incorporate by reference information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act in this prospectus, between the date of this prospectus and the termination of the offering of the securities described in this prospectus. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed filed with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that have previously been filed with the SEC:

Our Annual Report on Form 10-K for the year ended December 31, 2014, filed with the SEC on March 13, 2015.

The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2014 from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 2, 2015.

Our Current Report on Form 8-K filed with the SEC on March 19, 2015.

Table of Contents

The description of our ordinary shares contained in our Registration Statement on Form 10, dated and filed with the SEC on December 17, 2012, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference in this prospectus (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Prothena Corporation plc

c/o Prothena Biosciences Inc

650 Gateway Boulevard

South San Francisco, California 94080

(650) 837-8550

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus and any accompanying prospectus supplement.

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, goal, objective, plan, predict, potential, positioned, seek, should, target, will, would, and other similar expressions that are predictive of 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 future offerings;

our operating losses;

our ability to successfully complete research and development of our drug candidates;

our ability to develop and commercialize products;

our collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or collectively Roche, pursuant to the License, Development, and Commercialization Agreement, or the License Agreement, to develop and commercialize PRX002, as well as any future licensed products targeting alpha-synuclein;

our ability to protect our patents and other intellectual property;

our ability to hire and retain key employees;

tax treatment of our separation from Elan Corporation Limited, or Elan, and subsequent distribution of our ordinary shares;

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;

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

government regulation of our industry;

the volatility of our ordinary share price;

business disruptions; and

the other risks and uncertainties described in Risk Factors herein.

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. They 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 or incorporated by reference 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

Table of Contents

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; Incorporation By Reference](#).

Table of Contents

THE COMPANY

We are a late-stage clinical biotechnology company focused on the discovery, development and commercialization of novel protein immunotherapy programs for the potential treatment of diseases that involve amyloid or cell adhesion.

We are a public limited company formed under the laws of Ireland. We separated from Elan Corporation Limited (formerly Elan Corporation, plc), or Elan, which subsequently became a wholly owned subsidiary of Perrigo Company plc, or Perrigo, on December 20, 2012.

Our business consists of a substantial portion of Elan's former drug discovery business platform, including Neotope Biosciences Limited (now named Prothena Biosciences Limited) and its wholly owned subsidiaries, Onclave Therapeutics Limited (now named Prothena Therapeutics Limited) and Prothena Biosciences Inc, and related tangible assets and liabilities (which for the period prior to the separation and distribution from Elan we collectively 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 and currently trade on The NASDAQ Global Select Market.

Our principal executive offices are located at Alexandra House, The Sweepstakes, Ballsbridge, Dublin 4, Ireland, and our telephone number is 011-353-1-902-3519. 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 or the accompanying prospectus supplement.

Table of Contents

RISK FACTORS

Investment in our ordinary shares offered pursuant to this prospectus and the applicable prospectus supplement involves risks. You should carefully consider the risk factors incorporated by reference into this prospectus from our most recent Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q or Current Reports on Form 8-K that we have filed or that we file after the date of this prospectus, and all other information contained or incorporated by reference into this prospectus, as updated by our subsequent filings under the Exchange Act, and the risk factors and other information contained in the applicable prospectus supplement before acquiring any ordinary shares. The occurrence of any of these risks might cause you to lose all or part of your investment.

Table of Contents

USE OF PROCEEDS

We intend to use the net proceeds from the issue of ordinary shares as set forth in the applicable prospectus supplement.

Table of Contents

DESCRIPTION OF SHARE CAPITAL

*The following description of our share capital is not complete and may not contain all the information you should consider before investing in our share capital. This description is summarized from, and qualified in its entirety by reference to, our Memorandum and Articles of Association, which has been publicly filed with the SEC. See *Where You Can Find More Information; Incorporation by Reference.**

The following description of our ordinary shares and Euro Deferred Shares is a summary. This summary does not purport to be complete and is qualified in its entirety by reference to the Irish Companies Acts 1963-2013, or the Companies Acts, and the complete text of our Memorandum and Articles of Association. You should read those laws and documents carefully.

For the avoidance of any doubt, the ordinary shares are the subject of this registration statement. The Euro Deferred Shares are not listed on any stock exchange and are not the subject of any registration.

Capital Structure

Issued Share Capital

As of December 31, 2014, our issued share capital was 27,388,005 ordinary shares. We have no Euro Deferred Shares in issue. Our ordinary shares are listed on The NASDAQ Global Select Market, or NASDAQ, under the symbol *PRTA*.

Authorized Share Capital

The authorized share capital of the Company is \$1,000,000 and 220,000 consisting of 100,000,000 ordinary shares with a par value of \$0.01 per share and 10,000 Euro Deferred Shares with a par value of 22 per share. We may issue shares subject to the maximum authorized share capital contained in our Articles of Association. The authorized share capital may be increased or reduced by a resolution approved by a simple majority of the votes cast at a general meeting of our shareholders (referred to under Irish law as an *ordinary resolution*). The shares comprising our authorized share capital may be divided into shares of such nominal value as the resolution shall prescribe. As a matter of Irish law, the directors of a company may issue new ordinary shares or Euro Deferred Shares without shareholder approval once authorized to do so by the Articles of Association or by an *ordinary resolution* adopted by the shareholders at a general meeting. The authorization may be granted for a maximum period of five years, at which point it must be renewed by the shareholders by an *ordinary resolution*.

Our Articles of Association authorize our board of directors, or our Board, to issue new ordinary shares and Euro Deferred Shares for cash without shareholder approval for a period of five years from the date of adoption of such Articles of Association, which adoption was effective prior to the completion of the Separation and Distribution.

The rights and restrictions to which our ordinary shares and Euro Deferred Shares are subject are prescribed in our Articles of Association. We may, by *ordinary resolution* and without obtaining any vote or consent of the holders of any class or series of shares, unless expressly provided by the terms of that class or series of shares, provide from time to time for the issuance of other classes or series of shares and to establish the characteristics of each class or series, including the number of shares, designations, relative voting rights, dividend rights, liquidation and other rights, redemption, repurchase or exchange rights and any other preferences and relative, participating, optional or other rights and limitations not inconsistent with applicable law.

Irish law does not recognize fractional shares held of record. Accordingly, our Articles of Association do not provide for the issuance of fractional shares of the Company, and the official Irish share register of the Company will not reflect any fractional shares. Whenever as a result of an issuance, alteration, reorganisation,

Table of Contents

consolidation, division, or subdivision of the share capital of the Company would result in any shareholder becoming entitled to fractions of a share, no such fractions shall be issued or delivered to any shareholder. All such fractions of a share will be aggregated into whole shares and sold in the open market at prevailing market prices and the aggregate cash proceeds from such sale (net of tax, commissions, costs and other expenses) shall be distributed on a pro rata basis, rounding down to the nearest cent, to each shareholder who would otherwise have been entitled to receive fractions of a share.

Preemption Rights, Share Warrants and Share Options

Under Irish law, certain statutory preemption rights apply automatically in favor of shareholders where shares are to be issued for cash. However, we have opted out of these preemption rights in our Articles of Association as permitted under Irish law. Because Irish law requires this opt-out to be renewed every five years by a resolution approved by not less than 75% of the votes cast at a general meeting of our shareholders (referred to under Irish law as a special resolution), our Articles of Association provide that this opt-out must be so renewed. If the opt-out is not renewed, shares issued for cash must be offered to existing shareholders of the Company on a *pro rata* basis to their existing shareholding before the shares may be issued to any new shareholders. The statutory preemption rights do not apply (i) where shares are issued for non-cash consideration (such as in a share-for-share acquisition), (ii) to the issue of non-equity shares (that is, shares that have the right to participate only up to a specified amount in any income or capital distribution) or (iii) where shares are issued pursuant to an employee share option or similar equity plan.

Our Articles of Association provide that, subject to any shareholder approval requirement under any laws, regulations or the rules of any stock exchange to which we are subject, our Board is authorized, from time to time, in its discretion, to grant such persons, for such periods and upon such terms as it deems advisable, options to purchase such number of shares of any class or classes or of any series of any class as our Board may deem advisable, and to cause warrants or other appropriate instruments evidencing such options to be issued. The Companies Acts provide that directors may issue share warrants or options without shareholder approval once authorized to do so by the Articles of Association or an ordinary resolution of shareholders. We are subject to the rules of NASDAQ and the U.S. Internal Revenue Code of 1986, as amended, which require shareholder approval of certain equity plans and share issuances. Our Board may issue shares upon exercise of warrants or options without shareholder approval or authorization (up to the relevant authorized share capital limit).

Dividends

Under Irish law, dividends and distributions may only be made from distributable reserves. Distributable reserves generally means accumulated realized profits less accumulated realized losses and includes reserves created by way of capital reduction. In addition, no distribution or dividend may be made unless our net assets are equal to, or in excess of, the aggregate of our called up share capital plus undistributable reserves and the distribution does not reduce our net assets below such aggregate. Undistributable reserves include the share premium account, the capital redemption reserve fund and the amount by which our accumulated unrealized profits, so far as not previously utilized by any capitalization, exceed the Company's accumulated unrealized losses, so far as not previously written off in a reduction or reorganization of capital.

The determination as to whether or not we have sufficient distributable reserves to fund a dividend must be made by reference to the relevant accounts of the Company. The relevant accounts are either the last set of unconsolidated annual audited financial statements or other financial statements properly prepared in accordance with the Companies Acts, which give a true and fair view of our unconsolidated financial position and accord with accepted accounting practice. The relevant accounts must be filed in the Companies Registration Office (the official public registry for companies in Ireland).

Our Articles of Association authorize the Board to declare dividends without shareholder approval to the extent they appear justified by profits lawfully available for distribution. Our Board may also recommend a dividend to be approved and declared by the shareholders at a general meeting. Our Board may direct that the

Table of Contents

payment be made by distribution of assets, shares or cash, and no dividend issued may exceed the amount recommended by the directors. Dividends may be declared and paid in the form of cash or non-cash assets and may be paid in dollars or any other currency.

Our Board may deduct from any dividend payable to any shareholder any amounts payable by such shareholder to the Company in relation to the shares of the Company.

The Board may also authorize the Company to issue shares with preferred rights to participate in dividends declared by the Company from time to time, as determined by ordinary resolution. The holders of preferred shares may, depending on their terms, rank senior to our ordinary shares in terms of dividend rights and or be entitled to claim arrears of a declared dividend out of subsequently declared dividends in priority to ordinary shareholders.

Share Repurchases, Redemptions and Conversions

Overview

Our Articles of Association provide that any ordinary share that we have agreed to acquire shall be deemed to be a redeemable share. Accordingly, for Irish law purposes, the repurchase of ordinary shares by us may technically be effected as a redemption of those shares as described below under *Description of Share Capital Repurchases and Redemptions by Prothena*. If our Articles of Association did not contain such provision, repurchases by us would be subject to many of the same rules that apply to purchases of our ordinary shares by subsidiaries described below under *Description of Share Capital Purchases by Subsidiaries of Prothena*, including the shareholder approval requirements described below, and the requirement that any overseas market purchases be effected on a recognized stock exchange, which, for purposes of the Companies Acts, includes NASDAQ. Neither Irish law nor any of our constituent documents places limitations on the right of non-resident or foreign owners to vote or hold our ordinary shares. Except where otherwise noted, references in this registration statement to repurchasing or buying back our ordinary shares refer to the redemption of ordinary shares by us or the purchase of our ordinary shares by one of our subsidiaries, in each case in accordance with our Articles of Association and Irish company law as described below.

Repurchases and Redemptions by Prothena

Under Irish law, a company may issue redeemable shares and redeem them out of distributable reserves or the proceeds of a new issue of shares for that purpose. Please see also *Description of Share Capital Dividends*. We may only issue redeemable shares if the nominal value of the issued share capital that is not redeemable is not less than 10% of the nominal value of our total issued share capital. All redeemable shares must also be fully-paid and the terms of redemption of the shares must provide for payment on redemption. Redeemable shares may, upon redemption, be cancelled or held in treasury. Based on the provisions of our Articles of Association, shareholder approval will not be required to redeem our shares.

We may also be given an additional general authority for overseas market purchases of our ordinary shares by way of ordinary resolution, which would take effect on the same terms and be subject to the same conditions as applicable to purchases by our subsidiaries as described below.

Repurchased and redeemed shares may be cancelled or held as treasury shares. The nominal value of treasury shares held by us at any time must not exceed 10% of the nominal value of our issued share capital. We may not exercise any voting rights in respect of any shares held as treasury shares. Treasury shares may be cancelled by us or re-issued subject to certain conditions.

Purchases by Subsidiaries of Prothena

Under Irish law, an Irish or non-Irish subsidiary of the Company may purchase our shares by way of an: (i) overseas market purchase; or (ii) off-market purchase. For one of our subsidiaries to make overseas market

Table of Contents

purchases of our ordinary shares, our shareholders must provide general authorization for such purchase by way of ordinary resolution. However, as long as this general authority has been granted, no specific shareholder authority for a particular overseas market purchase by a subsidiary of our ordinary shares is required. For a purchase by one of our subsidiaries off-market, the proposed purchase contract must be authorized by special resolution of our shareholders before the contract is entered into. The person whose ordinary shares are to be bought back cannot vote in favor of the special resolution and, for at least 21 days prior to the special resolution being passed, the purchase contract must be on display or must be available for inspection by our shareholders at our registered office.

In order for one of our subsidiaries to make overseas market purchases of our shares, such shares must be purchased on a recognized stock exchange. NASDAQ, on which our ordinary shares are listed, is specified as a recognized stock exchange for this purpose in accordance with Irish law.

The number of shares held by our subsidiaries at any time will count as treasury shares and will be included in any calculation of the permitted treasury share threshold of 10% of the nominal value of our issued share capital. While a subsidiary holds our shares, it cannot exercise any voting rights in respect of those shares. The acquisition of our ordinary shares by a subsidiary must be funded out of distributable reserves of the subsidiary.

Lien on Shares, Calls on Shares and Forfeiture of Shares

Our Articles of Association provide that we have a first and paramount lien on every share that is not a fully paid up share for all amounts payable at a fixed time or called in respect of that share. Subject to the terms of their allotment, directors may call for any unpaid amounts in respect of any shares to be paid, and if payment is not made, the shares may be forfeited. These provisions are standard inclusions in the Articles of Association of an Irish public company limited by shares such as Prothena and are only applicable to our shares that have not been fully paid up. Irish stamp duty may be payable in respect of transfers of our ordinary shares at the rate of 1%.

Consolidation and Division; Subdivision

Under our Articles of Association, we may, by ordinary resolution, consolidate and divide all or any of our share capital into shares of larger nominal value than our existing shares or subdivide our shares into smaller amounts than are fixed by our Articles of Association.

Reduction of Share Capital

We may, by ordinary resolution, reduce our authorized share capital in any way. We also may, by special resolution and subject to confirmation by the Irish High Court, reduce or cancel our issued share capital in any manner permitted by the Companies Acts.

Annual Meetings of Shareholders

Under Irish company law, we are required to hold annual general meetings at intervals of no more than 15 months from the previous annual general meeting, provided that an annual general meeting is held in each calendar year following the first annual general meeting and no more than nine months after our fiscal year-end. Any of our annual general meetings may be held outside Ireland if a resolution so authorizing has been passed at the preceding annual general meeting.

Notice of an annual general meeting must be given to all of our shareholders and to our auditors. Our Articles of Association provide for a minimum notice period of 21 days' notice, which is the minimum permitted by the Irish Companies Acts.

Table of Contents

The only matters which must, as a matter of Irish company law, be transacted at an annual general meeting are the presentation of the annual accounts, balance sheet and reports of the directors and auditors, the appointment of new auditors and the fixing of the auditor's remuneration (or delegation of same). If no resolution is made in respect of the reappointment of an existing auditor at an annual general meeting, the existing auditor will be deemed to have continued in office.

Extraordinary General Meetings of Shareholders

Extraordinary general meetings of the Company may be convened by (i) our Board, (ii) on requisition of our shareholders holding not less than 10% of the paid up share capital of our carrying voting rights, (iii) on requisition of our auditors or (iv) in exceptional cases, by order of the Irish High Court. Extraordinary general meetings are generally held for the purpose of approving shareholder resolutions as may be required from time to time. At any extraordinary general meeting only such business shall be conducted as is set forth in the notice thereof.

Notice of an extraordinary general meeting must be given to all of our shareholders and to our auditors. Under Irish law and our Articles of Association, the minimum notice periods are 21 days' notice in writing for an extraordinary general meeting to approve a special resolution and 14 days' notice in writing for any other extraordinary general meeting.

In the case of an extraordinary general meeting convened by our shareholders, the proposed purpose of the meeting must be set out in the requisition notice. Upon receipt of any such valid requisition notice, our Board has 21 days to convene a meeting of our shareholders to vote on the matters set out in the requisition notice. This meeting must be held within two months of the receipt of the requisition notice. If our Board does not convene the meeting within such 21-day period, the requisitioning shareholders, or any of them representing more than one half of the total voting rights of all of them, may themselves convene a meeting, which meeting must be held within three months of our receipt of the requisition notice.

If our Board becomes aware that our net assets are not greater than half of the amount of our called-up share capital, it must convene an extraordinary general meeting of our shareholders not later than 28 days from the date that they learn of this fact to consider how to address the situation.

Quorum for General Meetings

Our Articles of Association provide that no business shall be transacted at any general meeting unless a quorum is present. One or more of our shareholders present in person or by proxy holding not less than one-half of our issued and outstanding shares entitled to vote at the meeting in question constitute a quorum.

Voting

Our Articles of Association provide that our Board or chairman may determine the manner in which the poll is to be taken and the manner in which the votes are to be counted.

Each Company shareholder is entitled to one vote for each ordinary share that he or she holds as of the record date for the meeting. Voting rights may be exercised by shareholders registered in our share register as of the record date for the meeting or by a duly appointed proxy, which proxy need not be a Company shareholder. Where interests in shares are held by a nominee trust company, such company may exercise the rights of the beneficial holders on their behalf as their proxy. All proxies must be appointed in the manner prescribed by our Articles of Association, which permit shareholders to notify us of their proxy appointments electronically in such manner as may be approved by our Board.

In accordance with our Articles of Association, we may from time to time be authorized by ordinary resolution to issue preferred shares. These preferred shares may have such voting rights as may be specified in

Table of Contents

the terms of such preferred shares (e.g., they may carry more votes per share than ordinary shares or may entitle their holders to a class vote on such matters as may be specified in the terms of the preferred shares). Treasury shares or our shares that are held by our subsidiaries are not entitled to be voted at general meetings of shareholders.

Irish law requires special resolutions of our shareholders at a general meeting to approve certain matters. Examples of matters requiring special resolutions include:

amending the objects or our Memorandum of Association;

amending our Articles of Association;

approving a change of name of Prothena;

authorizing the entering into of a guarantee or provision of security in connection with a loan, quasi loan or credit transaction to a director or connected person;

opting out of preemption rights on the issuance of new shares;

re-registration of Prothena from a public limited company to a private company;

variation of class rights attaching to classes of shares (where the Articles of Association do not provide otherwise);

purchase of our shares off-market;

reduction of issued share capital;

sanctioning a compromise/scheme of arrangement with creditors or shareholders;

resolving that we be wound up by the Irish courts;

resolving in favor of a shareholders voluntary winding-up; and

setting the re-issue price of treasury shares.

Variation of Rights Attaching to a Class or Series of Shares

Under our Articles of Association and the Companies Acts, any variation of class rights attaching to our issued shares must be approved by a special resolution of our shareholders of the affected class or with the consent in writing of the holders of three-quarters of all the votes of that class of shares.

Edgar Filing: Prothena Corp plc - Form 424B5

The provisions of our Articles of Association relating to general meetings apply to general meetings of the holders of any class of our shares except that the necessary quorum is determined in reference to the shares of the holders of the class. Accordingly, for general meetings of holders of a particular class of our shares, a quorum consists of the holders present in person or by proxy representing at least one-half of the issued shares of the class.

Inspection of Books and Records

Under Irish law, shareholders have the right to: (i) receive a copy of our Memorandum and Articles of Association and any act of the Irish Government which alters our Memorandum; (ii) inspect and obtain copies of

Table of Contents

the minutes of our general meetings and resolutions; (iii) inspect and receive a copy of the register of shareholders, register of directors and secretaries, register of directors' interests and other statutory registers we maintain; (iv) receive copies of balance sheets and directors' and auditors' reports which have previously been sent to shareholders prior to an annual general meeting; and (v) receive balance sheets of any of our subsidiaries which have previously been sent to shareholders prior to an annual general meeting for the preceding ten years. Our auditors also have the right to inspect all of our books, records and vouchers. The auditors' report must be circulated to the shareholders with our financial statements prepared in accordance with Irish law 21 days (not including the day of mailing or the day of the meeting) before the annual general meeting and must be laid before the shareholders at our annual general meeting.

Acquisitions