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

FORM 20-F

(Mark One)

☐ **REGISTRATION STATEMENT PURSUANT TO SECTION 12(b) OR (g) OF THE SECURITIES EXCHANGE ACT OF 1934**

OR

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

For the fiscal year ended December 31, 2015

OR

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

OR

☐ **SHELL COMPANY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Date of event requiring this shell company report: Not applicable

For the transition period from _____ to _____

Commission file number 001-36622

PROQR THERAPEUTICS N.V.
(Exact name of Registrant as specified in its charter)

The Netherlands
(Jurisdiction of incorporation or organization)

Darwinweg 24
2333 CR Leiden
The Netherlands
(Address of principal executive offices)

Smital Shah, Chief Financial Officer
Tel: +31 88 166 7000
sshah@proqr.com, Darwinweg 24, 2333 CR Leiden, The Netherlands
(Name, Telephone, E-mail and/or Facsimile number and Address of Company Contact Person)

Securities registered or to be registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Ordinary Shares, nominal value € 0.04 per share	NASDAQ Stock Market

Securities registered or to be registered pursuant to Section 12(g) of the Act:
None
(Title of Class)

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act:
None
(Title of Class)

Indicate the number of outstanding shares of each of the issuer's classes of capital or common stock as of the close of the period covered by the annual report.
Ordinary shares, nominal value € 0.04 per share: 23,345,965

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

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934. ☐ Yes ☒ No

Note – Checking the box above will not relieve any registrant required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 from their obligations under those Sections.

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act. (Check one):

☐ Large accelerated filer ☐ Accelerated filer ☒ Non-accelerated filer

Indicate by check mark which basis of accounting the registrant has used to prepare the financial statements included in this filing:

☐ U.S. GAAP ☒ International Financial Reporting Standards as issued by the International Accounting Standards Board ☐ Other

If "Other" has been checked in response to the previous question, indicate by check mark which financial statement item the registrant has elected to follow. ☐ Item 17 ☐ Item 18

If this is an annual report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). ☐ Yes ☒ No

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Introduction

This document contains information required for the annual report on Form 20-F for the year ended December 31, 2015 of ProQR Therapeutics N.V. (the "2015 Form 20-F"). Unless the context specifically indicates otherwise, references in this 2015 Form 20-F to "ProQR Therapeutics N.V.", "ProQR Therapeutics", "ProQR", "we", "our", "ours", "us", the "Company" or similar terms refer to ProQR Therapeutics N.V.

IFRS based information

The audited financial statements as at December 31, 2015 and 2014, and for the years ended December 31, 2015, December 31, 2014 and December 31, 2013, included in the 2015 Form 20-F have been prepared in accordance with International Financial Reporting Standards (IFRS) as issued by the International Accounting Standards Board (IASB) effective year-end 2015.

Non-GAAP information

In presenting and discussing our financial position, operating results and cash flows, management uses certain non-GAAP financial measures. These non-GAAP financial measures should not be viewed in isolation as alternatives to the equivalent IFRS measure and should be used in conjunction with the most directly comparable IFRS measure(s).

Exchange rates

All references in this annual report to "U.S. dollars" or "$" are to the legal currency of the United States, and all references to "€" or "euro" are to the currency of the European Economic and Monetary Union. Our business to date has been conducted primarily in the European Union, and we prepare our financial statements in euros.

Fair value information

In presenting our financial position, fair values are used for the measurement of various items in accordance with the applicable accounting standards. These fair values are based on market prices, where available, and are obtained from sources that are deemed to be reliable. Readers are cautioned that these values are subject to changes over time and are only valid at the balance sheet date. When quoted prices or observable market values do not exist, fair values are estimated using valuation models, which we believe are appropriate for their purpose. They require management to make significant assumptions with respect to future developments which are inherently uncertain and may therefore deviate from actual developments. Critical assumptions used are disclosed in the financial statements. In certain cases, independent valuations are obtained to support management's determination of fair values.

Trademarks

"ProQR" is our trademark. Other trademarks or trade names referred to in this annual report are the property of their respective owners. Solely for convenience, the trademarks and trade names in this annual report may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent permissible under applicable law, their rights thereto.

Forward-looking statements

Pursuant to provisions of the United States Private Securities Litigation Reform Act of 1995, ProQR is providing the following cautionary statement.

This document contains certain forward looking statements with respect to the financial condition, results of operations and business of ProQR and certain of the plans and objectives of ProQR with respect to these items. Although we believe that the expectations reflected in these forward-looking statements are reasonable, these statements relate to future events, including our clinical development plans or our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements, including in relation to the clinical development of QR-010, QR-110 or any other pipeline program, to be materially different from any future results, performance or achievements, including in relation to the clinical development of QR-010, QR-110 or any other pipeline program, expressed or implied by these forward-looking statements. Forward-looking statements can be identified generally as those containing words as “aim,” “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions, although not all forward-looking statements contain these identifying words.

Forward-looking statements appear in a number of places in this Annual Report and include, but are not limited to, statements regarding our intent, belief or current expectations. Forward-looking statements are based on our management’s beliefs and assumptions and on information currently available to management. By their nature, forward-looking statements involve risk and uncertainty, because they relate to events that depend on circumstances that will occur in the future. As a result, ProQR’s actual future results may differ materially from the plans, goals and expectations set forth in such forward-looking statements. For a discussion of factors that could cause future results to differ from such forward-looking statements, reference is made to the information in Item 3.D: “Risk Factors”.

Forward-looking statements speak only as of the date they are made, and we do not undertake any obligation to update them in light of new information or future developments or to release publicly any revisions to these statements in order to reflect later events or circumstances or to reflect the occurrence of unanticipated events.

Part I

Item 1: Identity of Directors, Senior Management and Advisers

A. Directors and senior management

Not applicable.

B. Advisers

Not applicable.

C. Auditors

Not applicable.

Item 2: Offer Statistics and Expected Timetable

A. Offer statistics

Not applicable.

B. Method and expected timetable

Not applicable.

Item 3: Key Information

A. Selected financial data

The following table sets forth selected financial data for ProQR Therapeutics N.V. for the periods indicated. The selected financial data as at December 31, 2014 and 2015 and the years ended December 31, 2013, 2014 and 2015 have been derived from our audited consolidated financial statements included elsewhere in this annual report. The selected financial data as at December 31, 2012 and 2013 and for the period from February 21, 2012 (inception) through December 31, 2012 are derived from the audited financial statements not appearing in this annual report.

Our historical results for any prior period are not necessarily indicative of results to be expected in any future period. The information set forth below should be read in conjunction with the information in Item 5: "Operating and Financial Review and Prospects" and with our audited consolidated financial statements and notes thereto included elsewhere in this annual report. Our financial statements are prepared in accordance with IFRS as issued by the IASB.

	Year Ended December 31, 2015	Year Ended December 31, 2014	Year Ended December 31, 2013	Period February 21 – December 31, 2012
	(€ in thousands, except for per share data)			
Statement of comprehensive loss data:				
Other income	3,235	313	116	23
Research and development costs	(23,401)	(10,267)	(2,569)	(285)
General and administrative costs	(6,837)	(6,507)	(786)	(157)
Operating result	**(27,003)**	**(16,461)**	**(3,239)**	**(419)**
Finance income and expense	6,171	4,334	(14)	1
Net loss (attributable to equity holders of the Company)	**(20,832)**	**(12,127)**	**(3,253)**	**(418)**
Other comprehensive income	1	—	—	—
Total comprehensive loss (attributable to equity holders of the Company)	**(20,831)**	**(12,127)**	**(3,253)**	**(418)**
Share information				
Weighted average number of shares outstanding	23,343,262	11,082,801	5,517,688	2,499,905
Earnings per share for result attributable to the equity holders of the Company (expressed in Euro per share)				
Basic and diluted loss per share	€ (0.89)	€ (1.09)	€ (0.59)	€ (0.17)

	As at December 31,			
	2015	2014	2013	2012
	(€ in thousands)			
Statement of financial position data:				
Cash and cash equivalents	94,865	112,736	4,129	249
Total assets	100,109	115,247	4,504	338
Total liabilities	10,310	5,843	4,593	239
Total shareholders' equity	89,799	109,404	(89)	99

Exchange rate information

Our business is primarily conducted in the European Union, and we maintain our books and records in euros. We have presented results of operations in euros. In this annual report, translations from euros to U.S. dollars were made at a rate of $ 1.0887 to € 1.00, the official exchange rate quoted by the European Central Bank at the close of business on December 31, 2015. As at March 8, 2016, the official exchange rate of Euro to U.S. dollars was $ 1.1028 to € 1.00. Such U.S. dollar amounts are not necessarily indicative of the amounts of U.S. dollars that could actually have been purchased upon exchange of euros at the dates indicated.

The following table presents information on the exchange rates between the euro and the U.S. dollar for the periods indicated:

	Period-end	Average for period	Low	High
		(€ per U.S. dollar)		
Year ended December 31,				
2012	1.3194	1.2848	1.2089	1.3454
2013	1.3791	1.3281	1.2768	1.3814
2014	1.2141	1.3285	1.2141	1.3953
2015	1.0887	1.1095	1.0552	1.2043
Month ended				
September 30, 2015	1.1203	1.1221	1.1138	1.1419
October 31, 2015	1.1017	1.1235	1.0930	1.1439
November 30, 2015	1.0579	1.0736	1.0579	1.1032
December 31, 2015	1.0887	1.0877	1.0600	1.0990
January 31, 2016	1.0920	1.0860	1.0742	1.0920
February 29, 2016	1.0888	1.1093	1.0884	1.1347

B. Capitalization and indebtedness

Not applicable.

C. Reasons for the offer and use of proceeds

Not applicable.

D. Risk factors

Our business is subject to numerous risks and uncertainties. If any of these risks actually occurs, our business, prospects, operating results and financial condition could suffer materially. These risks include, but are not limited to, the following:

Risks Related to Our Capital Needs and Financial Position

We are a clinical stage biopharmaceutical company with a history of losses. We expect to continue to incur significant losses for the foreseeable future and may never achieve or maintain profitability, which could result in a decline in the market value of our ordinary shares.

We are a clinical stage biopharmaceutical company with a limited operating history, engaged in the discovery and development of RNA-based therapeutics for the treatment of severe genetic disorders. Since our inception in February 2012, we have devoted a significant portion of our resources to the development of our lead product candidate in cystic fibrosis (CF), QR-010, as well as in other programs, including our lead product candidate in Leber's congenital amaurosis (LCA), QR-110. We have had significant operating losses since our inception. Our net losses for the years ended December 31, 2013, December 31, 2014 and December 31, 2015 were approximately € 3,253,000, € 12,127,000 and € 20,832,000 respectively. As of December 31, 2015, we had an accumulated deficit of € 36,630,000. Substantially all of our losses have resulted from expenses incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Our technologies and product candidates are in early stages of development, and we are subject to the risks of failure inherent in the development of product candidates based on novel technologies.

To date, the only income we have generated has been from the receipt of research grants. Our ability to generate revenue and become profitable depends upon our ability to obtain marketing approval and successfully commercialize QR-010, QR-110 or other product candidates that we may develop, in-license or acquire in the future.

Even if we are able to successfully achieve regulatory approval for these product candidates, we do not know when any of these product candidates will generate revenue for us, if at all. We have not generated, and do not expect to generate, any product revenue for the foreseeable future, and we expect to continue to incur significant operating losses for the foreseeable future due to the cost of research and development, pre-clinical studies and clinical trials and the regulatory approval process for product candidates. The amount of future losses is uncertain. Our ability to achieve profitability, if ever, will depend on, among other things, us or any future

collaborators successfully developing product candidates, obtaining regulatory approvals to market and commercialize product candidates, manufacturing any approved products on commercially reasonable terms, establishing a sales and marketing organization or suitable third party alternatives for any approved product and raising sufficient funds to finance business activities. If we or any future collaborators are unable to develop and commercialize one or more of our product candidates or if sales revenue from any product candidate that receives approval is insufficient, we will not achieve profitability, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our ability to generate revenue from QR-010, QR-110 or other product candidates also depends on a number of additional factors, including our ability to:

- successfully complete development activities, including the ongoing and planned pre-clinical and clinical studies for our product candidates;
- complete and submit New Drug Applications, or NDAs, to the U.S. Food and Drug Administration, or FDA, and Marketing Authorization Applications, or MAAs, to the European Medicines Agency, or EMA, and obtain regulatory approval for indications for which there is a commercial market;
- complete and submit applications to, and obtain regulatory approval from, other foreign regulatory authorities;
- set a commercially viable price for any products for which we may receive approval;
- obtain commercial quantities of our products at acceptable cost levels;
- develop a commercial organization capable of sales, marketing and distribution for the products we intend to sell ourselves in the markets in which we have retained commercialization rights;
- find suitable partners to help us market, sell and distribute our approved products that we do not intend to sell ourselves in one or more markets;
- achieve acceptance among patients, clinicians and advocacy groups for any product we develop; and
- obtain coverage and adequate reimbursement for our products from third-parties, including government payors.

In addition, because of the numerous risks and uncertainties associated with product development, including the risk that our product candidates may not advance through development or be shown to be safe and effective for their intended uses, the FDA, the EMA or other regulatory agencies may require additional clinical trials or pre-clinical studies or impose post-approval requirements.

We are unable to predict the timing or amount of increased expenses, or when or if we will be able to achieve or maintain profitability. Even if we are able to complete the processes described above, we anticipate incurring significant costs associated with commercializing our product candidates. Moreover, our first commercial sale of QR-010, if ever, will trigger a milestone payment to Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, of approximately $ 80 million pursuant to our agreement with CFFT, and we may not have sufficient funds to support this payment obligation. See “Item 5. Operating and Financial Review and Prospects—Clinical support agreement” and the notes to the financial statements included elsewhere in this annual report for more details on this transaction.

Even if we are able to generate revenues from the sale of QR-010, QR-110 or any other product candidate, we may not become profitable and may need to obtain additional funding to continue operations. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

We will require additional capital to fund our operations and if we fail to obtain necessary financing, we will not be able to complete the development and commercialization of our product candidates.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to conduct further research and development and pre-clinical testing and clinical trials of our product candidates, to seek regulatory approvals for our product candidates and to launch and commercialize any product candidates for which we receive regulatory

approval, including potentially building our own commercial organization to address the United States, the European Union and certain other markets. As at December 31, 2015, we had approximately € 94,865,000 in cash and cash equivalents. Based on our current operating plan, we believe that the existing cash and cash equivalents will be sufficient to fund our anticipated level of operations for at least through mid-2017. However, our future capital requirements and the period for which our existing resources will support our operations may vary significantly from what we expect. Our monthly spending levels will vary based on new and ongoing development and corporate activities. Because the length of time and activities associated with successful development of our product candidates is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of pre-clinical studies and clinical trials for our product candidates;
- the clinical development plans we establish for these product candidates;
- the number and characteristics of product candidates that we develop or may in-license, or programs that we may pursue in our innovation unit;
- the terms of any collaboration arrangements we may choose to enter into;
- the outcome, timing and cost of meeting regulatory requirements established by the FDA, the EMA and other comparable foreign regulatory authorities;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us or our product candidates;
- the effect of competing technological and market developments;
- the cost and timing of completion of commercial-scale outsourced manufacturing activities; and
- the cost of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our products or product candidates or one or more of our other research and development initiatives. We also could be required to seek collaborators for one or more of our current or future product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves.

Raising additional capital may cause dilution to our existing shareholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We may seek additional capital through a combination of private and public equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, existing ownership interests will be diluted and the terms of such financings may include liquidation or other preferences that adversely affect the rights of existing shareholders. Debt financings may be coupled with an equity component, such as warrants to purchase shares, which could also result in dilution of our existing shareholders' ownership. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business and may result in liens being placed on our assets and intellectual property. If we were to default on such indebtedness, we could lose such assets and intellectual property. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, or grant licenses on terms that are not favorable to us.

We have a limited operating history, which may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We were founded in February 2012 and began operations in May 2012. Our operations to date have been limited to organizing and staffing our company, acquiring and developing product and technology rights, and conducting development activities for our product candidates, including QR-010 and QR-110. Consequently, any predictions about our future success, performance or viability may not be as accurate as they could be if we had a longer operating history, more experience with clinical development or approved products on the market.

Risks Related to the Development and Regulatory Approval of our Product Candidates

We depend on the success of our product candidates, which are still in early phases of development. We cannot be certain that we will be able to successfully complete the clinical development of, obtain regulatory approval for, or successfully commercialize our product candidates.

We currently have no products on the market, and our most advanced product candidate, QR-010, has only recently entered clinical development. Our business depends on the successful clinical development, regulatory approval and commercialization of our product candidates, and will require additional pre-clinical testing and substantial additional clinical development and regulatory approval efforts before we are permitted to commence its commercialization, if ever. It will be several years before we can commence and complete a pivotal study for our product candidates, if ever. The clinical trials and manufacturing and marketing of QR-010, QR-110 and any other product candidates will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, the European Union and other jurisdictions where we intend to test and, if approved, market our product candidates. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through pre-clinical testing and clinical trials that the product candidate is safe and effective for use in each target indication, and potentially in specific patient populations, including the pediatric population. This process can take many years and may include post-marketing studies and surveillance, which would require the expenditure of substantial resources beyond our existing funds. Of the large number of drugs in development for approval in the United States and the European Union, only a small percentage successfully complete the FDA or EMA regulatory approval processes, as applicable, and are commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our research, development and clinical programs, we cannot assure you that any of our product candidates will be successfully developed or commercialized.

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

We are not permitted to market our product candidates in the United States or the European Union until we receive approval of an NDA from the FDA or an MAA from the European Commission, respectively, or in any other foreign countries until we receive the requisite approval from such countries. Prior to submitting an NDA to the FDA or an MAA to the EMA for approval of our product candidates, we will need to complete our ongoing pre-clinical and toxicology studies, as well as a proof-of-concept study and Phase 1, Phase 2 and Phase 3 clinical trials. Successfully initiating and completing our clinical program and obtaining approval of an NDA or a MAA is a complex, lengthy, expensive and uncertain process, and the FDA, the EMA or other comparable foreign regulatory authorities may delay, limit or deny approval of our product candidates for many reasons, including, among others:

- we may not be able to demonstrate that our product candidates are safe and effective in treating patients to the satisfaction of the FDA or the EMA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or the EMA for marketing approval;
- the FDA or the EMA may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the FDA or the EMA may require that we conduct additional clinical trials;
- the FDA or the EMA or other applicable foreign regulatory agencies may not approve the formulation, labeling or specifications of our product candidates;
- the clinical research organizations, or CROs, that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;

- the FDA or the EMA may find the data from pre-clinical studies and clinical trials insufficient to demonstrate that the clinical and other benefits of our products outweigh their safety risks;
- the FDA or the EMA may disagree with our interpretation of data from our pre-clinical studies and clinical trials;
- the FDA or the EMA may not accept data generated at our clinical trial sites;
- if our NDAs or MAAs, if and when submitted, are reviewed by the FDA or the EMA, as applicable, the regulatory agency may have difficulties scheduling the necessary review meetings in a timely manner, may recommend against approval of our application or may recommend that the FDA or the EMA, as applicable, require, as a condition of approval, additional pre-clinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA may require development of a Risk Evaluation and Mitigation Strategy as a condition of approval or post-approval, and the EMA may grant only conditional approval or impose specific obligations as a condition for marketing authorization, or may require us to conduct post-authorization safety studies;
- the FDA, the EMA or other applicable foreign regulatory agencies may not approve the manufacturing processes or facilities of third-party manufacturers with which we contract; or
- the FDA or the EMA may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market our product candidates. Any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

Changes in regulatory requirements, FDA guidance or unanticipated events during our clinical studies may occur, which may result in changes to clinical study protocols or additional clinical study requirements, which could result in increased costs to us and could delay our development timeline.

Changes in regulatory requirements, FDA guidance or unanticipated events during our clinical studies may force us to amend clinical study protocols or the FDA may impose additional clinical study requirements. Amendments to our clinical study protocols would require resubmission to the FDA and IRBs for review and approval, which may adversely impact the cost, timing and/or successful completion of a clinical study. If we experience delays completing—or if we terminate—any of our clinical studies, or if we are required to conduct additional clinical studies, the commercial prospects for our product candidates may be harmed and our ability to generate product revenue will be delayed.

Failures or delays in the commencement or completion of our pre-clinical studies or ongoing or planned clinical trials of our product candidates could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.

Successful completion of clinical trials is a prerequisite to submitting an NDA to the FDA or a MAA to the EMA and, consequently, the ultimate approval and commercial marketing of our product candidates. Clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. A product candidate can unexpectedly fail at any stage of clinical development. The historical failure rate for product candidates is high due to scientific feasibility, safety, efficacy, changing standards of medical care and other variables. We do not know whether our clinical trials will begin or be completed on schedule, if at all, as the commencement and completion of clinical trials can be delayed or prevented for a number of reasons, including, among others:

- delays in reaching or failing to reach agreement on acceptable terms with prospective CROs and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical trials;
- difficulties obtaining institutional review board, or IRB, or ethics committee approval to conduct a clinical trial at a prospective site or sites;

- challenges in recruiting and enrolling patients to participate in clinical trials, including the size and nature of the patient population, the proximity of patients to clinical sites, eligibility criteria for the clinical trial, the nature of the clinical trial protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;
- severe or unexpected drug-related side effects experienced by patients in our clinical trials or by individuals using drugs similar to our product candidates;
- reports from pre-clinical or clinical testing of other RNA therapies that raise safety or efficacy concerns; or
- difficulties retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to lack of efficacy, side effects, personal issues or loss of interest.

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

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA, the EMA or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;
- unforeseen safety issues, including any that could be identified in our ongoing toxicology studies, adverse side effects or lack of effectiveness;
- changes in government regulations or administrative actions;
- problems with clinical supply materials; and
- lack of adequate funding to continue the clinical trial.

Positive results from pre-clinical testing of our product candidates are not necessarily predictive of the results of our ongoing and planned clinical trials of QR-010, QR-110 or any other product candidate. If we cannot achieve positive results in our clinical trials for our product candidates, we may be unable to successfully develop, obtain regulatory approval for and commercialize them.

Positive results from our pre-clinical testing of QR-010, QR-110, or any of our other product candidates *in vitro* and *in vivo* may not necessarily be predictive of the results from our ongoing and planned clinical trials in humans. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical trials after achieving positive results in pre-clinical development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, pre-clinical findings made while clinical trials were underway or safety or efficacy observations made in clinical trials, including adverse events. Moreover, pre-clinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in pre-clinical studies and clinical trials nonetheless failed to obtain FDA or EMA approval. If we fail to produce positive results in our clinical trials of our lead product candidates, including QR-010 and QR-110, the development timeline and regulatory approval and commercialization prospects for those product candidates, and, correspondingly, our business and financial prospects would be materially adversely affected.

Our RNA repair technologies are unproven and may not result in marketable products.

We plan to develop a pipeline of product candidates using our proprietary RNA repair technologies for severe genetic disorders. We believe that targeting the mRNA to restore the production of normal protein is a unique approach that we believe offers advantages versus small molecule, gene therapy and other therapeutic approaches. However, the scientific research that forms the basis of our efforts to develop product candidates is both preliminary and limited.

We believe that we are the only company currently pursuing RNA repair technologies for the treatment of severe genetic disorders. We may discover that the molecules we develop to repair RNA do not possess certain properties required for a drug to be effective, such as the ability to remain stable in the human body for the period of time required for the drug to reach the target tissue or the ability to cross the cell wall and enter into cells within the target tissue for effective delivery. We may spend substantial funds attempting to introduce these properties and may never succeed in doing so. In addition, product candidates based on RNA repair may demonstrate different chemical and pharmacological properties in humans than they do in laboratory studies or animals. Even if our product candidates, such as QR-010 and QR-110, have successful results in animal studies, they may not demonstrate the same chemical and pharmacological properties in humans and may interact with human biological systems or other existing treatments in unforeseen, ineffective or harmful ways. Our RNA repair technologies may provoke an unwanted immune response, or immunogenicity, which may neutralize the therapeutic effects of our product candidates and could result in harmful outcomes for patients. As a result, we may never succeed in developing a marketable product, we may not become profitable and the value of our ordinary shares would decline.

Furthermore, the FDA and the EMA have relatively limited experience with therapeutics based on RNA repair. To our knowledge, no regulatory authority has granted approval to any person or entity, including us, to market and commercialize therapeutics using RNA repair technologies, which may increase the complexity, uncertainty and length of the regulatory approval process for our product candidates. Neither we nor any future collaborator may receive approval to market and commercialize any product candidate. Even if we or a collaborator were to obtain regulatory approval, the approval may be for disease indications or patient populations that are not as broad as we intended or may require labeling that includes significant use or distribution restrictions or safety warnings. We or a collaborator may be required to perform additional or unanticipated clinical trials to obtain approval or be subject to post-marketing testing requirements to maintain regulatory approval. If our RNA repair technology proves to be ineffective, unsafe or commercially unviable, our entire platform and pipeline would have little, if any, value, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

Failure to obtain regulatory approval in jurisdictions outside the United States and the European Union would prevent our product candidates from being marketed in those jurisdictions.

In order to market and sell our products in jurisdictions other than the United States and the European Union, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The regulatory approval process outside the United States and the European Union generally includes all of the risks associated with obtaining FDA and EMA approval, but can involve additional testing. We may need to partner with third parties in order to obtain approvals outside the United States and the European Union. In addition, in many countries worldwide, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States and the European Union on a timely basis, if at all. Even if we were to receive approval in the United States or the European Union, approval by the FDA or the EMA does not ensure approval by regulatory authorities in other countries or jurisdictions. Similarly, approval by one regulatory authority outside the United States and the European Union would not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA or the EMA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market. If we are unable to obtain approval of QR-010, QR-110 or any of our other product candidates by regulatory authorities in other foreign jurisdictions, the commercial prospects of those product candidates may be significantly diminished and our business prospects could decline.

If we are not able to maintain orphan product exclusivity for QR-010 or obtain such status for QR-110 or future product candidates for which we seek this status, or if our competitors are able to obtain orphan product exclusivity before we do, we may not be able to obtain approval for our competing products for a significant period of time.

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States who have been diagnosed as having the disease or condition at the time of the submission of the request for orphan drug designation. Under Regulation No. (EC) 141/2000 on Orphan Medicinal Products, a medicinal product may be designated as an orphan medicinal product if, among other things, it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the European Union when the application is made. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of market exclusivity. This exclusivity precludes the EMA or the FDA, as applicable, from approving another marketing application for the same or, in the EU, a similar drug for the same indication for that time period, unless, among other things, the later product is clinically superior. The applicable period is seven years in the United States and ten years in the European Union following marketing approval. The EU exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation, for example if the drug is sufficiently profitable so that market exclusivity is no longer justified.

Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective, or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition or if the incidence and prevalence of patients who are eligible to receive the drug in these markets materially increase. Although we have obtained orphan designation for QR-010 in the European Union and the United States, even after an orphan drug is approved, the same or, in the EU, a similar drug can subsequently be approved for the same condition if the competent regulatory agency concludes that the later drug is safer, more effective or otherwise clinically superior.

If we lose orphan drug exclusivity or if our competitors obtain orphan drug exclusivity for other rare diseases or conditions we are targeting before we do, we may be precluded from obtaining marketing authorization or we may lose out on the potential benefits of market exclusivity.

We have applied for Orphan Drug designation for QR-110 and may do so for our other product candidates, but we may not obtain such designation.

A breakthrough therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We intend to seek a breakthrough therapy designation for QR-010 and QR-110, and we may do so for other product candidates as well. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. For product candidates that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Product candidates designated as breakthrough therapies by the FDA are also eligible for accelerated approval.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe QR-010, QR-110 or another of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. The availability of breakthrough therapy designation was established with the passage of the Food and Drug Administration Safety and Innovation Act of 2012, and while the FDA has released guidance as to the criteria it uses in designating drugs as breakthrough therapies, we cannot be sure that our product candidates will meet the FDA's qualifying criteria for such designation. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

A fast track designation by the FDA may not actually lead to a faster development, regulatory review or approval process.

We intend to seek fast track designation for QR-010 and QR-110, and we may do so for other product candidates as well. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant this designation, and even if we believe QR-010, QR-110 or another of our product candidates is eligible for this designation, we cannot be sure that the FDA would decide to grant it. Even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

Risks Related to Our Dependence on Third Parties

Our development and commercialization strategy for our product candidates relies in part upon certain patent rights that we license from third parties, and termination of such license could have a materially adverse effect on our business, financial condition, results of operations and prospects.

Some of our RNA repair technologies rely in part upon certain patent rights that we license from third parties. Pursuant to our license agreements, we are obligated to use commercially reasonable efforts to develop and make available to the public products or processes as well as to achieve certain specified development, regulatory and commercial milestones. If we do not meet the specified milestones the third party may be able to terminate the license agreement. They may also terminate the license agreement if we are in breach of certain financial obligations or we are otherwise in default of certain obligations under the license agreement. If a license agreement were terminated, it could have a material adverse effect on our business, financial condition, results of operations and prospects.

If third parties on which we depend to conduct our pre-clinical studies or any clinical trials do not perform as contractually required, fail to satisfy regulatory or legal requirements or miss expected deadlines, our development programs could be delayed with materially adverse effects on our business, financial condition, results of operations and prospects.

We rely on CROs, clinical data management organizations and consultants to design, conduct, supervise and monitor pre-clinical studies and clinical trials for our product candidates. We and our CROs are required to comply with various regulations, including Good Clinical Practices, or GCP, which are enforced by the FDA, and guidelines of the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities to ensure that the health, safety and rights of patients are protected in clinical development and clinical trials, and that trial data integrity is assured. Regulatory authorities ensure compliance with these requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or other comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with such requirements. In addition, our clinical trials must be conducted with products produced under current Good Manufacturing Practice, or cGMP, requirements, which mandate the methods, facilities and controls used in manufacturing, processing and packaging of a drug product to ensure its safety and identity. Failure to comply with these regulations may require us to repeat pre-clinical and clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and pre-clinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. Additionally, any significant delays could cause us to miss diligence milestones under our license agreements and could cause licensors to terminate the agreements, which would further harm our business, financial condition, results of operations and prospects.

Because we have relied on third parties, our internal capacity to perform these functions is limited. Outsourcing these functions involves risk that third parties may not perform to our standards, may not produce results in a timely manner or may fail to perform at all. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers. To the extent we are unable to identify and successfully manage the performance of third-party service providers in the future, our business may be adversely affected. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of pre-clinical studies or clinical trials or meet expected deadlines, our clinical development programs could be delayed and otherwise adversely affected. In all events, we are responsible for ensuring that each of our pre-clinical studies and clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. The FDA and the EMA require clinical trials to be conducted in accordance with GCP, including for conducting, recording and reporting the results of pre-clinical studies and clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Any such event could have a material adverse effect on our business, financial condition, results of operations and prospects.

We rely on third-party manufacturers and suppliers and we intend to rely on third parties to produce pre-clinical, clinical and commercial supplies of our product candidates.

We rely on third parties to supply the materials and components for, and manufacture, our research and development, pre-clinical and clinical trial supplies. We also intend to rely on third-party manufacturers to manufacture the aerosol delivery device that we intend to use to deliver QR-010 to CF patients. We do not own manufacturing facilities or supply sources for such components and materials.

There can be no assurance that our supply of research and development, pre-clinical and clinical development drugs and other materials will not be limited, interrupted, restricted in certain geographic regions or of satisfactory quality or continue to be available at acceptable prices. In particular, any replacement of our drug product formulation manufacturer could require significant effort and expertise because there may be a limited number of qualified replacements.

The manufacturing process for a product candidate is subject to FDA, EMA and other foreign regulatory authority review. Suppliers and manufacturers must meet applicable manufacturing requirements and undergo rigorous facility and process validation tests required by regulatory authorities in order to comply with regulatory standards such as cGMP. In the event that any of our suppliers or manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into an agreement with another third party, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills or technology to another third party and a feasible alternative may not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget.

We expect to continue to rely on third party manufacturers if we receive regulatory approval for any product candidate. To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner consistent with contractual and regulatory requirements, including those related to quality control and assurance. If we are unable to obtain or maintain third-party manufacturing for product candidates, or to do so on commercially reasonable terms, we may not be able to develop and commercialize our product candidates successfully. Our or a third party's failure to execute on our manufacturing requirements could adversely affect our business in a number of ways, including:

- an inability to initiate or continue pre-clinical studies or clinical trials of product candidates under development;
- delay in submitting regulatory applications, or receiving regulatory approvals, for product candidates;
- loss of the cooperation of a collaborator;
- subjecting our product candidates to additional inspections by regulatory authorities;
- requirements to cease distribution or to recall batches of our product candidates; and
- in the event of approval to market and commercialize a product candidate, an inability to meet commercial demands for our products.

If a collaborative partner terminates or fails to perform its obligations under an agreement with us, the commercialization of our product candidates, if approved, could be delayed or terminated.

We are not currently party to any collaborative arrangements for the commercialization of any of our product candidates, although we may pursue such arrangements before any commercialization of our product candidates, if approved. For example, we intend to consider strategic alternatives that include spinouts, out-licensing or collaborative partnerships to develop and commercialize our RNA repair technologies or programs in indications outside of CF. If we entered into future collaborative arrangements for the commercialization of our product candidates or similar arrangements and any of our collaborative partners does not devote sufficient time and resources to a collaboration arrangement with us, we may not realize the potential commercial benefits of the arrangement, and our results of operations may be materially adversely affected. In addition, if any such future collaboration partner were to breach or terminate its arrangements with us, the commercialization of our product candidates could be delayed, curtailed or terminated.

Much of the potential revenue from future collaborations may consist of contingent payments, such as payments for achieving regulatory milestones or royalties payable on sales of drugs. The milestone and royalty revenue that we may receive under these collaborations will depend upon our collaborators' ability to successfully develop, introduce, market and sell new products. In addition, collaborators may decide to enter into arrangements with third parties to commercialize products developed under collaborations using our technologies, which could reduce the milestone and royalty revenue that we may receive, if any. Future collaboration partners may fail to develop or effectively commercialize products using our products or technologies because they:

- decide not to devote the necessary resources due to internal constraints, such as limited personnel with the requisite expertise, limited cash resources or specialized equipment limitations, or the belief that other drug development programs may have a higher likelihood of obtaining marketing approval or may potentially generate a greater return on investment;
- decide to pursue other technologies or develop other product candidates, either on their own or in collaboration with others, including our competitors, to treat the same diseases targeted by our own collaborative programs;
- do not have sufficient resources necessary to carry the product candidate through clinical development, marketing approval and commercialization; or
- cannot obtain the necessary marketing approvals.

Competition may negatively impact a partner's focus on and commitment to our product candidates and, as a result, could delay or otherwise negatively affect the commercialization of such product candidate. If any future collaboration partners fail to develop or effectively commercialize our product candidates for any of these reasons, our sales, if approved, may be limited, which would have a material adverse effect on our operating results and financial condition.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing approval. As a biopharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. Restrictions under applicable federal and state healthcare laws and regulations that may affect our ability to operate include the following:

- the U.S. federal healthcare Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- federal civil and criminal false claims laws and civil monetary penalty laws impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement or record to avoid, decrease or conceal an obligation to pay money to the federal government;
- the U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, and also created federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements or using or making any false or fraudulent document in connection with the delivery of or payment for healthcare benefits, items or services;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the U.S. federal physician payment transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Affordable Care Act, require applicable manufacturers of covered drugs, devices, biologics and medical supplies to report annually to HHS information related to payments and other transfers of value to physicians, and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations; and

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

Comparable laws and regulations exist in the countries within the European Economic Area, or EEA. Although such laws are partially based upon European Union law, they may vary from country to country. Both healthcare and industry specific, as well as general EU and national laws, regulations and industry codes constrain, for example, our interactions with government officials and healthcare practitioners, and the handling of healthcare data. Non-compliance with any of these laws or regulations could lead to criminal or civil liability.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any physicians or other healthcare providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA or EMA regulations or similar regulations of other foreign regulatory authorities, to provide accurate information to the FDA, the EMA or other foreign regulatory authorities, to comply with certain manufacturing standards, to comply with U.S. federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, to report financial information or data accurately or to disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted and implemented a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity, such as employee training on enforcement of the Code of Business Conduct and Ethics, may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Risks Related to Our Intellectual Property

We license patent rights from third-party owners or licensees and if we fail to comply with our obligations in our intellectual property licenses, we could lose rights that are fundamental to our business.

We rely, and will continue to rely, on intellectual property rights licensed from third parties to protect our technology. We are a party to licenses that give us rights to third-party intellectual property that are necessary or useful for our business. For instance, we have a license from MGH to certain patent rights that relate to certain RNA repair technologies. Pursuant to this agreement, we have an exclusive, sublicensable and royalty-bearing license from MGH for the exploitation of the in-licensed intellectual property rights in all therapeutic indications in the field of cystic fibrosis. See Item 4.B: "Business overview—Intellectual Property". We also intend to license additional third-party intellectual property in the future.

Our licensing arrangements impose diligence, development, regulatory and commercialization milestones, and royalty, insurance and other obligations on us. If we fail to comply with these obligations, licensors may have the right to terminate these agreements, in which case we might not be able to develop, manufacture or market any product that is covered by these agreements or may face other penalties under the agreements. Such an occurrence could materially adversely affect the value of the product candidate being

developed under any such agreement. Termination of this agreement or reduction or elimination of our rights under this agreement may result in our having to negotiate new or amended agreements with less favorable terms, or cause us to lose our rights under this agreement, including our rights to important intellectual property and technologies that form the basis of our RNA repair technology, which may then be in-licensed by one or more of our competitors.

If the third parties from whom we license patent rights do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, or if they retain or license to others any competing rights, our competitive position and business prospects may be adversely affected.

Our success will further depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. MGH, as well as our other licensors, may not successfully prosecute the patent applications licensed to us. Even if patents issue or are granted, MGH or our other licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue litigation less aggressively than we would. Further, we may not obtain exclusive rights, which would allow for third parties to develop competing products. Without protection for, or exclusive right to, the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the United States Patent and Trademark Office, or U.S. PTO, the European Patent Office, or EPO, and other foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign national or international patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of patent rights include, but are not limited to, failure to timely file national and regional stage patent applications based on our international patent application, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We or our licensors or any future collaborators or strategic partners may become subject to third party claims or litigation alleging infringement of patents or other proprietary rights or seeking to invalidate patents or other proprietary rights, and we may need to resort to litigation to protect or enforce our patents or other proprietary rights, all of which could be costly, time consuming, delay or prevent the development and commercialization of our product candidates, or put our patents and other proprietary rights at risk.

We or our licensors or any future collaborators or strategic partners may be subject to third-party claims for infringement or misappropriation of patent or other proprietary rights. We are generally obligated under our license or collaboration agreements to indemnify and hold harmless our licensors or collaborators for damages arising from intellectual property infringement by us. If we or our licensors, or any future collaborators or strategic partners are found to infringe a third party patent or other intellectual property rights, we could be required to pay damages, potentially including treble damages, if we are found to have willfully infringed. In addition, we or our licensors, or any future collaborators or strategic partners may choose to seek, or be required to seek, a license from a third party, which may not be available on acceptable terms, if at all. Even if a license can be obtained on acceptable terms, the rights may be non-exclusive, which could give our competitors access to the same technology or intellectual property rights licensed to us. If we fail to obtain a required license, we or any future collaborator may be unable to effectively market product candidates based on our technology, which could limit our ability to generate revenue or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. In addition, we may find it necessary to pursue claims or initiate lawsuits to protect or enforce our patent or other intellectual property rights. Pursuant to our license with MGH, MGH has the initial right to prosecute infringers when, in its sole judgment, such action may be reasonably necessary, proper and justified. In the event that MGH notifies us that it does not intend to prosecute an infringement, we may, after providing notice to MGH, initiate an infringement action against the infringer. The cost to us in defending or initiating any litigation or other proceeding relating to patent or other proprietary rights, even if resolved in our favor, could be substantial, and litigation would divert our management's attention. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts and limit our ability to continue our operations.

If we were to initiate legal proceedings against a third party to enforce a patent covering one of our products or our technology, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the U.S. and in most European countries, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on one or more of our products or certain aspects of our platform technology. Such a loss of patent protection could have a material adverse impact on our business. Patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without legally infringing our patents or other intellectual property rights.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidates, and to use our proprietary technologies without infringing the proprietary rights of third parties. We cannot guarantee that QR-010, QR-110 or any of our product candidates, their manufacture, use, sale, offer for sale, or importation into the United States or into any country of the EEA will not be held to infringe a third party patent. As a result, we may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including litigation in a Federal District court, or an interference or a post grant proceeding before the U.S. PTO or litigation in foreign courts or proceedings before foreign patent offices. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. We are aware of an issued U.S. patent with claims directed to purified DNA and RNA molecules encoding a CFTR protein or a mutant CFTR protein containing a ΔF508 mutation. Although we believe that the claims of this patent are not valid or infringed, particularly in light of a recent U.S. Supreme Court decision regarding the patentability of naturally-occurring nucleic acids, the patent owner may nonetheless initiate litigation. Any such litigation would cause us to incur substantial expenses, which would be costly and divert our management's attention, and there is no assurance that a court would find in our favor on questions of infringement or validity.

Furthermore, in the event a third party were to assert an infringement claim against us and we were ultimately found to infringe the third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and commercializing our products and technology. However, we may not be able to obtain an appropriate license on commercially reasonable terms or at all. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, in any such proceeding or litigation, we could be found liable for monetary damages. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Any claims by third parties that we have misappropriated their confidential information or trade secrets could have a similar negative impact on our business.

If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of our technology and products could be significantly diminished.

We rely on trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers, contract manufacturers, vendors and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, we cannot guarantee that we have executed these agreements with each party that may have or has had access to our trade secrets.

Any party with whom we or they have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any

of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they disclose such trade secrets, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third-party, our competitive position would be harmed.

We may be subject to claims that we or our employees or consultants have wrongfully used or disclosed alleged trade secrets of our employees' or consultants' former employers or their clients. These claims may be costly to defend and if we do not successfully do so, we may be required to pay monetary damages and may lose valuable intellectual property rights or personnel.

Many of our employees were previously employed at universities or biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. If we fail in defending such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. A loss of key research personnel or their work product could compromise our ability to commercialize, or prevent us from commercializing, our product candidates, which could severely harm our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

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

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may be able to export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, an April 2015 report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. As a result, proceedings to enforce our patent rights in certain foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

Risks Related to the Commercialization of Our Product Candidates

We face competition from entities that have developed or may develop product candidates for our target indications, including companies developing novel treatments for CF patients. If these companies develop technologies or product candidates more rapidly than we do or their technologies, including delivery technologies, are more effective, our ability to develop and successfully commercialize our product candidates may be adversely affected.

The development and commercialization of drugs is highly competitive. We compete with a variety of multinational pharmaceutical companies and specialized biotechnology companies, as well as technology being developed at universities and other research institutions. Our competitors have developed, are developing or will develop product candidates and processes competitive with our product candidates. Competitive therapeutic treatments include those that have already been approved and accepted by the medical community and any new treatments that enter the market. We believe that a significant number of products are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop product candidates. We are aware of multiple companies that are working in the field of CF therapeutics, including Vertex Pharmaceuticals Inc., Novartis International AG, Hoffmann-LaRoche Ltd., Pfizer Inc., Galapagos, AbbVie Laboratories, Shire, Genzyme (a Sanofi Company), Bayer AG, Proteostasis, Corbus Pharmaceuticals, Nivalis and other private companies.

If our lead product candidate, QR-010, is approved for the indications we are currently pursuing, it will compete with a range of therapeutic treatments that are either in development or currently marketed. For example, Vertex's Kalydeco is approved for use by the FDA and EMA and works to improve the function of the defective CFTR protein in CF patients with the G551D mutation and certain other gating mutations. Vertex's Orkambi, a combination of lumacaftor (VX-809) and ivacaftor, is approved for CF patients who are homozygous for the ΔF508 mutation in the U.S. and European Union.

There are also a number of products that are marketed or in clinical development for the treatment of co-morbidity and symptoms in CF patients. These treatments include inhaled antibiotics, mucus thinners, pancreatic enzymes and anti-inflammatory drugs.

Although there are several companies that have commercial products and/or product candidates in clinical development for LCA, we are not aware of any commercial products or product candidates in clinical development for the specific mutation (p.Cys998x) in the CEP290 gene that we target with QR-110. Our innovation unit is currently investigating multiple product candidates for possibilities for future development. Although we select our product candidates cautiously, chances are we may face competition by one of more competitors.

Many of our competitors possess significantly greater financial, technical, manufacturing, marketing, sales and supply resources or experience than us. If we successfully obtain approval for any product candidate, we will face competition based on many different factors, including the safety and effectiveness of our products, the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration, the timing and scope of regulatory approvals for these products, the availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position. Competing products could present superior treatment alternatives, including being more effective, safer, less expensive or marketed and sold more effectively than any products we may develop. Competitive products may make any products we develop obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan. Furthermore, in our clinical studies we could be competing for the same patient population, resulting in a smaller population of suitable candidates and possibly delays and additional costs.

If any of our product candidates is approved for marketing and commercialization and we are unable to develop sales, marketing and distribution capabilities on our own or enter into agreements with third parties to perform these functions on acceptable terms, we will be unable to successfully commercialize any such future products.

Although we currently intend to develop and commercialize QR-010 ourselves in major markets, if approved, we currently have no sales, marketing or distribution capabilities or experience. In addition, we intend to consider out-licensing, spinouts or collaborative partnerships to develop and commercialize our RNA repair technologies or programs in specific indications outside of CF. If any of our product candidates is approved, we will need to develop internal sales, marketing and distribution capabilities to commercialize such products, which would be expensive and time-consuming, or enter into collaborations with third parties to perform these services. If we decide to market our products directly, as we currently plan for QR-010, we will need to commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and supporting distribution, administration and compliance capabilities. If we rely on third parties with such capabilities to market our products or decide to co-promote products with collaborators, we will need to establish and maintain marketing and distribution arrangements with third parties, and there can be no assurance that we will be able to enter into such arrangements on acceptable terms or at all. In entering into third-party marketing or distribution arrangements, any revenue we receive will depend upon the efforts of the third parties and there can be no assurance that such third parties will establish adequate sales and distribution capabilities or be successful in gaining market acceptance of any approved product. If we are not successful in commercializing any product approved in the future, either on our own or through third parties, our business, financial condition, results of operations and prospects could be materially adversely affected.

Even if we receive marketing approval for any of our product candidates, it may not achieve broad market acceptance, which would limit the revenue that we generate from its sales.

The commercial success of any of our product candidates, if approved by the FDA, the EMA or other regulatory authorities, will depend upon the awareness and acceptance of the product among the medical community, including physicians, patients, patient advocacy groups and healthcare payors. Market acceptance of any of our product candidates, if approved, will depend on a number of factors, including, among others:

- our product candidates' demonstrated ability to treat patients and to provide patients with incremental therapeutic benefits, as compared with other available treatments;
- the relative convenience and ease of administration of our product candidates, including as compared with other treatments for patients;

- the prevalence and severity of any adverse side effects;
- limitations or warnings contained in the labeling approved for our product candidates by the FDA or the EMA;
- availability of alternative treatments, including therapies that improve the function of the defective CFTR protein already approved or expected to be commercially launched in the near future;
- pricing and cost effectiveness;
- the effectiveness of our sales and marketing strategies or those of our collaborators;
- our ability to increase awareness of our product candidates through marketing efforts;
- our ability to obtain sufficient third-party coverage or reimbursement; and
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage.

Moreover, our first commercial sale of QR-010, if ever, will trigger a milestone payment to CFFT of approximately $ 80 million pursuant to our agreement with CFFT. We may not have sufficient funds to support our milestone payment obligations to CFFT, which could have a material adverse effect on our business and prospects.

Even if we are able to commercialize any of our product candidates, the products may not receive coverage and adequate reimbursement from third-party payors, which could harm our business.

The availability of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates, if approved, will depend substantially on the extent to which the costs of these product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize any product candidate. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries.

The intended use of a drug product by a physician can also affect pricing. For example, CMS could initiate a National Coverage Determination administrative procedure, by which the agency determines which uses of a therapeutic product would and would not be reimbursable under Medicare. This determination process can be lengthy, thereby creating a long period during which the future reimbursement for a particular product may be uncertain.

Outside the United States, particularly in member states of the European Union, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations or the successful completion of health technology assessment procedures with governmental authorities can take considerable time after receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Certain countries allow companies to fix their own prices for medicines, but monitor and control company profits. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our RNA repair candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of any product candidate approved for marketing is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, financial condition, results of operations or prospects could be adversely affected.

Recently enacted and future legislation, including potentially unfavorable pricing regulations or other healthcare reform initiatives, may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and may negatively affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities or affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the Medicare Modernization Act, established the Medicare Part D program and provided authority for limiting the number of drugs that will be covered in any therapeutic class thereunder. The Medicare Modernization Act, including its cost reduction initiatives, could decrease the coverage and reimbursement rate that we receive for any of our approved products. Furthermore, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payors.

The Affordable Care Act, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug products. It also contains substantial new provisions intended to broaden access to health insurance, reduce or constrain the growth of health care spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on pharmaceutical and medical device manufacturers, and impose additional health policy reforms, any of which could negatively impact our business. A significant number of provisions are not yet, or have only recently become, effective, but the Affordable Care Act is likely to continue the downward pressure on pharmaceutical and medical device pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

We expect that the Affordable Care Act, as well as other healthcare reform measures that have been and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product, and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may compromise our ability to generate revenue, attain profitability or commercialize our products.

Even if any of our product candidates receive regulatory approval, they may still face future development and regulatory difficulties and any approved products will be subject to extensive post-approval regulatory requirements.

If we obtain regulatory approval for any of our product candidates, it would be subject to extensive ongoing requirements by the FDA, the EMA and foreign regulatory authorities governing the manufacture, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting of safety and other post-market information. The safety profile of any product will continue to be closely monitored by the FDA, the EMA and comparable foreign regulatory authorities after approval. If the FDA, the EMA or comparable foreign regulatory authorities become aware of new safety information after approval of any of our product candidates, these regulatory authorities may require labeling changes or establishment of a risk management strategy, impose significant restrictions on a product's indicated uses or marketing, impose ongoing requirements for potentially costly post-approval studies or post-market surveillance or impose a recall.

In addition, manufacturers of therapeutic products and their facilities are subject to continual review and periodic inspections by the FDA, the EMA and other regulatory authorities for compliance with cGMP regulations. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

- issue untitled letters or warning letters;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;

- require us to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical studies;
- refuse to approve pending applications or supplements to applications filed by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of products, or require us to initiate a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our products and generate revenue.

We are subject to anti-corruption laws, as well as export control laws, customs laws, sanctions laws and other laws governing our operations. If we fail to comply with these laws, we could be subject to civil or criminal penalties, other remedial measures and legal expenses, which could adversely affect our business, results of operations and financial condition.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or Bribery Act, the U.S. Foreign Corrupt Practices Act, or FCPA, and other anti-corruption laws that apply in countries where we do business and may do business in the future. The Bribery Act, FCPA and these other laws generally prohibit us, our officers, and our employees and intermediaries from bribing, being bribed or making other prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. We intend to operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we may participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions on countries and persons, customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by U.K., U.S. or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

If we receive regulatory approvals, we intend to market our product candidates in multiple jurisdictions where we have limited or no operating experience and may be subject to increased business and economic risks that could affect our financial results.

If we receive regulatory approvals, we plan to market our product candidates in jurisdictions where we have limited or no experience in marketing, developing and distributing our products. Certain markets have substantial legal and regulatory complexities that we may not have experience navigating. We are subject to a variety of risks inherent in doing business internationally, including:

- risks related to the legal and regulatory environment in non-U.S. jurisdictions, including with respect to privacy and data security, and unexpected changes in laws, regulatory requirements and enforcement;
- burdens of complying with a variety of foreign laws in multiple jurisdictions;
- potential damage to our brand and reputation due to compliance with local laws;

- fluctuations in currency exchange rates;
- political, social or economic instability;
- difficulty of effective enforcement of contractual provisions in local jurisdictions;
- the potential need to recruit and work through local partners;
- reduced protection for or increased violation of intellectual property rights in some countries;
- inadequate data protection against unfair commercial use;
- difficulties in managing global operations and legal compliance costs associated with multiple international locations;
- compliance with the Bribery Act, the FCPA, the OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, and similar laws in other jurisdictions;
- natural disasters, including earthquakes, tsunamis and floods;
- inadequate local infrastructure;
- compliance with trade control laws;
- the effects of applicable foreign tax structures and potentially adverse tax consequences; and
- exposure to local banking, currency control and other financial-related risks.

If we are unable to manage our international operations successfully, our financial results could be adversely affected.

Recent federal legislation and actions by state and local governments may permit reimportation of drugs from foreign countries into the United States, including foreign countries where the drugs are sold at lower prices than in the United States, which could materially adversely affect our operating results.

We may face competition in the United States for our product candidates, if approved, from CF therapies sourced from foreign countries that have placed price controls on pharmaceutical products. In the United States, the Medicare Modernization Act contains provisions that may change U.S. importation laws and expand pharmacists' and wholesalers' ability to import cheaper versions of an approved drug and competing products from Canada, where there are government price controls. These changes to U.S. importation laws will not take effect unless and until the Secretary of the HHS certifies that the changes will pose no additional risk to the public's health and safety and will result in a significant reduction in the cost of products to consumers. The Secretary of the HHS has so far declined to approve a reimportation plan. Proponents of drug reimportation may attempt to pass legislation that would directly allow reimportation under certain circumstances. Legislation or regulations allowing the reimportation of drugs, if enacted, could decrease the price we receive for any products that we may develop, including QR-010 and QR-110, and adversely affect our future revenues and prospects for profitability.

The FDA, the EMA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. If we are found to have improperly promoted off-label uses, we may become subject to significant liability.

The FDA, the EMA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products if approved. In particular, a product may not be promoted for uses that are not approved by the FDA, the EMA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for our product candidates, physicians may nevertheless prescribe them to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability.

In the United States, engaging in impermissible promotion of our products for off-label uses can also subject us to false claims litigation under federal and state statutes, which can lead to civil and criminal penalties and fines and agreements that materially restrict the manner in which we promote or distribute those products. These false claims statutes include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical or medical device company on behalf of the federal

government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government prevails in the lawsuit, the individual will share in any fines or settlement funds. Since 2004, these False Claims Act lawsuits against pharmaceutical and medical device companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements based on certain sales practices promoting off-label drug uses. This growth in litigation has increased the risk that a company will have to defend a false claim action, pay settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations, and be excluded from the Medicare, Medicaid, and other federal and state healthcare programs. If we do not lawfully promote our approved products, we may become subject to such litigation and, if we are not successful in defending against such actions, those actions may have a material adverse effect on our business, financial condition and results of operations.

Adverse decisions of tax authorities or changes in tax treaties, laws, rules or interpretations could have a material adverse effect on our business, results of operations, financial condition and cash flows.

The tax laws and regulations in the Netherlands, the jurisdiction of our incorporation and our current resident state for tax purposes, may be subject to change and there may be changes in enforcement of tax law. Additionally, European and other tax laws and regulations are complex and subject to varying interpretations. We cannot be sure that our interpretations are accurate or that the responsible tax authority agrees with our views. If our tax positions are challenged by the tax authorities, we could incur additional tax liabilities, which could increase our costs of operations and have a material adverse effect on our business, financial condition, and results of operations.

Further changes in the tax laws of the jurisdictions in which we operate could arise as a result of the base erosion and profit shifting (BEPS) project being undertaken by the Organisation for Economic Co-operation and Development (OECD). The OECD, which represents a coalition of member countries that encompass certain of the jurisdictions in which we operate, is undertaking studies and publishing action plans that include recommendations aimed at addressing what they believe are issues within tax systems that may lead to tax avoidance by companies. It is possible that the jurisdictions in which we do business could react to the BEPS initiative or their own concerns by enacting tax legislation that could adversely affect us or our shareholders through increasing our tax liabilities.

Risks Related to Our Business and Strategy

Any inability to attract and retain qualified key management and technical personnel would impair our ability to implement our business plan.

Our success largely depends on the continued service of key management and other specialized personnel. The loss of one or more members of our management board or other key employees or advisors could delay our research and development programs and materially harm our business, financial condition, results of operations and prospects. The relationships that our key managers have cultivated within our industry make us particularly dependent upon their continued employment with us. We are dependent on the continued service of our technical personnel because of the highly technical nature of our product candidates and technologies and the specialized nature of the regulatory approval process. Because our management board and key employees are not obligated to provide us with continued service, they could terminate their employment or services with us at any time without penalty, subject to providing any required advance notice. Our future success will depend in large part on our continued ability to attract and retain other highly qualified scientific, technical and management personnel, as well as personnel with expertise in clinical testing, manufacturing, governmental regulation and commercialization. We face competition for personnel from other companies, universities, public and private research institutions, government entities and other organizations.

We may experience difficulties in managing our growth and expanding our operations.

We have limited experience in drug development. As our product candidates enter and advance through pre-clinical studies and clinical trials, we will need to expand our development, regulatory and manufacturing capabilities or contract with other organizations to provide these capabilities for us. In the future, we expect to have to manage additional relationships with collaborators or partners, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

Our internal computer systems, or those of our CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs and adversely affect our business.

Despite the implementation of security measures, our information technology and other internal infrastructure systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. A significant disruption in the availability of our information technology and other internal infrastructure systems could cause interruptions in our collaborations with our partners and delays in our research and development work. For instance, the loss of pre-clinical data or data from any future clinical trial involving our product candidates could result in delays in our development and regulatory filing efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed.

Our current operations are concentrated and any events affecting this location may have material adverse consequences.

Although we have offices in Palo Alto, California, our current operations are primarily located in our facilities in Leiden, the Netherlands. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemics, power shortage, telecommunication failure or other natural or manmade accidents or incidents that result in us being unable to fully utilize the facilities may have a material adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions. Loss of access to these facilities may result in increased costs, delays in the development of our product candidates or interruption of our business operations. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Additionally, the lease agreement covering our current laboratories is scheduled to expire on December 31, 2020. To the extent that we are unable to find new facilities for our current operations or we are delayed in finding new facilities, any business interruption could have a material adverse effect on our business, financial position, results of operations and prospects.

The investment of our cash and cash equivalents is subject to risks which may cause losses and affect the liquidity of these investments.

As at December 31, 2015, we had approximately € 94,865,000 in cash and cash equivalents. To date, our cash and cash equivalents have been deposited primarily in savings and deposit accounts with original maturities of twelve months or less. Savings and deposit accounts generate a small amount of interest income. Any future investments may include term deposits, corporate bonds, money market funds and government securities, all in accordance with our cash management policy. These investments are subject to general credit, liquidity, market and interest rate risks. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our financial statements.

In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition.

Our business entails a significant risk of product liability and our ability to obtain sufficient insurance coverage could have a material effect on our business, financial condition, results of operations or prospects.

The use of our product candidates in pre-clinical studies, in clinical trials and the sale of any of our product candidates if approved, exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers or others selling or otherwise coming into contact with our product candidates. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, including as a result of interactions with alcohol or other drugs, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things:

- withdrawal of patients from our clinical trials;

- substantial monetary awards to patients or other claimants;
- decreased demand for any of our current or future product candidates following marketing approval, if obtained;
- damage to our reputation and exposure to adverse publicity;
- increased FDA or EMA warnings on product labels;
- litigation costs;
- distraction of management's attention from our primary business;
- loss of revenue; and
- the inability to successfully commercialize any of our current or future product candidates, if approved.

We will need to maintain product liability insurance coverage for our clinical trials. We may not be able to obtain such coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our share price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our financial condition, business and prospects could be materially adversely affected.

Our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.

Our ability to use our net operating losses, or NOLs, in the Netherlands is currently limited and may be further limited. Under Dutch income tax law, tax loss carry-forwards are subject to a time limitation of nine years. As at December 31, 2015, we had a total of approximately € 46.9 million tax loss carry-forwards available for offset against future taxable profits. The first amount of the tax loss carry-forwards will expire in 2021. There is also a risk that due to regulatory changes such as suspensions on the use for NOLs, our existing NOLs could expire or otherwise become unavailable to offset future income tax liabilities. For these reasons, we may not be able to use a material portion of the NOLs, even if we attain profitability.

Changes in accounting rules and regulations, or interpretations thereof, could result in unfavorable accounting charges or require us to change our compensation policies.

Accounting methods and policies for biopharmaceutical companies, including policies governing revenue recognition, research and development and related expenses and accounting for share-based compensation, are subject to review, interpretation and guidance from relevant accounting authorities, including the SEC. Changes to accounting methods or policies, or interpretations thereof, may require us to reclassify, restate or otherwise change or revise our financial statements, including those contained in this annual report.

Risks Related to Ownership of our Ordinary Shares

We cannot predict what the market price of our ordinary shares will be. As a result it may be difficult for you to sell your ordinary shares at or above the price at which you purchased them.

An active trading market for our shares may not be sustained. The market value of our ordinary shares may decrease from time to time. As a result of these and other factors, you may be unable to resell your shares of our ordinary shares at or above the price at which you purchased them. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair market value of your shares. Further, an inactive market may also impair our ability to raise capital by selling our ordinary shares and may impair our ability to enter into strategic partnerships or acquire companies or products by using our ordinary shares as consideration. The market price of our shares may be volatile, and you could lose all or part of your investment.

The trading price of our ordinary shares is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. For example, the price of our ordinary shares, which reached its high record of $24.99 per share at the close of the trading on March 10, 2015, decreased as low as $3.71 per share at the close of the trading on February 8, 2016. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this annual report, these factors include:

- the presentation of data at industry conferences by us and/or our competitors;
- the responses to any of our IND applications with the FDA and any of our CTA applications with the EMA;
- any current or future pre-clinical or clinical trials of our product candidates, including any delays in enrollment rates or timing of these trials;
- regulatory actions with respect to our products or our competitors' products;
- the recruitment or departure of key personnel;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- results of clinical trials of our competitors;
- the success of competitive products or technologies;
- actual or anticipated changes in our growth rate relative to our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the level of expenses related to any of our product candidates or pre-clinical or clinical development programs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;
- announcement or expectation of additional financing efforts;
- sales of our ordinary shares by us, our insiders or our other shareholders;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry and market conditions.

In addition, the stock market in general, and pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have sometimes been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our ordinary shares, regardless of our actual operating performance. The realization of any of the above risks or any of a broad range of other risks, including those described in these "Risk Factors," could have a dramatic and material adverse impact on the market price of our ordinary shares.

If securities or industry analysts publish inaccurate or unfavorable research or cease to publish research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares depends in part on the research and reports that securities or industry analysts publish about us or our business. In the event securities or industry analysts, who cover us downgrade our ordinary shares, publish inaccurate or unfavorable research about our business, or cease publishing about us, our share price would likely decline. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Sales of a substantial number of our ordinary shares in the public market could cause our share price to fall.

Sales of a substantial number of our ordinary shares in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our ordinary shares. As at December 31, 2015, we have 23,345,965 outstanding ordinary shares.

Members of our management board and supervisory board and our principal shareholders and their affiliates have significant control over our company, which will limit your ability to influence corporate matters and could delay or prevent a change in corporate control.

The holdings of the members of our management board and supervisory board and our principal shareholders and their affiliates, represent significant ownership, in the aggregate, of our outstanding ordinary shares (as set out in "Item 7.A. Major Shareholders"). As a result, these shareholders, if they act together, will be able to influence our management and affairs and control the outcome of matters submitted to our shareholders for approval, including the election of directors and any sale, merger, consolidation, or sale of all or substantially all of our assets. These shareholders may have interests, with respect to their ordinary shares, that are different from other investors and the concentration of voting power among these shareholders may have an adverse effect on the price of our ordinary shares. In addition, this concentration of ownership might adversely affect the market price of our ordinary shares by:

- delaying, deferring or preventing a change of control of us;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

Please see "Item 7.A. Major Shareholders" for more information regarding the ownership of our outstanding ordinary shares by our management board and supervisory board and our principal shareholders and their affiliates.

Because we do not anticipate paying any cash dividends on our ordinary shares in the foreseeable future, capital appreciation, if any, will be your sole source of potential gain.

We have never declared or paid cash dividends on our ordinary shares. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our ordinary shares will be your sole source of gain for the foreseeable future.

We are an "emerging growth company" and we intend to take advantage of reduced disclosure and governance requirements applicable to emerging growth companies, which could result in our ordinary shares being less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act, and we are taking advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We do not know if investors will find our ordinary shares less attractive because we are relying on these exemptions. We may take advantage of these reporting exemptions until we are no longer an emerging growth company, which could be for up to five years after our initial public offering in September 2014.

If investors find our ordinary shares less attractive as a result of our reduced reporting requirements, there may be a less active trading market for our ordinary shares and our share price may be more volatile. We may also be unable to raise additional capital as and when we need it.

We have been a listed company since September 2014, and therefore, have a limited history operating as a public company and complying with public company obligations. Complying with all requirements, particularly after we are no longer an "emerging growth company" that enjoys reduced requirements, will increase our costs, require additional management resources and qualified accounting and financial personnel, and we may fail to meet all of these obligations.

We face increased legal, accounting, administrative and other costs and expenses as a public company. Compliance with the Sarbanes-Oxley Act of 2002, the Dodd-Frank Act of 2010, the Dutch Financial Supervision Act and the rules promulgated thereunder, as well as rules of the SEC and NASDAQ and the Dutch Corporate Governance Code, or DCGC, for example, are expected to result in ongoing increases in our legal, audit and financial compliance costs, particularly after we are no longer an "emerging growth company." The Securities Exchange Act of 1934, as amended, or the Exchange Act, requires, among other things, that we file certain periodic reports with respect to our business and financial condition. Our management board, officers and other personnel need to devote a substantial amount of time to these compliance initiatives. We expect to incur significant expense and devote substantial management effort toward ensuring compliance with Section 404 of the Sarbanes-Oxley Act of 2002 in preparation for and once we lose our status as an "emerging growth company." We currently do not have an internal audit group, and we will need to continue to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge, and it may be difficult to recruit and maintain such personnel. Implementing any appropriate changes to our internal controls may require specific compliance training for our directors, officers and employees, entail substantial costs to modify our existing accounting systems, and take a significant period of time to complete. Such changes may not, however, be effective in maintaining the adequacy of our internal controls, and any failure to maintain that adequacy, or consequent inability to produce accurate financial statements or other reports on a timely basis, could increase our operating costs and could materially impair our ability to operate our business.

If we fail to establish and maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ordinary shares.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act of 2002, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ordinary shares.

We will be required to disclose changes made in our internal controls and procedures on a quarterly basis and our management board will be required to assess the effectiveness of these controls annually. However, for as long as we are an "emerging growth company" under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. We could be an "emerging growth company" for up to five years. An independent assessment of the effectiveness of our internal controls could detect problems that our management's assessment might not. Undetected material weaknesses in our internal controls could lead to financial statement restatements and require us to incur the expense of remediation.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Risks Related to Investing in a Foreign Private Issuer or a Dutch Company

We are a foreign private issuer and, as a result, we are not subject to U.S. proxy rules and are subject to Exchange Act reporting obligations that, to some extent, are more lenient and less frequent than those of a U.S. domestic public company.

We report under the Exchange Act as a non-U.S. company with foreign private issuer status. Because we qualify as a foreign private issuer under the Exchange Act and although we are subject to Dutch laws and regulations with regard to such matters and intend to furnish quarterly financial information to the SEC, we are exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including:

- the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations in respect of a security registered under the Exchange Act;
- the sections of the Exchange Act requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades made in a short period of time; and
- the rules under the Exchange Act requiring the filing with the SEC of quarterly reports on Form 10-Q containing unaudited financial and other specified information, or current reports on Form 8-K, upon the occurrence of specified significant events.

In addition, foreign private issuers are not required to file their annual report on Form 20-F until 120 days after the end of each fiscal year, while U.S. domestic issuers that are accelerated filers are required to file their annual report on Form 10-K within 75 days after the end of each fiscal year. Foreign private issuers are also exempt from the Regulation Fair Disclosure, aimed at preventing issuers from making selective disclosures of material information. As a result of the above, you may not have the same protections afforded to shareholders of companies that are not foreign private issuers.

We may lose our foreign private issuer status which would then require us to comply with the Exchange Act's domestic reporting regime and cause us to incur significant legal, accounting and other expenses.

We are a foreign private issuer and therefore we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. In order to maintain our current status as a foreign private issuer, either:

- a majority of our ordinary shares must be either directly or indirectly owned of record by non-residents of the United States; or
- a majority of our "executive officers" or directors may not be U.S. citizens or residents, more than 50% of our assets cannot be located in the United States and our business must be administered principally outside the United States.

If we lose this status, we would be required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers.

We may also be required to make changes in our corporate governance practices in accordance with various SEC and NASDAQ rules. The regulatory and compliance costs to us under U.S. securities laws if we are required to comply with the reporting requirements applicable to a U.S. domestic issuer may be significantly higher than the costs we would incur as a foreign private issuer. As a result, we expect that a loss of foreign private issuer status would increase our legal and financial compliance costs and would make some activities more time consuming and costly. We also expect that if we were required to comply with the rules and regulations applicable to U.S. domestic issuers, it would make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our supervisory board.

We currently report our financial results under IFRS, which differ in certain significant respect from U.S. GAAP.

Currently we report our financial statements under IFRS. There have been and there may in the future be certain significant differences between IFRS and U.S. GAAP, including differences related to revenue recognition, share-based compensation expense, income tax and earnings per share. As a result, our financial information and reported earnings for historical or future periods could be significantly different if they were prepared in accordance with U.S. GAAP. In addition, we do not intend to provide a reconciliation between IFRS and U.S. GAAP unless it is required under applicable law. As a result, you may not be able to meaningfully compare our financial statements under IFRS with those companies that prepare financial statements under U.S. GAAP.

Provisions of our articles of association or Dutch corporate law might deter acquisition bids for us that might be considered favorable and prevent or frustrate any attempt to replace or remove the management board and supervisory board.

Certain provisions of our articles of association may make it more difficult for a third party to acquire control of us or effect a change in our management board or supervisory board. These provisions include:

- the authorization of a class of preferred shares that may be issued against payment of 25% of the nominal value thereof to a protection foundation, for which we have granted a perpetual and repeatedly exercisable call option to such protection foundation, for up to such number of preferred shares as equals, at the time of exercise of the call option, the lesser of: (i) the total number of shares equal to our issued share capital at that time minus the number of preferred shares already held by the protection foundation at that time (if any) or (ii) the maximum number of preferred shares that may be issued under our authorized share capital under our articles of association from time to time;
- the staggered four-year terms of our supervisory board members, as a result of which only approximately one-fourth of our supervisory board members will be subject to election in any one year;
- a provision that our management board members and supervisory board members may only be appointed upon a binding nomination by our supervisory board, which can be set aside by a two-thirds majority of our shareholders representing more than half of our issued share capital;
- a provision that our management board members and supervisory board members may only be removed by our general meeting of shareholders by a two-thirds majority of votes cast representing more than 50% of our issued share capital (unless the removal was proposed by the supervisory board); and
- a requirement that certain matters, including an amendment of our articles of association, may only be brought to our shareholders for a vote upon a proposal by our management board that has been approved by our supervisory board.

As indicated above, we have adopted an anti-takeover measure by granting a perpetual and repeatedly exercisable call option to the protection foundation, which confers upon the protection foundation the right to acquire, under certain conditions, the number of preferred shares described above. The issuance of such preferred shares will occur upon the protection foundation's exercise of the call option and will not require shareholder consent. Such a measure has the effect of making a takeover of us more difficult or less attractive and as a result, our shareholders may be unable to benefit from a change of control and realize any potential change of control premium which may materially and adversely affect the market price of our ordinary shares.

We are not obligated to and do not comply with all the best practice provisions of the Dutch Corporate Governance Code. This may affect your rights as a shareholder.

As a Dutch company we are subject to the DCGC. The DCGC contains both principles and best practice provisions that regulate relations between the management board, the supervisory board and the shareholders (i.e. the general meeting of shareholders). The DCGC is based on a "comply or explain" principle. Accordingly, companies are required to disclose in their annual reports, filed in the Netherlands, whether they comply with the provisions of the DCGC. If they do not comply with those provisions (e.g., because of a conflicting NASDAQ requirement), we are required to give the reasons for such non-compliance.

The DCGC applies to all Dutch companies listed on a government-recognized stock exchange, whether in the Netherlands or elsewhere, including NASDAQ. We do not comply with all the best practice provisions of the DCGC. This may affect your rights as a shareholder and you may not have the same level of protection as a shareholder in a Dutch company that fully complies with the DCGC.

We intend to rely in certain cases on NASDAQ Stock Market rules that permit us to comply with applicable Dutch corporate governance practices, rather than the corresponding domestic U.S. corporate governance practices, and therefore your rights as a shareholder will differ from the rights you would have as a shareholder of a domestic U.S. issuer.

As a foreign private issuer whose ordinary shares are listed on The NASDAQ Global Market, we are permitted in certain cases to follow Dutch corporate governance practices instead of the corresponding requirements of the NASDAQ Marketplace Rules. A foreign private issuer that elects to follow a home country practice instead of NASDAQ requirements must submit to NASDAQ in advance a written statement from an independent counsel in such issuer's home country certifying that the issuer's practices are not prohibited by the home country's laws. In addition, a foreign private issuer must disclose in its annual reports filed with the SEC each

such requirement that it does not follow and describe the home country practice followed instead of any such requirement. We intend to follow Dutch corporate governance practices with regard to the quorum requirements applicable to meetings of shareholders and the provision of proxy statements for general meetings of shareholders, rather than the corresponding domestic U.S. corporate governance practices. In accordance with Dutch law and generally accepted business practices, our articles of association do not provide quorum requirements generally applicable to general meetings of shareholders. Although we do intend to provide shareholders with an agenda and other relevant documents for the general meeting of shareholders, Dutch law does not have a regulatory regime for the solicitation of proxies and the solicitation of proxies is not a generally accepted business practice in the Netherlands. Accordingly, our shareholders may not be afforded the same protection as provided under NASDAQ's corporate governance rules.

U.S. holders of our ordinary shares may suffer adverse tax consequences if we are characterized as a passive foreign investment company.

Generally, if, for any taxable year, at least 75% of our gross income is passive income, or at least 50% of the value of our assets is attributable to assets that produce passive income or are held for the production of passive income, including cash, we would be characterized as a passive foreign investment company, or PFIC, for U.S. federal income tax purposes. For purposes of these tests, passive income includes dividends, interest, and gains from the sale or exchange of investment property and rents and royalties other than rents and royalties which are received from unrelated parties in connection with the active conduct of a trade or business. If we are characterized as a PFIC, our U.S. shareholders may suffer adverse tax consequences, including having gains realized on the sale of our ordinary shares treated as ordinary income, rather than capital gain, the loss of the preferential rate applicable to dividends received on our ordinary shares by individuals who are U.S. holders, and having interest charges apply to distributions by us and the proceeds of share sales. See Item 10.E: "Taxation" for more information.

Since PFIC status depends on the composition of our income and the composition and value of our assets (which, if we are not a "controlled foreign corporation" under Section 957(a) of the Code or we are publicly traded for the entire year being tested, may be determined in large part by reference to the market value of our ordinary shares, which may be volatile) from time to time, there can be no assurance that we will not be considered a PFIC for any taxable year. Although the matter is not free from doubt, we believe that we were not a PFIC with respect to our 2015 taxable year.

Any U.S. or other foreign judgments you may obtain against us may be difficult to enforce against us in the Netherlands.

We are incorporated under the laws of the Netherlands. We currently have only limited operations in the United States. Most of our assets are currently located in the Netherlands. The majority of our management board, supervisory board and officers reside outside the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce against them or us in U.S. courts, including judgments predicated upon the civil liability provisions of the federal securities laws of the United States. In addition, it is not clear whether a Dutch court would impose civil liability on us or any of our managing directors or supervisory directors in an original action based solely upon the federal securities laws of the United States brought in a court of competent jurisdiction in the Netherlands.

The United States and the Netherlands currently do not have a treaty providing for the reciprocal recognition and enforcement of judgments, other than arbitration awards, in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the Netherlands. In order to obtain a judgment which is enforceable in the Netherlands, the party in whose favor a final and conclusive judgment of the U.S. court has been rendered will be required to file its claim with a court of competent jurisdiction in the Netherlands. Such party may submit to the Dutch court the final judgment rendered by the U.S. court. If and to the extent that the Dutch court finds that the jurisdiction of the U.S. court has been based on grounds which are internationally acceptable and that proper legal procedures have been observed, the Dutch court will, in principle, give binding effect to the judgment of the U.S. court, unless such judgment contravenes principles of public policy of the Netherlands. Dutch courts may deny the recognition and enforcement of punitive damages or other awards. Moreover, a Dutch court may reduce the amount of damages granted by a U.S. court and recognize damages only to the extent that they are necessary to compensate actual losses or damages. Enforcement and recognition of judgments of U.S. courts in the Netherlands are solely governed by the provisions of the Dutch Code of Civil Procedure.

Based on the lack of a treaty as described above, U.S. investors may not be able to enforce against us or our management board or supervisory board members, representatives or certain experts named herein who are residents of the Netherlands or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

The rights and responsibilities of our shareholders are governed by Dutch law and differ in some important respects from the rights and responsibilities of shareholders under U.S. law.

Our corporate affairs are governed by our articles of association, our internal rules and by the laws governing companies incorporated in the Netherlands. The rights of our shareholders and the responsibilities of members of our supervisory board under Dutch law are different than under the laws of some U.S. jurisdictions. In the performance of their duties, our management board and our supervisory board are required by Dutch law to consider the interests of ProQR Therapeutics, its shareholders, its employees and other stakeholders and not only those of our shareholders. Also, as a Dutch company, we are not required to solicit proxies or prepare proxy statements for general meetings of shareholders. Dutch law does not have a regulatory regime for U.S.- style proxy solicitations and, even though Dutch law accommodates voting by proxy, the solicitation of proxies is not a widely used business practice in the Netherlands. In addition, the rights of holders of shares and many of the rights of shareholders as they relate to, for example, the exercise of shareholder rights, are governed by Dutch law and our articles of association and differ from the rights of shareholders under U.S. law. For example, Dutch law does not grant appraisal rights to a company's shareholders who wish to challenge the consideration to be paid upon a merger or consolidation of the company.

Item 4: Information on the Company

A. History and development of the company

ProQR Therapeutics is dedicated to changing lives through the creation of transformative RNA medicines for the treatment of severe orphan diseases such as cystic fibrosis and Leber's congenital amaurosis. Based on our unique proprietary RNA repair platform technologies we are growing our pipeline with patients and loved ones in mind.

Our legal name is ProQR Therapeutics N.V. and we were incorporated in the Netherlands, on February 21, 2012. We reorganized from a private company with limited liability to a public company with limited liability on September 23, 2014. Our Company has its statutory seat in Leiden, the Netherlands. The address of its headquarters and registered office is Darwinweg 24, 2333 CR Leiden, the Netherlands, telephone number +31 88 166 7000. The name and address of our agent for service in the United States is C T Corporation System, 111 Eighth Avenue, New York, NY 10011.

Since September 18, 2014, our ordinary shares have been listed on the NASDAQ Global Market under the ticker symbol PRQR.

B. Business overview

Overview

We are an innovative biopharmaceutical company engaged in the discovery and development of RNA-based therapeutics for the treatment of severe genetic orphan disorders. Utilizing our unique proprietary RNA repair technologies we are building a pipeline in severe genetic disorders. We believe we can target rare genetic disorders in which a single protein is defective due to certain types of genetic mutations. We design our therapeutic candidates to specifically target and repair the defective messenger RNA, or mRNA, that is transcribed from a mutated gene in order to restore functional or normal (wild-type) protein and therefore, we believe, has the potential to modify the disease. We believe that this unique approach offers several advantages compared with small molecule, gene therapy and other therapeutic approaches in the treatment of certain genetic diseases. Our current clinical stage molecule is QR-010, a single stranded RNA-based oligonucleotide that is designed to repair the genetic defect in the most prevalent mutation in cystic fibrosis, or CF. We are currently studying this molecule in two global clinical trials in 80 CF patients. Our second molecule is QR-110, a single stranded RNA-based oligonucleotide that targets the most prevalent mutation in the CEP290 gene for Leber's congenital amaurosis, or LCA, patients and is currently in preclinical development. Beyond that, our in-house discovery engine that we call the innovation unit has been active in building a pipeline based upon our toolbox of RNA technologies that we have in-licensed or developed in-house. We have launched a number of discovery programs including programs in dystrophic epidermolysis bullosa, Usher syndrome, Fuchs endothelial corneal dystrophy (FECD), Huntington's disease, Alzheimer's disease and Friedreich's ataxia.

QR-010 and Cystic Fibrosis (CF)

CF is a genetic disease that affects an estimated 70,000 to 100,000 patients worldwide and causes early morbidity and mortality. CF currently has no cure. The median age of death for CF patients in the US is 27 years, and more than 90% of CF patients die from respiratory failure. To date, all but two of the therapies approved to treat CF patients are designed to treat the symptoms of CF rather than address the underlying cause. CF is caused by mutations in the gene that encodes for a protein called cystic fibrosis

transmembrane conductance regulator, or CFTR. Although there are more than 1,900 different genetic mutations that cause CF, the ΔF508 mutation that we are targeting is the most prevalent and is present in approximately 70% of all CF patients. In CF patients, this mutated gene and the resulting defective protein lead to the dysfunction of multiple organ systems, including the lungs, pancreas and gastrointestinal tract. In the lung airways, absence of functional CFTR protein leads to unusually thick, sticky mucus that clogs the lungs and increases vulnerability to chronic, life-threatening lung infections.

Our lead product candidate in the CF space, QR-010, a first-in-class RNA-based oligonucleotide, is designed to address the underlying cause of the disease by repairing the mRNA defect encoded by the ΔF508 mutation in the CFTR gene of CF patients and subsequently producing wild-type, or normal CFTR protein. QR-010 is designed to be self-administered through a small, handheld aerosol delivery device, or nebulizer, in the form of a mist inhaled into the lungs. In pre-clinical studies we have shown this method could allow maximum exposure of QR-010 to the primary target organ, the lung, as well as significant exposure to other affected organs through systemic absorption into the blood. Based on our extensive pre-clinical studies on safety, delivery and efficacy in relevant cell and animal models we have started two global clinical studies of QR-010 in 2015.

In June 2015, we started enrollment in our first clinical trial directly in CF patients. This Phase 1b clinical trial, which we refer to as PQ-010-001, is a randomized, double-blind, placebo-controlled, 28-day dose-escalation study that is conducted in 23 sites in North America and Europe. The primary endpoint of the study is to evaluate the safety, tolerability and absorption, distribution and degradation, or pharmacokinetics, of single and multiple ascending doses of inhaled QR-010 in 64 CF patients carrying two copies (homozygotes) of the ΔF508 mutation. As exploratory efficacy endpoints, this study will also assess sweat chloride, weight gain, CFQ-R Respiratory Symptom Score and lung function, measured by FEV_1. These measures could be indicative of the potential efficacy of QR-010 although the study is not powered for statistical significance on these endpoints. In parallel with our Phase 1b trial we are conducting a proof-of-concept, or POC, study, which we refer to as PQ-010-002, designed to investigate the drug candidate's ability to restore CFTR function in the nasal lining of eight ΔF508 homozygous (carry two allelic copies) and eight compound heterozygous (carry one copy of the ΔF508 mutation and one other disease causing mutation). We expect to report top-line data from both our Phase 1b trial and our POC study in mid to late 2016.

QR-010 has been granted orphan drug designation in the United States and the European Union. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of market exclusivity. This exclusivity precludes the U.S. Food and Drug Administration, or FDA, or the European Medicines Agency, or EMA, as applicable, from approving another marketing application for the same or, in the European Union, a similar drug for the same indication for that time period, unless the later product is clinically superior. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

QR-110 and Leber's Congenital Amaurosis (LCA)

LCA is the most common genetic cause of blindness in childhood. LCA is caused by a genetic defect in 19 or more associated genes. The most common mutation is the p.Cys998X (also known as c.2991+1655A>G) in the CEP290 (Centrosomal protein of 290 kDa) gene. Although diagnosis rates vary, based on our estimations we believe this mutation occurs in approximately 2,000 patients in the Western world. Most patients affected by this mutation lose sight in the first few years of life. There is currently no disease modifying therapy available on the market or being tested in clinical development for this specific subtype of the disease. In LCA patients, this mutation leads to significant decrease of active CEP290 protein in the photoreceptor cells in the retina in the eye. The absence of this essential protein causes blindness.

Our lead product candidate in the LCA space, QR-110, a first-in-class oligonucleotide, is designed to treat the disease by repairing the underlying cause in the mRNA, which results in the production of wild-type CEP290 protein. The p.Cys998X mutation is a substitution of one nucleotide in the pre-mRNA that leads to a defective mRNA and non-functional protein. QR-110 is designed to bind to the mutated location in the pre-mRNA, thereby leading to normally spliced or wild-type mRNA, which could produce wild-type or normal protein. QR-110 is designed to be administered through intravitreal injections in the eye. We believe the activity in pre-clinical models of LCA provides support for the clinical development and therapeutic potential of QR-110. In 2016 we intend to start our first clinical trial directly in LCA patients. There is recent precedent for an accelerated development path in another LCA mutation, and we believe this accelerated development pathway can also be applied to QR-110.

We have filed for orphan drug designation for QR-110 in the U.S. and the European Union.

Innovation pipeline

Beyond CF and LCA, our innovation unit, which is our internal discovery engine, is currently evaluating over 100 disease targets through our internal research or that of external collaborators. These disease targets are based on our multiple RNA technologies that were discovered internally or in-licensed. We have a rigorous evaluation process in identifying programs for our pipeline that includes establishing genetic causality, ability to deliver to the target organ, intellectual property protection, strong proof of concept, and a high unmet need. Our early stage programs are in various stages of discovery and target different severe genetic disorders where we believe our technologies have the potential to make a life altering impact for affected patients. These include programs for epidermolysis bullosa, a severe genetic skin disorder that impacts young children, Usher syndrome and Fuchs endothelial corneal dystrophy (FECD) programs in areas of ophthalmology with high unmet medical need, programs in our early central nervous system, or CNS, franchise that include Huntington's disease and Alzheimer's disease as well as a program for Friedreich's ataxia.

ProQR was founded in February 2012 by Daniel de Boer, Gerard Platenburg, Henri Termeer and Dinko Valerio. Mr. de Boer is a passionate and driven entrepreneur and advocate for CF patients, and has assembled an experienced team of successful biotech executives as co-founders and early investors. The team has extensive experience in discovery, development and commercialization of products in multiple therapeutic areas and RNA therapeutics. To date, we have raised approximately €133 million in gross proceeds from our initial public offering of shares on the NASDAQ Global Market and private placements of equity securities. In addition, we have received grants, loans and other funding from CF-focused patient organizations and government institutions supporting our program for CF, including from Cystic Fibrosis Foundation Therapeutics, Inc., a subsidiary of the Cystic Fibrosis Foundation and the European Union under their Horizon 2020 research and innovation programme, grant agreement No. 633545. ProQR headquarters are in Leiden, the Netherlands and we have an office in Palo Alto, CA, United States.

Our Strategy

We are dedicated to improving the lives of patients through the development of RNA-based therapies for severe genetic orphan diseases and have an initial focus on patients with CF and LCA. Key elements of our strategy include:

- ***Rapidly advance QR-010 for the treatment of CF.*** Our lead product candidate in the CF space, QR-010, has generated compelling data in pre-clinical studies, which we believe support its potential as a disease-modifying therapy for CF patients. We are currently running two global clinical studies of QR-010 in 80 CF patients with the ΔF508 mutation, which affects approximately 70% of all CF patients. Top-line data is expected to be released mid to late 2016. We are studying applications of our RNA repair technologies for mutations other than ΔF508.

- ***Rapidly advance our ophthalmology franchise, including QR-110 for the treatment of LCA.*** We recognize the great opportunity for oligonucleotides in the ophthalmology space and therefore have established an ophthalmology franchise that now has one program in development and several in the discovery pipeline. These include LCA, Usher syndrome and Fuchs endothelial corneal dystrophy (FECD). We are developing QR-110 to treat patients with the most common mutation causing LCA, the leading genetic cause of blindness in childhood. We conducted further pre-clinical studies during 2015 and expect to start our first clinical trial in LCA patients in 2016. We intend to advance our Usher and Fuchs programs towards pre-clinical development in 2016.

- ***Utilize our proprietary RNA repair technologies and know-how to develop additional product candidates targeting genetic diseases with high unmet medical need.*** We are developing a product pipeline targeting severe genetic diseases that have significant unmet need and are caused by mutations that we believe can be treated with our RNA technologies. We are currently working on approximately 100 potential target indications in several therapeutic areas and have organized our discovery effort in franchises such as respiratory, ophthalmology, dermatology, CNS and neuromuscular disorders.

- ***Independently commercialize QR-010.*** We intend to commercialize QR-010 ourselves, if approved, and retain all commercial rights in major markets. For QR-010, there are extensive CF patient registries, and CF patients are treated in centralized, specialized care centers. Because of this well-organized CF community, we believe we will be able to market QR-010 effectively, if approved, with an initially small, targeted sales force in the United States and Europe.

- ***Consider outlicensing, spinouts or collaborative partnerships to develop and commercialize our RNA repair technologies or programs in specific indications outside of CF.*** To continue to advance the programs in our discovery pipeline and ensure that these programs have the potential to make an impact for patients in these areas of unmet need, we will consider strategic alternatives that include spinouts, outlicensing or collaborative partnerships with pharmaceutical companies. These partnerships may provide us with further validation of our RNA repair technologies, funding to advance our product candidates and access to development, manufacturing and commercial expertise and capabilities.

Our RNA Technologies

Genes are the specific sequences of DNA that provide the blueprint used by the human body's cells to make proteins, which are enzymes or other molecules in cells that serve a functional purpose. Each gene consists of a specific sequence of nucleotides that leads to the production of a specific protein. The gene's coding DNA sequence is transcribed into mRNA, which is subsequently translated into the specific protein. A mutation, or defect, in a specific gene can result in the transcription of abnormal mRNA, which then can produce a defective, misfolded or truncated protein that is unable to carry out its normal function.

In the maturing RNA therapeutics space and the developments in understanding their potential, we have gathered a toolbox of different novel RNA technologies with which we believe we can repair and modulate defective mRNA in order to restore protein functionality. This is unlike other approaches in the RNA therapeutics field, such as RNAi and antisense that use RNA molecules to downregulate genes. All our approaches employ single-stranded RNA-based oligonucleotides that are chemically modified (phosphorothioate backbone and 2' O-methyl modifications) so that no vector or envelope is needed for delivery. Our molecules are designed to act as guide sequences to repair or modulate the targeted abnormal mRNA. The repaired mRNA then acts as a template to generate protein. We believe these RNA approaches will allow us to develop novel therapies for genetic disorders that are currently untreatable or have limited effective treatment options.

For CF, QR-010 is designed to repair the defective mRNA by guiding the insertion of the three nucleotides missing in the ΔF508 mutation, thus resulting in the production of wild-type CFTR protein that is expected to have the same functionality as CFTR protein in healthy individuals. We believe we are the only company currently pursuing this RNA repair approach for CF patients.

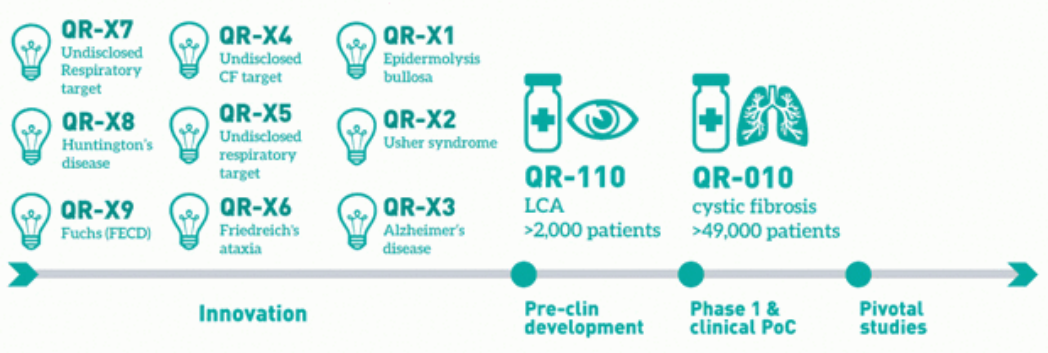
For LCA, QR-110 is designed to repair the defective pre-mRNA due to a single nucleotide substitution mutation called the p.Cys998X mutation in the CEP290 gene. By binding to the mutation site, QR-110 masks the cryptic splice site that is the result of the mutation. Correct splicing of the pre-mRNA can then occur restoring production of wild-type CEP290 protein that is expected to have the same functionality as CEP290 protein in healthy individuals. We believe we are the only company currently pursuing this RNA repair approach for this specific mutation of LCA.

Our product candidates

In selection of discovery programs to bring into our development pipeline we apply a rigorous process of review by a committee of internal and external key opinion leaders, or KOLs to all key aspects of a program. Among others we look at the following criteria:

- ✓ High unmet medical need
- ✓ A pre-clinical proof-of-concept that shows strong promise for translation to the clinic
- ✓ Well understood relationship between the genetic defect and the disease manifestations
- ✓ Feasibility of delivery to target organ(s)
- ✓ Strong IP position and initial freedom to operate established

We believe our current pipeline represents a mix of high-value indications where we can make a big impact to the lives of patients:



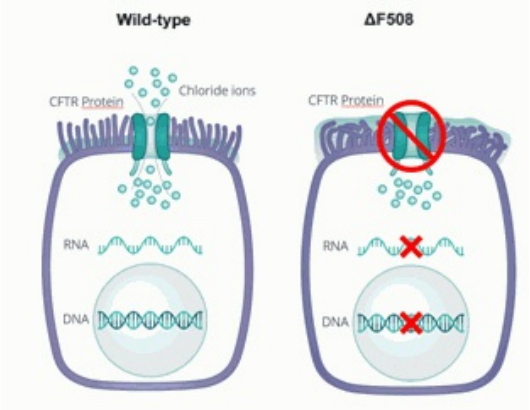
Cystic Fibrosis

Cystic Fibrosis Background

CF is the most common fatal inherited disease in the Western world and affects an estimated 70,000 to 100,000 patients worldwide. There is no cure for CF. CF patients require lifelong treatment with multiple daily medications, frequent hospitalizations and ultimately lung transplants, which can extend life for five years on average. The quality of life for CF patients is compromised by approximately four hours of self-care per day and frequent outpatient doctor visits and hospitalizations.

CF is caused by mutations in a gene that encodes the CFTR protein. The CFTR protein channel regulates the movement, or efflux, of specific ions in and out of the cells of organs like the lungs, pancreas and gastrointestinal tract. Through regulation of these ions, the amount of salts in the fluid both inside and outside the cell remains balanced. In CF patients, however, the CFTR protein is defective and cannot perform its normal function of transporting ions across the cell membrane, and this results in an environment characterized by thick mucus in vital organs such as the lung, the pancreas and the gastrointestinal tract. The figure below illustrates a defective CFTR protein hampering the efflux of chloride in lung epithelial cells.

Chloride Ion Flow by Wild-Type CFTR and ΔF508 CFTR



The lack of functional CFTR in CF patients is particularly problematic in the lungs, where the build-up of thick mucus obstructs parts of the lung, allows bacteria to grow unfettered and impairs the functionality of the local immune system. Of all the manifestations of CF, lung disease is the most critical and is characterized by a combination of airway obstruction, infection and inflammation such that more than 90% of all CF patients die of respiratory failure. In the pancreas, the buildup of mucus prevents the release of digestive enzymes that help the body break down food and absorb important nutrients. In the GI tract, the thick mucus leads to impaired ability to absorb nutrients. The median age of death for all CF patients in the U.S. is 27 years.

According to the medical literature, restoration of as little as approximately 15% of wild-type CFTR function in CF patients should result in a therapeutic benefit.

Cystic Fibrosis Genetics

CF is an autosomal recessive disease. A normal, healthy gene has two alleles that encode for a given protein. In an autosomal recessive disease such as CF, a patient has a mutation in both alleles. Non-affected carriers have a mutation in only one of the alleles. CF patients have a defect in the gene encoding for the CFTR protein, and they either have two copies of the same mutation, referred to as homozygotes, or one copy of two different mutations, referred to as compound heterozygotes. Although over 1,900 CF-causing gene mutations have been identified, approximately 70% of all CF patients are affected by the ΔF508 mutation. Among all CF patients, approximately 50% are homozygous for the ΔF508 mutation and approximately 20% are heterozygous for the ΔF508 mutation.

In the ΔF508 mutation, the genetic defect is a deletion of three of the coding base pairs, or nucleotides, in the CFTR gene that results in the transcription of defective mRNA, which results in the production of CFTR protein that is misfolded and can neither migrate to its normal location on the surface of epithelial cells nor perform its normal function. The figure below illustrates the missing three nucleotide sequence in the mRNA.

Cystic Fibrosis Incidence and Diagnosis

CF affects one out of 3,500 live births in the United States and one out of 2,500 live births in Western Europe. Many individuals are also non-affected carriers of a mutated CFTR gene. Carrier results across ethnic groups in the United States are well established, and reports from the American College of Obstetricians and Gynecologists indicate rates of one out of 25 in non-Hispanic Caucasians, one out of 58 in Hispanic Caucasians, one out of 61 in African Americans, and one out of 94 in Asian Americans. While the life expectancy of CF patients has improved over the last three decades, the median age of death is still only 27 years in the U.S.

Most CF patients in the United States, the European Union, Canada and Australia are now diagnosed at birth through newborn screening, and more than 75% of CF patients are diagnosed by the age of two. CF can be diagnosed by conducting a Nasal Potential Difference, or NPD, test that measures CFTR activity in the nose, or a pilocarpine iontophoretic sweat chloride test, which measures the amount of salt in a person's sweat. A genetic test is also often used to confirm a CF diagnosis and/or identify the disease-causing mutations. In a genetic test, a blood sample or cells from the inside of the cheek are taken and sent to a laboratory that specializes in genetic testing.

Approaches to the Treatment of Cystic Fibrosis

Treatment overview

There is no cure for CF, and to date, all but one of the therapies approved to treat CF patients have been designed to treat the symptoms rather than address the underlying cause. CF patients require lifelong treatment with multiple daily medications, frequent hospitalizations and ultimately lung transplant, which is life-extending but not curative. In the United States, the average CF patient incurs approximately $50,000 per year in expenses for outpatient medications and services and substantial additional costs for frequent hospitalizations. As the median age of death for CF patients is 27, this results in an average lifetime cost per CF patient in the U.S. of $1,350,000 in outpatient expenses alone. CF patients who can be treated with Vertex's Kalydeco or Orkambi have additional annual costs of approximately $300,000. Standards of care are generally similar across Western European nations.

Palliative treatments

The current standard of care for CF patients includes palliative treatment to manage the symptoms of the disease. In CF patients, the thick mucus that builds up in the lungs and other vital organs such as the pancreas and gastrointestinal tract hampers mucus clearance and leads to airway obstruction and difficulty absorbing nutrients, leading to poor growth and development. Primary treatment options include inhaled therapies such as rhDNase, marketed as Pulmozyme, which thins the mucus in the lungs, as well as pancreatic enzyme replacement therapy, which improves absorption of nutrients. Due to the proliferation of bacteria on the mucus build-up, CF patients often develop chronic lung infections that require inhaled antibiotics treatments, such as TOBI or Cayston, to suppress the infections. CF patients also take a number of other prescribed and over-the-counter medications to alleviate the symptoms of CF and reduce complications, including bronchodilators, inhaled corticosteroids, and ursodeoxycholic acid for biliary tree dysfunction.

Potentiators for certain non-ΔF508 mutations

For a subset of patients who suffer from the G551D and other gating mutations of the CFTR gene, Vertex Pharmaceuticals has developed a so-called "potentiator" molecule marketed under the trade name Kalydeco (ivacaftor). This product was approved by the FDA in 2012 to treat patients with the G551D CFTR mutation and, in 2014, the label was expanded to include eight additional gating mutations. In 2015, the label was further expanded to include a total of ten gating mutations and children as young as two years old. Vertex has estimated that approximately 2,400 CF patients in the U.S., Europe and Australia have a G551D or a non-G551D gating mutation. Gating mutations are characterized by the presence of CFTR at the cell surface that does not open and close the ion channels properly. Kalydeco is believed to keep the ion channels open for longer. For this population of CF patients, medication costs are approximately $300,000 per year for Kalydeco prescriptions. Kalydeco is an exciting development as it provides a proof of concept that it is possible to target the defective CFTR protein that causes CF and improve key symptoms of the disease.

The ΔF508 mutation affects approximately 70% of all CF patients. Unlike the "gating" mutations, ΔF508 is a "processing" mutation, and as such, CFTR with the ΔF508 mutation is not expressed at the cell surface and cannot be potentiated by small potentiating molecules like Kalydeco.

Potentiator/corrector combination for ΔF508 mutations

For patients aged 12 years and above and homozygous for the ΔF508 mutation, Vertex Pharmaceuticals received regulatory approval for Orkambi in July 2015. Orkambi is a fixed-dose combination of lumacaftor and ivacaftor (Kalydeco). Lumacaftor is a new molecular entity also referred to as a CFTR "corrector" that is purported to work by stabilizing and promoting the folding of the defective ΔF508CFTR and thereby increasing the likelihood that the CFTR channel will be found at the cell membrane. Kalydeco purportedly potentiates the activity of CFTR channel at the cell surface. We believe the clinical benefit of Orkambi for the homozygous ΔF508 patients is not commensurate with the benefit demonstrated by Kalydeco in the G551D population, but is comparable to some of the symptom relief medications approved for use with CF. Approximately 8,500 US patients could be treated with Orkambi at an annual cost of approximately $260,000 in addition to the cost of standard of care. Vertex Pharmaceuticals along with multiple other pharmaceutical and biotech companies (e.g Pfizer, Bayer, Galapagos, Nivalis, Proteostasis, Parion) are also developing additional correctors and potentiator molecules. We believe these studies validate that ΔF508 CFTR is a treatable target and indicate there is need for more efficacious therapies.

Gene therapy

Gene therapy is a process in which a functional gene is introduced into a cell to override the effects of a defective gene. The CFTR gene was first identified in 1989. Since that time, several academic consortia and drug-development companies have attempted to develop gene therapies targeting mutations in the CFTR gene. These companies aimed to permanently correct the CFTR gene at the DNA level by delivering full-length CFTR genes to lung epithelial cells to express wild-type CFTR protein. However, these programs encountered limitations faced by gene therapy in general as well as limitations specific to the CFTR gene. These barriers included safety concerns, challenges in delivery of the gene therapy constructs to target cells in the lungs, challenges of both delivery and incorporation into the genome given the size and complexity of the CFTR gene, and immunologic responses to the gene therapy vectors. The most advanced effort in gene therapy for CF is with an academic consortium in the U.K. In 2015, the Gene Therapy Consortium presented results of a 136-patient trial using a CFTR gene delivered in a liposome envelope. While the trial showed no overall efficacy, specific subgroups did show a modest benefit in lung function compared to the placebo group. The Gene Therapy Consortium has announced that they will conduct a follow-up trial of gene therapy in the future but that a different vector will be needed for delivery of the gene.

Our solution—RNA repair

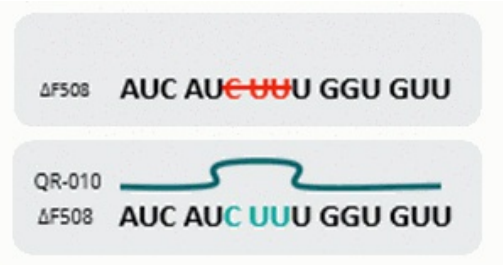
Our approach, RNA repair, aims to repair the basic defect in the CFTR mRNA and subsequently restore expression of wild-type CFTR protein that can normalize the ion transport in the key organs affected by CF, particularly the lung. We believe we are currently the only company pursuing this novel approach for CF patients.

QR-010 for Treatment of CF

We are developing QR-010 as a treatment for CF patients. QR-010 is an RNA-based oligonucleotide designed to restore wild-type CFTR function in CF patients with the ΔF508 gene mutation. QR-010 is 33 nucleotides long and is designed to bind to the CFTR mRNA sequences that are adjacent to the deleted F508 region of the mRNA.

The figure below illustrates wild-type mRNA, the site of the ΔF508 mRNA deletion and where QR-010 is designed as an antisense template to bind on either side of the deletion mutation to potentially introduce the three deleted nucleotides.

QR-010 Binds to mRNA and Guides Insertion of Deleted Nucleotides



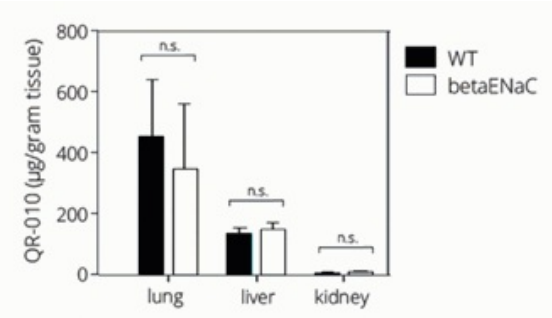
The resulting CFTR protein is expected to be processed similarly to any other wild-type CFTR protein and potentially result in restoration of wild-type CFTR functions, including chloride transport, chloride-bicarbonate exchange and regulation of the epithelial sodium channel, or ENaC. We are currently conducting experiments to expand our understanding of this novel mechanism of action and novel technology.

The figure below represents, from left to right, wild-type CFTR function in a normal cell, impaired CFTR function in a cell with a ΔF508 mutation and a ΔF508 mutated cell treated with QR-010, which would be expected to result in restoration to wild-type levels of chloride efflux.

Chloride Ion Flow: Potential Full Restoration through QR-010

As shown in the figure below, after orotracheal delivery of QR-010 to the lungs of wild-type mice and mice specifically engineered to have a CF-like lung phenotype, called the betaENaC overexpressing mouse, we observed significant exposure of QR-010 to the lungs as well as to other CF-affected organs with no significant difference between wild-type and betaENaC overexpressing mice. We believe this beneficial bio-distribution pattern may potentially allow us to treat not just the lung but also other organs affected by CF and shows that the thick mucus layer that is present in the lungs of CF patients is unlikely to be a barrier for uptake of QR-010. We believe this method will allow maximum exposure of QR-010 to the primary target organ, the lung, as well as significant exposure to other affected organs through systemic absorption into the blood.

Bio-Distribution of QR-010 to Organs in wild-Type and CF-like Lung Phenotype



To achieve broad distribution to CF-affected organs, we deliver QR-010 through inhalation by means of a small handheld nebulizer, a method of drug delivery used to administer medication in the form of a mist inhaled into the lungs. On October 8, 2014 we entered into an agreement with PARI Pharma GmbH, pursuant to which the Company is granted an exclusive license to the use of PARI's eFlow technology for the administration of oligonucleotide-based drugs in the ΔF508 mutation in cystic fibrosis. The nebulizer device rapidly and efficiently processes a therapeutic agent through the microscopic holes of a mesh and creates a mist to provide rapid and consistent delivery to the lungs. Commercially-available nebulizers are currently used for other CF therapies and in other clinical studies involving inhaled oligonucleotides.

Clinical Development Plan for QR-010

ProQR is conducting two clinical trials of QR-010 in parallel. Study PQ-010-001 is a Phase 1b safety and tolerability study. This study opened for enrollment in June 2015. Study PQ-010-002 is a proof of concept study evaluating topical administration of QR-010 and its effect on the nasal potential difference, a biomarker of CFTR function. This study opened for enrollment in September 2015.

PQ-010-001 Phase 1b Safety and Tolerability Study

The first clinical trial with QR-010 is a Phase 1b, randomized, double-blind, placebo-controlled, 28-day dose-escalation trial to evaluate the safety, tolerability and pharmacokinetics of QR-010. QR-010 is given as a nebulized solution to the lower airways after chest physiotherapy, which is a standard procedure used with other currently administered inhaled medications. This method of drug administration is common in CF patients and has been used with oligonucleotides in development in other indications. The primary outcome measures are to characterize safety, tolerability and pharmacokinetics. We are also assessing exploratory efficacy outcome measures, including lung functionality, chloride levels in sweat, weight gain and other quality-of-life measures specific to CF, which we believe could be indicative of the potential efficacy of QR-010. Because of its relative small size the study is not powered for statistical significance on any of the exploratory efficacy outcome measures. The study includes CF patients that are homozygous for ΔF508 and age 18 years and above. Pharmacokinetics will be assessed with serum measurements over time. Exploratory clinical measurements, including evaluation of early changes in lung function, reduction in symptoms and weight gain are also performed to inform the design of future trials. The trial will be conducted at approximately 20 sites in North America and select EU countries and will enroll 64 patients. Randomization will be 3:1, meaning 25% of patients will receive placebo. We anticipate that top-line data will be available by mid to late 2016.

PQ-010-002 Proof-of Concept NPD study

The NPD assay is a standard test for detection and quantification of CFTR function in the airways in CF patients. The NPD test is a well-accepted diagnostic tool and has been used in multiple therapeutic intervention trials to demonstrate the restoration of CFTR mediated ion transport in preclinical animal models and in CF patients. Our POC study is designed to investigate the ability of QR-010 to restore CFTR function in patients, as was observed in pre-clinical NPD studies in mouse models. The primary outcome measures will determine the effect of topical administration of QR-010 to the nasal mucosa on the restoration of CFTR function, as measured by nasal potential difference (NPD) relative to baseline, in the nasal epithelium of CF patients with the ΔF508 CFTR mutation.

Secondary outcome measures and exploratory outcomes measures will also be evaluated in this observation study to evaluate the restoration of CFTR function. Nasal mucosal samples will be obtained to assess the proposed mechanism of action of QR-010, including measuring the presence of repaired CFTR mRNA and wild-type CFTR. The nasal passages are not the intended target site for QR-010. However, the nasal epithelium is the most accessible site for measuring CFTR function in humans and provides a human model of epithelial cell uptake and restoration of CFTR function. This study will enroll up to 32 subjects. All subjects are adults over 18 years old with CF either homozygous for the ΔF508 mutation or compound heterozygotes with one copy of the ΔF508 mutation and one copy of another disease causing mutation. The study is being conducted in five sites in the U.S., France and Belgium. We anticipate that top-line data from our POC study will be available in mid to late 2016.

Pre-Clinical Data to Support QR-010

We have conducted extensive *in vitro* and *in vivo* pre-clinical studies that support the development and therapeutic potential of QR-010. QR-010 has been shown to increase the function of CFTR as demonstrated by enhancing chloride efflux *in vitro* and *in vivo* models that carry the same mutation as ΔF508 patients. *In vitro* QR-010 demonstrated improved chloride ion efflux in a fluorescent chloride ion indicator, or MQAE, assay and in a well-accepted model, the Ussing Chamber assay using human bronchial epithelial cells with the ΔF508 mutation. Most notably, and distinct from other molecules in development for CFTR mutation specific molecules, in two independent *in vivo* activity assays in ΔF508-CFTR mice that are similar to human diagnostic tests, QR-010 restored CFTR function up to wild-type levels. The first was a study of Nasal Potential Difference, or NPD, in ΔF508-CFTR mice in which QR-010 restored NPD in response to specific stimuli to normal levels. The second was a saliva secretion assay, a mouse equivalent of the sweat chloride test, in which QR-010 restored saliva secretion to normal levels in female mice.

Overview of Pre-clinical Data to Support QR-010

Safety

Oligonucleotides with similar chemistry to that of QR-010 have been studied extensively in large groups of patients with different indications. Through these studies, a detailed safety profile of these molecules has been described, indicating that these molecules are generally well tolerated even after several years of chronic treatment. We believe the results from these studies reduce the risk of our development program.

Our pre-clinical studies evaluated QR-010 in two animal safety models—mice and monkeys. We selected the mouse because of the well-characterized homozygous mouse model of the ΔF508 gene mutation that exists with homology to the human mRNA transcript in the region where QR-010 binds. Since QR-010 is 100% homologous to the complementary portion of the antisense strand of the CFTR gene for both mice and humans, it is expected that binding of QR-010 to the target mRNA in humans will be identical to that observed in the mouse model. We selected cynomolgus monkeys as the non-rodent species for toxicology studies because these monkeys are a well characterized model for human toxicology studies. The cynomolgus monkey has a specific advantage over other non-rodent species because there is sequence identity with humans in the targeted region of wild-type CFTR mRNA. We completed two 28-day toxicity studies, involving both systemic and inhaled administration of QR-010, in mouse and monkey models. In both animal models, administration of QR-010 at high average doses was well tolerated. Results of these 28-day toxicity studies supported the start of our Phase 1b SAD/MAD clinical trial and POC NPD study in 2015.

Pharmacology

To date, we have conducted pre-clinical studies in CFPAC-1 cells, in a ΔF508 patient derived cell-line, in CF HBE cells, and in mice homozygous for the ΔF508 mutation. *In vitro* results demonstrated QR-010 activity in cell lines and primary epithelial cells from ΔF508 CF patients. *In vivo* studies with mice homozygous for the ΔF508 mutation demonstrated QR-010 activity by restoration of transepithelial NPD responses to standard challenges. In addition, we observed functional CFTR activity, repair of CFTR mRNA and detection of CFTR protein.

QR-010 demonstrated improved CFTR function in several distinct *in vitro* and *in vivo* assays, including:

- an Ussing Chamber assay using CF HBE cells affected with ΔF508 mutations, in which we observed changes in potential difference consistent with increased CFTR function;
- a mouse NPD assay, in which we gave ΔF508 mice QR-010 intranasally and observed normalization of NPD as well as responses to specific challenges; and

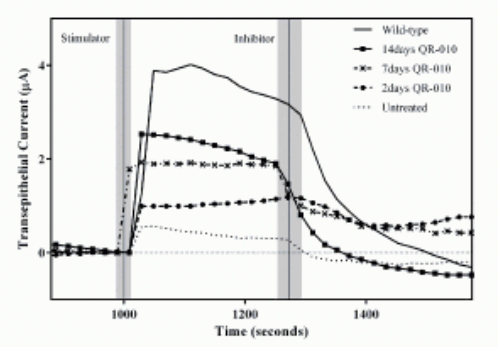
- a mouse saliva secretion assay, in which we gave ΔF508 mice QR-010 orotracheally and observed changes in saliva volume consistent with improved CFTR function.

QR-010 Increases CFTR Activity in Ex Vivo Primary Lung Cells from CF Patients

The Ussing Chamber assay measures the electrical current over a monolayer of epithelial cells and is a commonly used pre-clinical assay to measure the chloride efflux resulting from CFTR activity. This assay has been used to test the effect of a variety of agents on CFTR activity in cells and is performed using fully differentiated HBE cells with the ΔF508 mutation grown in a manner to resemble the lung epithelium with an airway liquid interface. As reduced efficiency of transfection, or delivery of oligonucleotides into a cell, is predicted in this model, we investigated the effect of QR-010 (100 nanomolars (nMs), twice weekly) in CF HBE cultures following repeated treatments over 14 days. The goal of the study was to show improvement in CFTR activity over time. The study achieved its goal by demonstrating that treatment over 14 days with QR-010 enhanced its effect on CFTR activity. The figure below shows the results of the Ussing Chamber assay and the efficacy of QR-010 treatment on CFTR activity over different QR-010 treatment periods. After the addition of a cAMP stimulator, forskolin, to activate the CFTR protein, we observed an increase in ion current across the cell membrane that represents CFTR activity. To confirm that the observed result was due to restored CFTR function and not an alternative pathway, a CFTR inhibitor was administered and the effect on ion current was extinguished in a selective manner.

As shown in the figure below, we observed a small effect after just two days of treatment with QR-010. After 14 days of treatment, we observed a four- to five-fold, or approximately 60%, increase in the CFTR-specific response, compared to control. As we did not observe a plateau of effect at 14 days of treatment, longer treatment periods may increase the CFTR response even further.

QR-010 Increases CFTR Function and is Dose Dependent (*in vitro*)

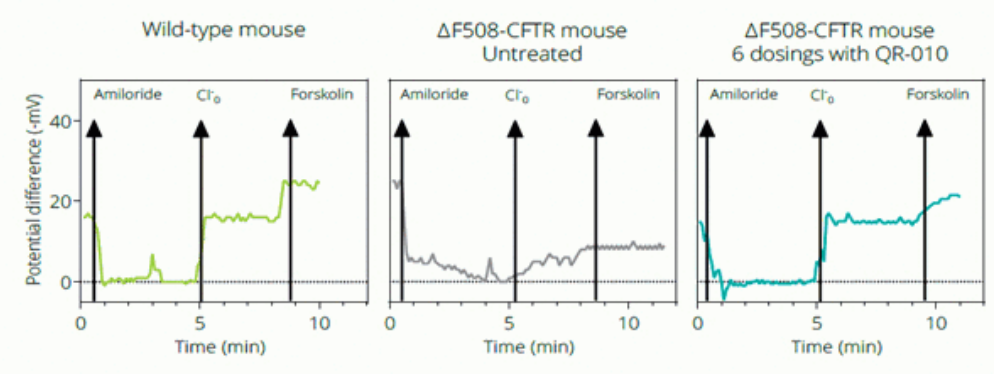


NPD Measurements in ΔF508-CFTR Mice

Nasal Potential Difference, or NPD, is a standard test for detection and quantification of CFTR function in the airways in CF patients. The NPD assay has also served as an important endpoint for the diagnosis of CF since 1981. It has been used extensively and is standardized to assess the ability of new therapeutics to restore defective ion transport in CF patients and several pre-clinical animal models.

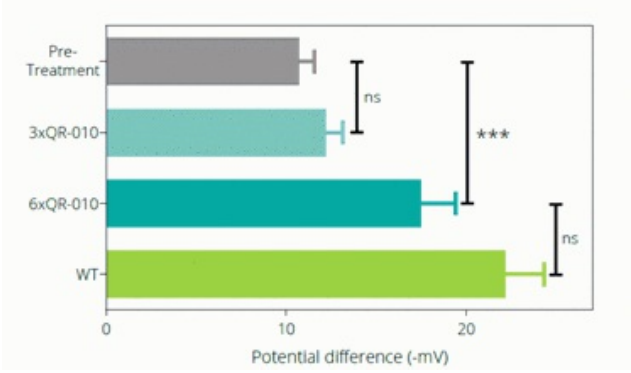
To assess whether or not QR-010 could restore CFTR function *in vivo*, we assessed NPD in ΔF508 mice before and after treatment. ΔF508 mice were treated with three or six doses of 40 μg per dose per animal of QR-010 intranasally. We then assessed NPD by measuring the current through their nasal epithelial cells. We initially administered amiloride, an ENaC blocker, to block the ENaC signal, drop the signal to baseline and isolate the CFTR signal. Subsequently, we administered chloride-free buffer, or 0Cl, and forskolin, which increases levels of cAMP, and a stimulator to activate chloride efflux through CFTR. As chloride flowed, the voltage signal increased over baseline and represents the level of CFTR activity. The goal of this study was to show improvement in CFTR activity in the nasal epithelium of ΔF508 mice after being treated with six doses of QR-010. The study achieved its goal by showing that CFTR activity improved significantly after treatment with six doses of QR-010, increasing from 10.14 mV to 17.44 mV, which is 79% of the activity level of wild-type CFTR ($p=0.0005$). The p-value represents the probability that the result is due to chance rather than the drug effect, and when that probability is less than 5%, or $p<0.05$, the result is considered statistically significant. The figure below shows, from left to right, the results of NPD measurements in wild-type mice, in ΔF508 mice receiving no treatment, and in ΔF508 mice treated with QR-010. Notably, the pattern of response in the ΔF508 mice treated with QR-010 returns the phenotype as measured by this assay to that of a wild-type mouse. The control treated mice did not respond in this fashion.

QR-010 Normalizes NPD Baseline and CFTR Responses (*in vivo*)



As part of the NPD assessment, we treated 18 ΔF508 mice with six doses each of QR-010 over 14 days and conducted periodic NPD assessment. As illustrated by the figure below, the level of CFTR activity as measured by chloride response in the treated mice was not significantly increased after 7 days (3 doses), but after 14 days (6 doses), the CFTR activity in the treated mice increased significantly.

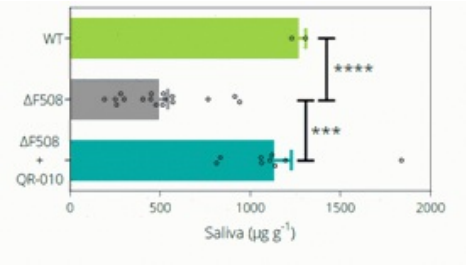
QR-010 Restores CFTR Function to Wild-Type Levels in 6 Doses *(in vivo)*



QR-010 Improves Saliva Secretion in ΔF508 Mice

The saliva secretion assay in mice is a surrogate for the human sweat test, which is a widely accepted diagnostic tool for CF in humans. Human sweat glands normally respond to stimuli, but CF patients do not demonstrate the same response. Similarly, the saliva glands of wild-type mice respond to these stimuli by producing more saliva, but the saliva glands of ΔF508 mice do not increase saliva production when stimulated. In an experiment involving nine ΔF508 mice, we tested whether orotracheal administration of QR-010 would result in increased saliva secretion. A wild-type cohort was also included as a control. The goal of the study was to assess the improvement in CFTR activity in the saliva glands after administering QR-010 to the lungs of mice. The results in saliva secretion (body weight adjusted) are shown in the figure below and demonstrate that CFTR activity in the saliva glands of female ΔF508 mice improved significantly ($p<0.0001$) towards wild-type levels after treatment with two doses of 10 mg/kg of QR-010 over a three-day period. It is well-recognized that male mice salivary response is not as dependent on CFTR therefore, only data from female mice is presented in the figure below. The sex specific response reflects the specificity of QR-010 to increase CFTR function, and we believe this does not imply that QR-010 will not work in human males.

QR-010 Restores Saliva Secretion to Wild-Type Levels (*in vivo*)



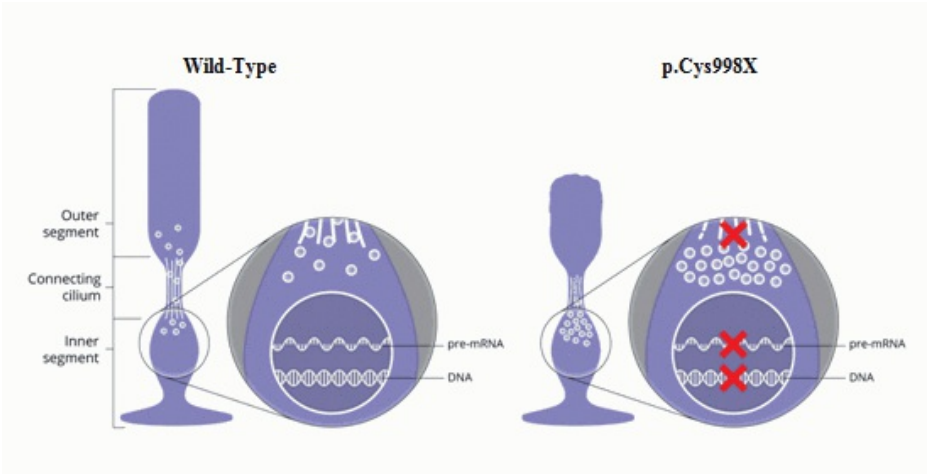
Research Grants

In August 2014, we entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide us with up to $ 3 million to support the clinical development of QR-010. In 2015, the Company and its academic partners received a grant from the European Union under the Horizon 2020 research and innovation programme under grant agreement No. 633545. The maximum amount of € 6.0 million was granted to support the clinical development of QR-010. ProQR also received additional tranches totaling €1.6 million under the Innovation credit program or "Innovatiekrediet" by the Dutch government, through its agency RVO (previously: "AgentschapNL") of the Ministry of Economic Affairs, for the cystic fibrosis development program.

Leber's Congenital Amaurosis

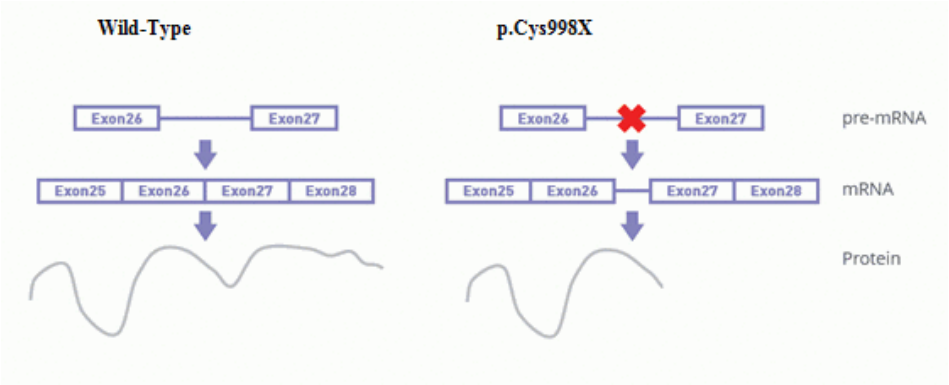
LCA background

LCA is the most common genetic blindness in childhood. We believe that the p.Cys998X mutation (also known as c.2991+1655A>G) in the CEP290 (Centrosomal protein of 290 kDa) gene is the most prevalent mutation which generally accounts for the most severe LCA disease phenotype. Most patients affected by this mutation lose sight in the first years of life. There is currently no disease modifying therapy available on the market or being tested in clinical development for this specific subtype of the disease. In LCA patients this mutation leads to significant decrease of CEP290 protein within the photoreceptor cells in the retina. Clinical features of CEP290-mediated LCA include congenital or early onset loss of vision, involuntary eye movement or nystagmus, amaurotic pupils and no light response on electroretinography (ERG).



LCA mechanism

The p.Cys998X mutation is a single nucleotide substitution in the CEP290 gene that creates a new splice site, also called a cryptic site, between exon 26 and 27. During the splicing of the pre-mRNA this causes a part of the intron, or pseudoexon, to be included in the mRNA. The pseudoexon contains a premature stop codon thus the mRNA is not translated into the full length CEP290 protein. The CEP290 protein is involved in the formation and stability of the connecting cilium in photoreceptor cells which facilitates the transport of proteins from the inner segment to the outer segment. When CEP290 is absent there is protein build-up in the inner segment and the outer segment is shorter and does not perform its light transducing function.



LCA prevalence and Diagnosis

We believe that approximately 116,000 patients worldwide suffer from LCA. LCA is caused by a genetic defect in 19 or more associated genes. The most common mutation is the p.Cys998X in the CEP290 gene. Although diagnosis rates vary, based on our estimations we believe this mutation occurs in approximately 2,000 patients in the Western world.

Patients are initially diagnosed through the presence of clinical symptoms. Nystagmus tends to be the first symptom visible as well as oculo-digital movements, in the most severe cases; vision impairment or blindness becomes obvious as age increases. After ophthalmological examination, LCA is diagnosed. A genetic screening including all known mutations causing LCA is performed to distinguish between LCA and other possible retinal diseases and to give the patient the most accurate prognosis possible (approximately 30% of all patients carry a mutation that has not been described to date).

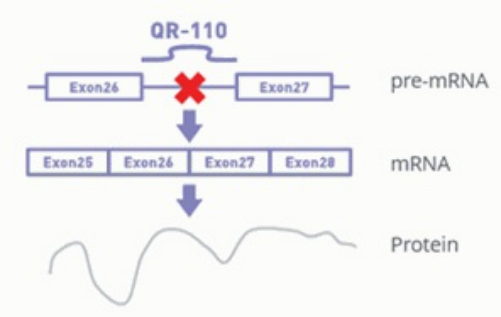
Approaches for the Treatment of LCA

There are currently no disease modifying treatments approved or potential treatments in clinical trials for patients with p.Cys998X associated LCA, a form of LCA type 10. There are other approaches in pre-clinical development for the p.Cys998X mutation that target the disease at the DNA level. However, we believe our RNA technology has significant advantages over these approaches in terms of delivery and safety. From a regulatory perspective, there is precedent with three oligonucleotide based products approved, out of which two were for ophthalmologic indications that are also administered through intravitreal injections. No gene therapy product has been so far approved by FDA and only one is approved in the EU. Spark Therapeutics is currently conducting gene therapy trials in patients with a form of LCA type 2 due to the epithelial cell based mutation RPE65.

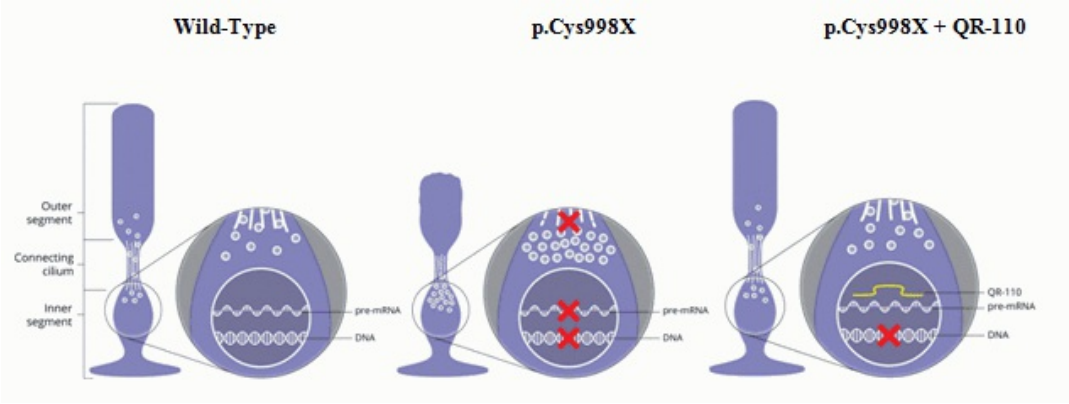
QR-110 treatment approach to LCA type 10

Our lead product candidate in the LCA space, QR-110, a first-in-class RNA-based oligonucleotide, is designed to treat the disease by binding to the pre-mRNA and thereby masking the cryptic splice site. The splicing machinery can thus splice the pre-mRNA correctly resulting in normal mRNA and we expect the production of full-length functional wild-type CEP290 protein.

QR-110 Binds to pre-mRNA and Masks the Cryptic Splice Site
Leading to production of Normal mRNA



Connecting Cilium Function:
Potential Full Restoration Through QR-110



The eye is highly suitable for oligonucleotide therapies as it is a contained organ with physical cellular barriers (i.e. efficient blood-retina barrier and lack of efferent lymphatics) which strongly limits the free entry and exit of cells and larger molecules in and out of the eye therefore limiting the systemic exposure of locally administered therapies. Out of the three FDA-approved oligonucleotide products, two are eye products which are dosed by intravitreal injection. QR-110 is also designed to be administered by intravitreal (IVT) injection. QR-110 was tested in early *in vivo* and *in vitro* non-clinical safety studies and was found to be well tolerated.

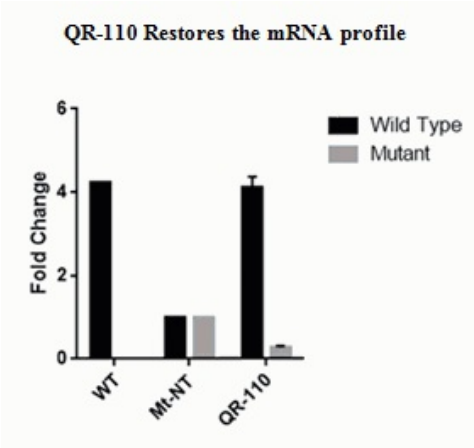
We believe that our comprehensive data package supports advancing QR-110 into further development. Currently, we are conducting several pre-clinical safety studies and other IND-enabling work to advance this program towards the clinic in 2016.

Pre-clinical data to support QR-110

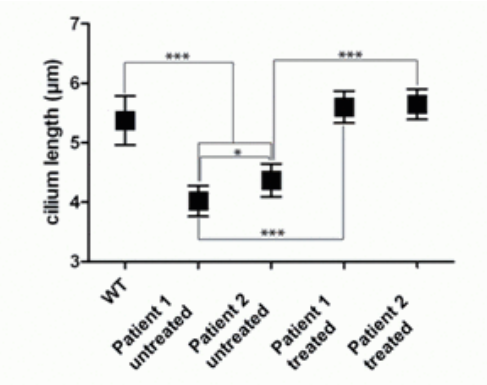
We have conducted extensive *in vitro* and *in vivo* pre-clinical studies that support the development and therapeutic potential of QR-110. In pre-clinical studies to date, QR-110 has demonstrated full restoration of correctly-spliced, or wild-type mRNA in real-time polymerase chain reaction in cultured fibroblast cells of LCA patients homozygous for the p.Cys998X mutation. Increases in CEP290 protein levels of more than 50% were observed in a Western blot assay.

Academic research groups have used RNA antisense oligonucleotides of the same chemistry and mode of action as QR-110 to restore the mRNA profile of CEP290 in fibroblasts from LCA patients that are homozygous for the p.Cys998X mutation. After the restoration of the mRNA profile they showed rescue of ciliation and cilium length comparable to normal levels which is indicative of CEP290 protein function restoration.

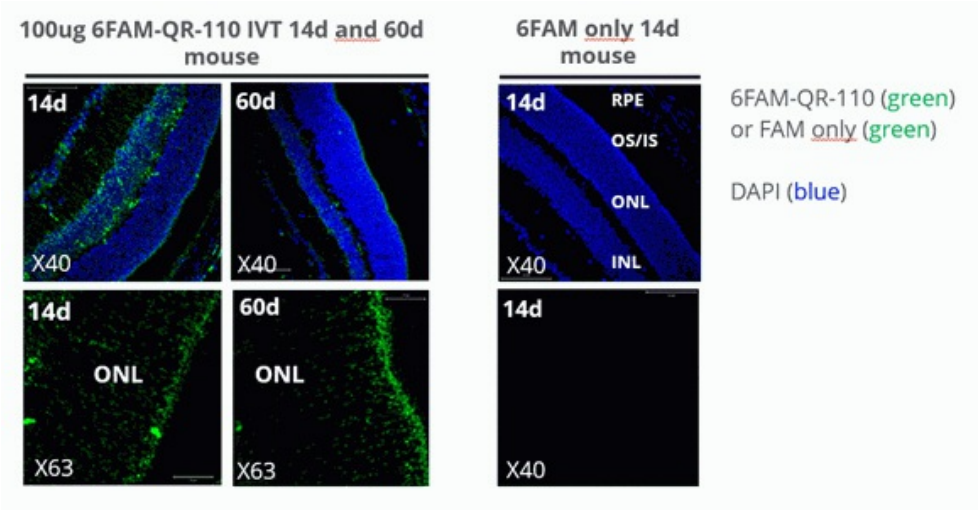
The localization of labeled QR-110 was assessed and the molecule was shown to reach the outer nuclear layer, or ONL, after intravitreal injection in vivo.



AON3 Restores Cilium Length in Fibroblasts from p.Cys998X Patients



QR-110 Localizes to the Outer Nuclear Layer (ONL) After IVT Injections in Mouse Eyes



We believe the activity seen in our pre-clinical models of LCA provides strong support for the clinical development and therapeutic potential of QR-110. We expect to advance this program towards the clinic in 2016.

Other Research and Development

Our internal discovery engine that we call the innovation unit, is a dedicated group in our company that focuses on the discovery and early development of RNA repair therapeutics in genetic indications with a high unmet medical need. Leveraging our experience with RNA therapeutics, we are screening for therapeutic molecules that can be used to treat severe genetic disorders beyond CF and LCA. We have built a diverse toolbox of RNA technologies that we believe can address underlying genetic defects in a novel way. We have grouped the different programs in franchises by therapeutic area so that we can leverage our expertise in the different fields and create synergies between programs. We have identified five therapeutic areas that show high potential for RNA based oligonucleotides: respiratory, ophthalmology, dermatology, CNS and neuromuscular disorders. We go through a thorough selection process prior to advancing programs into development, and consider criteria including: high unmet medical need, a pre-clinical proof-of-concept that shows strong promise for translation to the clinic, well understood relationship between the genetic defect and disease manifestations, feasibility of delivery to target organ(s), and strong IP position and initial freedom to operate.

Respiratory

Besides our program for CF caused by the ΔF508 mutation we are working on other CFTR mutations that can potentially be treated using our RNA technologies. We could potentially target an additional 5% of the CF population with these programs.

Ophthalmology

Our ophthalmology group was founded on the basis that the eye is a well validated target for oligonucleotides. Given the long half-life of these molecules and the lower risk of systemic exposure, we believe oligonucleotide based therapies have the potential to be an important class of drugs for ophthalmic indications. Since we have advanced our LCA program into preclinical development we have started several additional discovery stage programs, including those targeting Usher syndrome and Fuchs endothelial corneal dystrophy (FECD).

Usher syndrome is a genetic orphan disease that is the leading cause of combined deafness and blindness. Usher syndrome type II is most commonly caused by mutations in the USH2A gene. Patients with this syndrome generally progress to a stage in which they have severely limited central vision and moderate to severe deafness. The moderate to severe deafness that patients experience with this subtype of the disease is manageable with cochlear implants. However, there are currently no available treatment options for the vision loss associated with this disease. In this particular mutation, the disease is caused by a genetic defect that results in the lack of a

functional USH2A protein. Similar to CEP290, this protein is responsible for the maintenance of the connecting cilium in photoreceptor cells and lack of a fully functional USH2A protein results in reduced protein trafficking to the photoreceptor outer segments with a consequent impact on photo-transduction. With our program, called QRX-411, we aim to treat the specific mutation in the USH2A gene that leads to this vision loss. In this mutation, there is an inclusion of a pseudoexon in the mRNA disrupting the function of the protein. Our single stranded RNA oligonucleotide is designed to bind to the pre-mRNA and restore a wild-type sequence in the mRNA leading to wild-type mRNA and functional protein. The intended route of administration is by intravitreal injections.

FECD is a common inherited condition characterized by the dysfunction and degeneration of the corneal endothelium. The disease segregates into early-onset and age-related FECD that are caused by different mutations. Early signs of FECD are the presence of corneal guttae and a large proportion of patients over 40 years old have evident corneal guttae. A portion of these patients develop advanced disease with corneal edema and corneal clouding. These symptoms can worsen leading to complete vision loss and the requirement for surgical intervention and a corneal transplant. There are currently no other treatment options for any form of FECD patients with vision loss, apart from corneal transplantation. However, transplantation has several limitations, including the availability of donors, risk of rejection, the inherent risk of an invasive procedure and is only available to patients with advanced FECD. The majority of age-related FECD is caused by a repeat expansion mutation in the TCF4 gene. Such expansions result in toxic RNA species which aggregate as nuclear foci and sequester important splicing proteins rendering the cell devoid of the splicing proteins for other important genes. The impact of acquired splicing defects in these other genes are thought to result in corneal endothelial dysfunction and Fuchs. Our program, called QRX-504, aims to prevent the buildup of RNA-protein foci that cause the corneal dystrophy in patients with expansion repeat mutation in the TCF4 gene by using a single stranded RNA oligonucleotide.

Dermatology

Dystrophic Epidermolysis Bullosa (DEB) is a severe genetic orphan disease that affects the connective tissues including the skin and mucosal tissues.Children with DEB are often referred to as ‘Butterfly children’ due to their fragile skin; blistering and skin erosions occur upon the slightest touch or even spontaneously. DEB is caused by mutation(s) in the COL7A1 gene that codes for type VII collagen protein. Decreased levels of functional type VII collagen leads to lack or dysfunction of the anchoring fibrils that bind the different skin layers together. Symptoms include open wounds, skin infections, fusion of fingers and toes (pseudosyndactyly) and eventually patients develop lethal squamous cell carcinoma. There is no approved disease modifying treatment available. Mutations can occur in different parts of the COL7A1 gene. Our program, called QRX-313, targets all DEB caused by mutations in exon 73 and, by excluding this exon from the mRNA we hope to restore functionality of type VII collagen.

CNS

In our CNS group we are working on product candidates for several disease targets, including Alzheimer’s disease and Huntington’s disease. Alzheimer’s disease is a progressive neurodegenerative disease and the most common form of dementia leading to memory loss and cognitive dysfunction. Currently there is no disease modifying therapy available. The underlying pathology of Alzheimer’s disease is the aggregation and plaque formation of a toxic peptide called Amyloid beta. Our molecule, called QRX-203, aims to prevent the incorporation of the Amyloid beta peptide into the larger APP protein. This is designed to prevent or delay the Amyloid beta cascade and the subsequent aggregation and plaque formation that leads to disease progression.

Neuromuscular

Friedreich’s ataxia, or FA, is the most common inherited ataxia that causes progressive damage to the nervous system. The disease is caused by GAA repeat expansion mutations in the gene that codes for the Frataxin protein. The expanded repeat mutations cause silencing of the gene leading to decreased levels of the Frataxin protein. Symptoms range from muscle weakness and speech problems to heart disease. With only palliative treatments available, most patients are wheelchair bound within 10–15 years after diagnosis and do not live beyond early adulthood. Frataxin is an essential mitochondrial protein involved in the regulation of energy production in cells and enzymes that contain an iron-sulfur cluster. We have identified a potential treatment, called QRX-604, with the aim to increase Frataxin levels.

Animal welfare

It is required by regulatory authorities to demonstrate the quality, safety and efficacy of a new drug in both animals and humans, before the authorities can approve the new product and will provide Marketing authorization. ProQR attaches great importance to minimalizing the number of animals needed in the obligatory animal studies and guarding their welfare. Our aim is to monitor continually that animal experiments will be performed only if there are no viable or legal alternatives.

External collaborators contracted for the execution of our in-vivo pre-clinical studies (contract research organizations, CROs) are selected based on their expertise, quality and accreditations for laboratory animal care and welfare. The housing and husbandry must comply with the highest international standards. Personnel responsible for housing, husbandry and care of the animals must have received adequate and relevant documented education.

We strive for welfare improvements to be implemented in CRO policies. An important achievement in 2014 was that on our request our preferred CRO has replaced the housing which was compliant with their national legislations and installed new group housings with significantly more living space that to a larger extent take in consideration the physiological and behavioral needs of the laboratory animals concerned. This will also contribute to higher welfare standards in the studies for other (future) clients.

Intellectual Property

We strive to protect our technology platforms and our product candidates through a variety of approaches, including obtaining and maintaining patent and trade secret protection for our current and future technology platforms, our product candidates as well as their methods of use and processes for their manufacture, and any other inventions or discoveries that are commercially important to our business. We seek to obtain domestic and international patent protection and endeavor to promptly file patent applications or in-license patent rights relating to new, commercially valuable inventions to expand our intellectual property portfolio.

Our commercial success will depend in part upon obtaining and maintaining patent and trade secret protection for our current and future technology platforms and product candidates, as well as successfully defending our patent rights against third-party challenges. Our ability to prevent or stop third parties from making, using, selling, offering to sell or importing our product candidates will depend in part upon whether we have valid and enforceable patent rights that cover the activities of third parties.

We cannot be sure that patents will be granted with respect to any of our own or our in-licensed pending patent applications or with respect to any patents applications we may own or in-license in the future, nor can we be sure that any of our own or in-licensed patents or any patents we may own or license in the future will be useful in protecting our technology. Please see “Risk Factors—Risks Related to Our Intellectual Property” for additional information on the risks associated with our intellectual property strategy and portfolio.

Patent Rights

We have been building and will continue to build our patent portfolio. Where possible, we pursue or plan to pursue multi-tiered patent protection for our technology platforms and our product candidates as well as their manufacture, formulation and use. In addition to the United States, we file, and in the future plan to file, patent applications in various countries and regions where we think such filings are likely to be cost effective.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file or plan to file, the patent term is 20 years from the earliest date of filing of a non-provisional patent application. In the United States, a patent’s term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. PTO in granting a patent. However, the term of a United States patent may be shortened if a patent is terminally disclaimed by its owner over another patent. In addition, depending upon the circumstances, certain United States patents may be eligible for a patent term extension which compensates a patentee for administrative delays by the FDA in granting marketing approval for a patented product or use of a product. In Europe, a similar mechanism is available, such that certain patents may be eligible for a supplementary protection certificate to compensate for the time lost in obtaining marketing authorization for the product.

Patent Rights Relating to Our Cystic Fibrosis Program

With regard to our lead product candidate in the CF space, QR-010, we own a family of patent applications that we filed in the U.S., as well as in other countries and regions including Australia, Brazil, Canada, China, Europe, India, Israel, Mexico, New Zealand, Russia, and South Korea relating to certain aspects of our RNA repair technology platform, including method of use claims relating to the use of certain single stranded oligonucleotides, particularly modified RNA oligonucleotides, for making a change in the sequence of a target RNA molecule in a living cell, as well as composition of matter claims relating to our QR-010 product candidate. The term of any patents resulting from these applications, if issued, would be expected to extend to July 2033.

In addition, in May 2012, we entered into an exclusive license agreement with Massachusetts General Hospital, or MGH, to obtain rights to a patent family with claims directed to an alternative RNA repair platform that uses an RNA oligonucleotide complex rather than a single stranded oligonucleotide. This patent family includes two issued U.S. patents, the first of which has a composition of matter claim directed to an RNA oligonucleotide complex containing two specific oligonucleotide sequences for modulating the expression or activity of a CFTR gene product. The second U.S. patent has method of use claims relating to the treatment of a symptom of cystic fibrosis in a subject by administering to the subject an RNA oligonucleotide complex comprising two oligonucleotides, as well as a composition of matter claim directed to a specific RNA complex for modulating the activity of a CFTR gene product. The issued claims, however, cover elements of our RNA repair technologies, but may not cover the QR-010 product or its use. The term of the first issued U.S. patent is expected to extend to October 2027, and the term of the second issued U.S. patent is expected to extend to May 2025. In addition, we have rights in a pending U.S. patent application in which we are pursuing composition of matter claims relating to QR-010. The term of any patent resulting from this application, if issued, would be expected to extend to March 2025.

Patent Rights Relating to Our LCA Program

With regard to our LCA Program, in April 2014, we entered into an exclusive license agreement with the Radboud University Medical Center, Nijmegen, the Netherlands, to obtain rights in a patent family with composition of matters claims directed to certain antisense oligonucleotides for treating LCA and method of use claims relating to modulation of the splicing of the CEP290 gene product. Patent applications currently are pending in the U.S. as well as Brazil, Canada, Australia, Europe, and Eurasia. The term of any patents resulting from these applications, if issued, would be expected to extend to 2032.

Trade Secrets

In addition to patent protection, we rely on trade secrets and know-how to develop and maintain our competitive position. Trade secrets and know-how can be difficult to protect. Nevertheless, we seek to protect our trade secrets and know-how via, among other things, confidentiality and invention assignment agreements with our employees and consultants. We also seek to preserve the confidentiality of our trade secrets and know-how by implementing and maintaining security of our premises and information, and limiting access to our trade secrets and know-how.

License Agreement with MGH

In May 2012, we entered into a license agreement with MGH. Under the terms of this license agreement, we have an exclusive, royalty-bearing license under certain MGH patent rights to make, use and sell any product or process that is covered by the licensed patent rights for use in all therapeutic indications in the field of cystic fibrosis. We may sublicense our rights unless MGH objects to a potential sublicensee because of a conflict of interest. Our sublicensees may not further sublicense nor assign their rights without MGH's consent. MGH retains the right for it, its affiliates and other academic, government and not-for-profit institutions to use the licensed patents rights for internal research and educational purposes. If we ever desire to expand the license field beyond CF, we must provide to MGH a development plan that demonstrates we have sufficient resources to commercially develop a therapeutic indication in that field and MGH would then engage in good faith negotiations with us for a license covering such field on substantially the same terms as those contained in the license agreement.

Pursuant to the terms of the license agreement, in lieu of an upfront license payment to MGH, we are obligated to reimburse MGH, on a pro rata basis based on the number of licensees under the licensed patent rights, the fees and costs incurred by MGH in preparing, filing, prosecuting and maintaining the licensed patent rights. Currently, we are the sole licensee of the MGH patent rights and have paid approximately $ 165,000 in patent fee reimbursements to MGH. We are also obligated to pay MGH up to $ 700,000 in milestone payments upon the achievement of certain development and regulatory milestones and, beginning after our first commercial sale of a product covered by the licensed patent rights, a $ 10,000 annual license fee which is creditable against royalties due to MGH in the same calendar year. In addition, we are obligated to pay MGH 2% of any net sales by us, our affiliates or sublicensees on licensed products made or sold in the United States, as well as a low double-digit percentage of any payments that we may receive from any sublicensee anywhere in the world.

MGH is responsible for the preparation, filing, prosecution and maintenance of the licensed patent rights. MGH has the first right to protect the licensed patent rights from alleged infringement. If MGH declines to prosecute the alleged infringement, we may, at our expense, initiate legal proceedings against the alleged infringer, provided that we must give prior notice to MGH, obtain MGH's prior written consent in some cases, reasonably cooperate with MGH regarding the proposed action and not settle any proceeding without MGH's prior written consent. We must also indemnify MGH against any costs, expenses and liabilities incurred in connection with any such legal proceeding we initiate. Any award recovered from the alleged infringer after we and MGH are reimbursed for our expenses are shared so that we receive an amount equal to our lost profits or a reasonable royalty on the infringing sales, MGH receives an amount equal to the royalties or other payments we would have paid MGH if we had sold the infringing product, and any remainder is shared equally.

We are obligated to use commercially reasonable efforts to develop and make available to the public one or more CF therapeutic products or processes in the United States under the licensed MGH patent rights. We also must achieve certain specified development, regulatory and commercial milestones. If we do not meet the specified milestones, MGH may terminate the license agreement or grant us an extension and require us to pay additional milestone fees and, in some cases, an increased royalty on net sales, depending upon the length of our delay. The license agreement will remain in effect until the date on which all issued patents and filed patent applications under the licensed patent rights have expired or been abandoned. We may terminate the license agreement for any reason by giving MGH 90 days advance written notice of termination. MGH may terminate the license agreement upon our default of certain obligations under the license agreement which is not cured within a specified period of time or if we, our affiliates or sublicensees challenge the validity of the licensed patent rights. If we challenge the validity of the licensed patent rights during the term of the license agreement and they are found to be valid and enforceable, we must reimburse MGH for its legal costs and expenses in defending the challenge. Upon a termination of the agreement, MGH will allow those of our sublicensees who are in compliance with their sublicense agreement and agree to assume our obligations under the license agreement to retain their rights.

Other License Agreements

On June 8, 2015, ProQR Therapeutics and Radboud University Medical Center have entered into a Patent License Agreement in the field of antisense oligonucleotide-based therapy for Usher Syndrome, under which the Company is granted a world-wide exclusive license and under which the Company may have certain royalty obligations in relation to products.

On January 18, 2016, The Company entered into an agreement with Leiden University Medical Center which gives the Company a world-wide, exclusive, royalty-bearing license in the field of amyloid-beta related diseases, notably Alzheimer's disease and Katwijk's disease, under certain patent rights of LUMC regarding antisense oligonucleotide based therapies. This license agreement contains certain diligence obligations for the Company coupled to milestone payments and complements the Company's intellectual property relating to its CNS program.

Manufacturing and Supply

We do not currently own or operate manufacturing facilities for the production of preclinical or our planned clinical or commercial quantities of any of our product candidates. We currently contract with two drug product formulation manufacturers for the production of QR-010 solution for nebulization and QR-110 solution for intravitreal injection, and we expect to continue to do so to meet the preclinical and planned clinical requirements of our product candidates.

Currently, each of our active ingredients for our manufacturing activities are supplied by single source suppliers. We have agreements for the supply of such active ingredients with manufacturers or suppliers that we believe have sufficient capacity to meet our demands. In addition, we believe that adequate alternative sources for such supplies exist. We typically order supplies and services on a purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements.

We do have manufacturing processes developed at a back-up GMP manufacturer. Manufacturing is subject to extensive regulations that impose various procedural and documentation requirements, which govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance, among others. The contract manufacturing organizations we currently use manufactures our product candidates under cGMP conditions. cGMP is a regulatory standard for the production of pharmaceuticals that will be used in humans.

Competition

The pharmaceutical industry is highly competitive and subject to rapid and significant technological change. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, academic institutions, government agencies and research institutions. Key competitive factors affecting the commercial success of our product candidates are likely to be efficacy, safety and tolerability profile, reliability, convenience of dosing, price and reimbursement. Many of our existing or potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA, EMA and other regulatory approvals of products and the commercialization of those products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of our competitors. Accordingly, our competitors may be more successful than we may be in obtaining FDA or EMA approval for therapies and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product candidate we may commercialize and may render our therapies obsolete or non-competitive before we can recover development and commercialization expenses.

A number of companies are seeking to identify and develop drug candidates for the treatment of CF, including Vertex, Novartis, Roche, Pfizer, Galapagos/AbbVie, Shire, Genzyme (a Sanofi Company), Bayer, Proteostasis, Corbus, Nivalis and various other private companies. Of these, Vertex's Kalydeco and Orkambi are the only drugs approved to treat an underlying cause of CF, rather than the symptoms. Other drugs that have been approved for CF patients are palliative treatments that manage the symptoms of the disease, such as Novartis' TOBI and Gilead's Cayston, which are used to suppress chronic lung infections, and Roche's Pulmozyme, which is an inhaled therapy used to thin mucus.

Our other competitors have research and development programs directed at identifying and developing CFTR potentiators, CFTR correctors and drug candidates with other mechanisms of action that seek to address the underlying cause of CF. Vertex's success in developing and commercializing Kalydeco and Orkambi could increase the resources that our competitors allocate to the development of these potential treatments for CF.

Our competitors may also obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. See "Risk Factors—Risks Related to our Business and Strategy—We face competition from entities that have developed or may develop product candidates for our target disease indications, including companies developing novel treatments for CF patients. If these companies develop technologies or product candidates more rapidly than we do or their technologies, including delivery technologies, are more effective, our ability to develop and successfully commercialize product candidates may be adversely affected" and elsewhere in this annual report for more information regarding competitors and competitive products.

Regulatory Matters

Government Regulation and Product Approval

Government authorities in the United States at the federal, state and local level, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing, export and import of products such as those we are developing.

U.S. Drug Development Process

The process of obtaining regulatory approvals and compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process, or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, voluntary product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of pre-clinical laboratory tests, animal studies and formulation studies according to Good Laboratory Practices, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials according to GCP to establish the safety and efficacy of the proposed drug for its intended use;
- preparation and submission to the FDA of an NDA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with cGMP; and
- satisfactory completion of an FDA audit of clinical trial sites to assess compliance with GCP.

The testing and approval process requires substantial time, effort and financial resources and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Once a pharmaceutical product candidate is identified for development, it enters the pre-clinical testing stage. Pre-clinical tests include laboratory evaluations of product chemistry, toxicity, formulation and stability, as well as animal studies. An IND sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data and any available clinical data or literature, to the FDA as part of the IND. The sponsor must also include a protocol detailing, among other things, the objectives of the initial clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated if the initial clinical trial lends itself to an efficacy evaluation. Some pre-clinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions related to a proposed clinical trial and places the trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Clinical holds also may be imposed by the FDA at any time before or during clinical trials due to safety concerns or non-compliance, and may be imposed on all drug products within a certain class of drugs. The FDA also can impose partial clinical holds, for example, prohibiting the initiation of clinical trials of a certain duration or for a certain dose.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCP regulations. These regulations include the requirement that all research subjects provide informed consent in writing before their participation in any clinical trial. Further, an IRB must review and approve the plan for any clinical trial before it commences at any institution, and the IRB must conduct continuing review and reapprove the study at least annually. An IRB considers, among other things, whether the risks to individuals participating in the clinical trial are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the information regarding the clinical trial and the consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed.

Each new clinical protocol and any amendments to the protocol must be submitted for FDA review, and to the IRBs for approval. Protocols detail, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- *Phase 1.* The product is initially introduced into a small number of healthy human subjects or patients and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion and, if possible, to gain early evidence on effectiveness. In the case of some products for severe or life-threatening diseases, especially when the product is suspected or known to be unavoidably toxic, the initial human testing may be conducted in patients.
- *Phase 2.* Involves clinical trials in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage and schedule.
- *Phase 3.* Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit relationship of the product and provide an adequate basis for product labeling.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and safety reports must be submitted to the FDA and the investigators for serious and unexpected suspected adverse events, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator's brochure, or any findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product drug. Phase 1, Phase 2 and Phase 3 testing may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. Review and Approval Processes

The results of product development, pre-clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the drug, proposed labeling and other relevant information, are submitted to the FDA as part of an NDA for a new drug, requesting approval to market the product. The submission of an NDA is subject to the payment of a substantial user fee; a waiver of such fee may be obtained under certain limited circumstances. For example, the agency will waive the application fee for the first human drug application that a small business or its affiliate submits for review. The sponsor of an approved NDA is also subject to annual product and establishment user fees.

The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be re-submitted with the additional information. The re-submitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure the product's identity, strength, quality and purity. Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA may refer the NDA to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. An advisory committee is a panel of experts, including clinicians and other scientific experts, who provide advice and recommendations when requested by the FDA. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations when making decisions.

The approval process is lengthy and difficult and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information. Even if such data and information are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. The FDA will issue a complete response letter if the agency decides not to approve the NDA in its present form. The complete response letter usually describes all of the specific deficiencies that the FDA identified in the NDA that must be satisfactorily addressed before it can be approved. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application or request an opportunity for a hearing.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may require post-approval studies, including Phase 4 clinical trials, to further assess a drug's safety and effectiveness after NDA approval and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may require a Risk Evaluation and Mitigation Strategy, or REMS, program as a condition of approval, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

Regulation of Combination Products in the United States

Certain products may be comprised of components that are regulated under separate authorities and by different centers at the FDA. These products are known as combination products. A combination product is comprised of a combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, a device, and a biological product. Under regulations issued by the FDA, a combination product may be:

- a product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

- a drug, biological product or device packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, biological product or device where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- any investigational drug, biological product or device packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, biological product or device where both are required to achieve the intended use, indication, or effect.

Under the Federal Food, Drug, and Cosmetic Act, or FDCA, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. That determination is based on the "primary mode of action" of the combination product, which is the single mode of action that provides the most important therapeutic action of the combination product, *i.e.*, the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. Thus, if the primary mode of action of a device-drug combination product is attributable to the drug product, the FDA center responsible for premarket review of the drug product would have primary jurisdiction for the combination product. The FDA's Office of Combination Products addresses issues surrounding combination products and provides guidance regarding the regulatory review process. That office serves as a focal point for combination product issues for agency reviewers and industry. It is also responsible for developing guidance and regulations to clarify the regulation of combination products, and for assignment of the FDA center that has primary jurisdiction for review of combination products where the jurisdiction is unclear or in dispute.

Fast Track Designation and Accelerated Approval

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition for which there is no effective treatment and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug may request the FDA to designate the drug as a Fast Track product concurrently with, or at any time after, submission of an IND, and the FDA must determine if the drug candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request.

Under FDA's accelerated approval regulations, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. In clinical trials, a surrogate endpoint is a marker, such as a measurement of laboratory or clinical signs of a disease or condition that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A drug candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of post-approval clinical trials sometimes referred to as Phase 4 trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or to confirm a clinical benefit during post-marketing studies, will allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

In addition to other benefits, such as the ability to use surrogate endpoints and engage in more frequent interactions with the FDA, the FDA may initiate review of sections of a Fast Track drug's NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of each portion of the NDA and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Breakthrough Designation

The Food and Drug Administration Safety and Innovation Act, or FDASIA, amended the FDCA to require the FDA to expedite the development and review of a breakthrough therapy. A drug product can be designated as a breakthrough therapy if it is intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that it may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. A sponsor may request that a drug product be

designated as a breakthrough therapy concurrently with, or at any time after, the submission of an IND, and the FDA must determine if the drug candidate qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor's request. If so designated, the FDA shall act to expedite the development and review of the product's marketing application, including by meeting with the sponsor throughout the product's development, providing timely advice to the sponsor to ensure that the development program to gather pre-clinical and clinical data is as efficient as practicable, involving senior managers and experienced review staff in a cross-disciplinary review, assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor, and taking steps to ensure that the design of the clinical trials is as efficient as practicable.

Priority Review

The FDA may grant an NDA a priority review designation, which sets the target date for FDA action on the application for a new molecular entity at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of ten months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Post-Approval Requirements

Any products for which we receive FDA approval are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, complying with certain electronic records and signature requirements and complying with FDA promotion and advertising requirements. Moreover, each component of a combination product retains their regulatory status (as a drug or device, for example) and is subject to the requirements established by the FDA for that type of component. The FDA strictly regulates labeling, advertising, promotion and other types of information on products that are placed on the market. Products may be promoted only for the approved indications and in accordance with the provisions of the approved label. Further, manufacturers must continue to comply with cGMP requirements, which are extensive and require considerable time, resources and ongoing investment to ensure compliance. In addition, changes to the manufacturing process generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Manufacturers and other entities involved in the manufacturing and distribution of approved products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. The cGMP requirements apply to all stages of the manufacturing process, including the production, processing, sterilization, packaging, labeling, storage and shipment of the product. Manufacturers must establish validated systems to ensure that products meet specifications and regulatory standards, and test each product batch or lot prior to its release. We rely, and expect to continue to rely, on third parties for the production of clinical quantities of our product candidates. Future FDA and state inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution or may require substantial resources to correct.

The FDA may withdraw a product approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market. Further, the failure to maintain compliance with regulatory requirements may result in administrative or judicial actions, such as fines, untitled or warning letters, holds on clinical trials, product seizures, product detention or refusal to permit the import or export of products, refusal to approve pending applications or supplements, restrictions on marketing or manufacturing, injunctions or civil or criminal penalties.

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition to new legislation, FDA regulations, guidances, and policies are often revised or reinterpreted by the agency in ways that may significantly affect our business and our product candidates. It is impossible to predict whether further legislative or FDA regulation or policy changes will be enacted or implemented and what the impact of such changes, if any, may be.

Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration dates, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA; however, there can be no assurance that any such extension will be granted to us.

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the pre-clinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Pediatric exclusivity is another type of exclusivity in the United States. Pediatric exclusivity, if granted, provides an additional six months to an existing exclusivity or statutory delay in approval resulting from a patent certification. This six-month exclusivity, which runs from the end of other exclusivity protection or patent delay, may be granted based on the voluntary completion of a pediatric clinical trial in accordance with an FDA-issued "Written Request" for such a clinical trial.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition—generally a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease or condition with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same disease or condition, except in limited circumstances, such as if the second applicant demonstrates the clinical superiority of its product to the product with orphan drug exclusivity through a demonstration of superior safety, superior efficacy, or a major contribution to patient care. "Same drug" means, with respect to a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug. Orphan drug exclusivity does not prevent FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA application user fee.

Pediatric Information

Under the Pediatric Research Equity Act of 2003, NDAs or supplements to NDAs must contain data adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDASIA amended the FDCA to require that a sponsor who is planning to submit a marketing application for a drug product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-phase 2 meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of data or full or partial waivers. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from pre-clinical studies, early phase clinical trials, and/or other clinical development programs.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated products, including drugs, are required to register and disclose certain clinical trial information, which is publicly available at www.clinicaltrials.gov. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we may obtain regulatory approval. In the United States, sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Third-party payors are increasingly challenging the price and examining the medical need and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical need and cost-effectiveness of any products, in addition to the costs required to obtain regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

The U.S. government and state legislatures have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Affordable Care Act, contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs reimbursed by Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on cost containment measures in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval of our products, we will be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order, or recommendation of, an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent, or making a false statement or record material to payment of a false claim or avoiding, decreasing, or concealing an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- the federal transparency laws, including the provision of the Affordable Care Act referred to as the federal Physician Payment Sunshine Act, that requires applicable manufacturers of covered drugs to disclose payments and other transfers of value provided to physicians and teaching hospitals and physician ownership and investment interests;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The Affordable Care Act broadened the reach of the fraud and abuse laws by, among other things, amending the intent requirement of the federal Anti-Kickback Statute and the applicable criminal healthcare fraud statutes contained within 42 U.S.C. § 1320a-7b. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs.

The federal False Claims Act prohibits anyone from, among other things, knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services that are false or fraudulent. Although we would not submit claims directly to payors, manufacturers can be held liable under these laws if they are deemed to ‘‘cause’’ the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state, and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. For example, pharmaceutical companies have been prosecuted under the federal False Claims Act in connection with their off-label promotion of drugs. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties of between $ 5,500 and $ 11,000 for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. In addition, private individuals have the ability to bring actions under the federal False Claims Act and certain states have enacted laws modeled after the federal False Claims Act.

Patient Protection and Affordable Health Care Act

In March 2010, the Affordable Care Act was enacted, which includes measures that have or will significantly change the way health care is financed by both governmental and private insurers. Among the provisions of the Affordable Care Act of greatest importance to the pharmaceutical industry are the following:

- The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Effective in 2010, the Affordable Care Act made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs from 15.1% of average manufacturer price, or AMP, to 23.1% of average manufacturer price, or AMP, and adding a new rebate calculation for ''line extensions'' (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP. The Affordable Care Act also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization as of 2010 and by expanding the population potentially eligible for Medicaid drug benefits, to be phased-in by 2014. The Centers for Medicare & Medicaid Services, or CMS, have proposed to expand Medicaid rebate liability to the territories of the United States as well. In addition, the Affordable Care Act provides for the public availability of retail survey prices and certain weighted average AMPs under the Medicaid program. The implementation of this requirement by the CMS may also provide for the public availability of pharmacy acquisition of cost data, which could negatively impact our sales.
- In order for a pharmaceutical product to receive federal reimbursement under the Medicare Part B and Medicaid programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the AMP and Medicaid rebate amounts reported by the manufacturer. Effective in 2010, the Affordable Care Act expanded the types of entities eligible to receive discounted 340B pricing, although, under the current state of the law, with the exception of children's hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs when used for the orphan indication. In addition, as 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase.
- Effective in 2011, the Affordable Care Act imposed a requirement on manufacturers of branded drugs to provide a 50% discount off the negotiated price of branded drugs dispensed to Medicare Part D patients in the coverage gap (i.e., the "donut hole").
- Effective in 2011, the Affordable Care Act imposed an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications.
- The Affordable Care Act required pharmaceutical manufacturers to track certain financial arrangements with physicians and teaching hospitals, including any ''transfer of value'' made or distributed to such entities, as well as any investment interests held by physicians and their immediate family members. Manufacturers were required to begin tracking this information in 2013 and to report this information to CMS beginning in 2014. The reported information will be made publicly available in a searchable format on a CMS website beginning in September 2014.
- As of 2010, a new Patient-Centered Outcomes Research Institute was established pursuant to the Affordable Care Act to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products.
- The Affordable Care Act created the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. Under certain circumstances, these recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings.

- The Affordable Care Act established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

European Union Drug Review Approval

In the European Economic Area, or EEA (which is comprised of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations: the Community MA, which is issued by the European Commission through the Centralized Procedure based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, a body of the EMA, and which is valid throughout the entire territory of the EEA; and the National MA, which is issued by the competent authorities of the Member States of the EEA and only authorized marketing in that Member State's national territory and not the EEA as a whole.

The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, advanced-therapy medicines such as gene-therapy, somatic cell-therapy or tissue-engineered medicines, and medicinal products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto- immune and other immune dysfunctions, viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or for products which are in the interest of public health in the European Union. The National MA is for products not falling within the mandatory scope of the Centralized Procedure. In general, there are three alternative routes to authorize medicinal products at a national level in the European Union:

1. *Decentralized Procedure.* Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one European Union country of medicinal products that have not yet been authorized in any European Union country and that do not fall within the mandatory scope of the Centralized Procedure. The competent authority of the reference member state will lead in the assessment of the application.
2. *Mutual Recognition Procedure.* In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other European Union countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.
3. *National Procedure.* Applicants following the national procedure will be granted a marketing authorization that is valid only in a single member state. This procedure is not available for applicants seeking approval in more than one member state.

Regulation in the European Union

Product development, the regulatory approval process, and safety monitoring of medicinal products and their manufacturers in the European Union proceed in much the same manner as they do in the United States. Therefore, many of the issues discussed above apply similarly in the context of the European Union. In addition, drugs are subject to the extensive price and reimbursement regulations of the various European Union Member States.

Clinical trials

As is the case in the United States, the various phases of preclinical and clinical research in the European Union are subject to significant regulatory controls. The Clinical Trials Directive 2001/20/EC, as amended, (and which will be replaced from May 2016 or later by Regulation (EU) No 536/2014) provides a system for the approval of clinical trials in the European Union via implementation through national legislation of the Member States. Under this system, approval must be obtained from the competent national authorities of the European Union Member States in which the clinical trial is to be conducted. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the clinical trial application, which must be supported by an investigational medicinal product dossier with supporting information prescribed by the Clinical Trials Directive and corresponding national laws of the Member States and further detailed in applicable guidance documents. The sponsor of a clinical trial, or its legal representative, must be based in the European Economic Area. European regulators and ethics committees also require the submission of adverse event reports during a study and a copy of the final study report.

Marketing approval

Marketing approvals under the European Union regulatory system may be obtained through a centralized or decentralized procedure. The centralized procedure results in the grant of a single marketing authorization that is valid for all—currently 28—European Union Member States.

Pursuant to Regulation (EC) No. 726/2004, as amended, the centralized procedure is mandatory for drugs developed by means of specified biotechnological processes, advanced therapy medicinal products as defined in Regulation (EC) No. 1394/2007, drugs for human use containing a new active substance for which the therapeutic indication is the treatment of specified diseases, including but not limited to acquired immune deficiency syndrome, neurodegenerative disorders, auto-immune diseases and other immune dysfunctions, as well as drugs designated as orphan drugs pursuant to Regulation (EC) No. 141/2000. The CHMP also has the discretion to permit other products to use the centralized procedure if it considers them sufficiently innovative or they contain a new active substance. Given the fact that QR-010 has been granted orphan designation in the EU, it qualifies for the centralized procedure.

In the marketing authorization application, or MAA, the applicant has to properly and sufficiently demonstrate the quality, safety and efficacy of the drug. Under the centralized approval procedure, the CHMP, possibly in conjunction with other committees, is responsible for drawing up the opinion of the EMA on any matter concerning the admissibility of the files submitted in accordance with the centralized procedure, such as an opinion on the granting, variation, suspension or revocation of a marketing authorization, and pharmacovigilance.

The CHMP and other committees are also responsible for providing guidance and have published numerous guidelines that may apply to our product candidates. These guidelines provide additional guidance on the factors that the EMA will consider in relation to the development and evaluation of drug products and may include, among other things, the preclinical studies required in specific cases; and the manufacturing and control information that should be submitted in a MAA; and post-approval measures required to monitor patients and evaluate the long term efficacy and potential adverse reactions. Although these guidelines are not legally binding, we believe that our compliance with them is likely necessary to gain approval for any of our product candidates.

The maximum timeframe for the evaluation of an MAA by the CHMP under the centralized procedure is 210 days after receipt of a valid application. This period will be suspended until such time as any supplementary information requested by the CHMP, has been provided by the applicant. Likewise, this time-limit will be suspended for the time allowed for the applicant to prepare oral or written explanations. When an application is submitted for a marketing authorization in respect of a drug which is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. If the CHMP accepts such request, the time-limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time-limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment.

If the CHMP concludes that the quality, safety and efficacy of the product is sufficiently proven, it adopts a positive opinion. This is sent to the European Commission which drafts a decision. After consulting with the Member States, the European Commission adopts a decision and grants a marketing authorization, which is valid for the whole of the European Union. The marketing authorization may be subject to certain conditions, which may include, without limitation, the performance of post-authorization safety and/or efficacy studies.

European Union legislation also provides for a system of regulatory data and market exclusivity. According to Article 14(11) of Regulation (EC) No. 726/2004, as amended, and Article 10(1) of Directive 2001/83/EC, as amended, upon receiving marketing authorization, new chemical entities approved on the basis of complete independent data package benefit from eight years of data exclusivity and an additional two years of market exclusivity. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder, or MAH, obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the innovator is able to gain the period of data exclusivity, another company nevertheless could also market another version of the drug if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical test, pre-clinical tests and clinical trials. However, products designated as orphan medicinal products enjoy, upon receiving marketing authorization, a period of 10 years of orphan market exclusivity—see also "—Orphan Drug Regulation". Depending upon the timing and duration of the EU marketing authorization process, products may be eligible for up to five years' supplementary protection certification, or SPC, pursuant to Regulation (EC) No. 469/2009. Such SPCs extend the rights under the basic patent for the drug.

Additional rules apply to medicinal products for pediatric use under Regulation (EC) No. 1901/2006. Potential incentives include a six-month extension of any supplementary protection certificate granted pursuant to Regulation (EC) No. 469/2009, however not in cases in which the relevant product is designated as orphan medicinal products pursuant to Regulation (EC) No. 141/2000, as amended. Instead, medicinal products designated as orphan medicinal product may enjoy an extension of the ten-year market exclusivity period granted under Regulation (EC) No. 141/2000 to twelve years subject to the conditions applicable to orphan drugs.

Orphan drug regulation

In the European Union, Regulation (EC) No. 141/2000, as amended, states that a drug will be designated as an orphan drug if its sponsor can establish:

- that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that the marketing of the drug in the European Union would generate sufficient return to justify the necessary investment; and
- that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, that the drug will be of significant benefit to those affected by that condition.

Regulation (EC) No. 847/2000 sets out further provisions for implementation of the criteria for designation of a drug as an orphan drug. An application for the designation of a drug as an orphan drug must be submitted at any stage of development of the drug before filing of a marketing authorization application. A designation of QR-010 as an orphan drug has been granted by the European Commission (EU orphan designation number: EU/3/13/1195).

If a European Union-wide community marketing authorization in respect of an orphan drug is granted pursuant to Regulation (EC) No. 726/2004 or if all the European Union Member States have granted marketing authorizations in accordance with the procedures for mutual recognition, the European Union and the Member States will not, for a period of 10 years, accept another application for a marketing authorization, or grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar drug. This period may however be reduced to six years if, at the end of the fifth year, it is established, with respect to the drug concerned, that the criteria for orphan drug designation are no longer met, in other words, when it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. Notwithstanding the foregoing, a marketing authorization may be granted, for the same therapeutic indication, to a similar drug if:

- the holder of the marketing authorization for the original orphan drug has given its consent to the second applicant;
- the holder of the marketing authorization for the original orphan drug is unable to supply sufficient quantities of the drug; or
- the second applicant can establish in the application that the second drug, although similar to the orphan drug already authorized, is safer, more effective or otherwise clinically superior.

Regulation (EC) No. 847/2000 lays down definitions of the concepts ‘similar drug’ and ‘clinical superiority’. Other incentives available to orphan drugs in the European Union include financial incentives such as a reduction of fees or fee waivers and protocol assistance. Orphan drug designation does not shorten the duration of the regulatory review and approval process.

Manufacturing and Manufacturers’ License

Pursuant to Directive 2003/94/EC, as transposed into the national laws of the Member States, the manufacturing of investigational medicinal products and approved drugs is subject to a separate manufacturer’s license and must be conducted in strict compliance with cGMP requirements, which mandate the methods, facilities, and controls used in manufacturing, processing, and packing of drugs to assure their safety and identity. Manufacturers must have at least one qualified person permanently and continuously at their disposal.

The qualified person is ultimately responsible for certifying that each batch of finished product released onto the market has been manufactured in accordance with cGMP and the specifications set out in the marketing authorization or investigational medicinal product dossier. cGMP requirements are enforced through mandatory registration of facilities and inspections of those facilities. Failure to comply with these requirements could interrupt supply and result in delays, unanticipated costs and lost revenues, and subject the applicant to potential legal or regulatory action, including but not limited to warning letters, suspension of manufacturing, seizure of product, injunctive action or possible civil and criminal penalties.

Advertising

In the European Union, the promotion of prescription medicines is subject to intense regulation and control, including EU and national legislation as well as self-regulatory codes (industry codes). Advertising legislation inter alia includes a prohibition on direct-to-consumer advertising. All prescription medicines advertising must be consistent with the product's approved summary of products characteristics, and must be factual, accurate, balanced and not misleading. Advertising of prescription medicines pre-approval or off-label is not allowed. Some jurisdictions require that all promotional materials for prescription medicines be subjected to either prior internal or regulatory review and approval.

Other Regulatory Requirements

A holder of a marketing authorization for a medicinal product is legally obliged to fulfill a number of obligations by virtue of its status as an MAH. The MAH can delegate the performance of related tasks to third parties, such as distributors or marketing partners, provided that this delegation is appropriately documented and the MAH maintains legal responsibility and liability.

The obligations of an MAH include:

- *Manufacturing and batch release.* MAHs should guarantee that all manufacturing operations comply with relevant laws and regulations, applicable good manufacturing practices, with the product specifications and manufacturing conditions set out in the marketing authorization and that each batch of product is subject to appropriate release formalities.
- *Pharmacovigilance.* MAHs are obliged to establish and maintain a pharmacovigilance system, including a qualified person responsible for oversight, submit safety reports to the regulators and comply with the good pharmacovigilance practice guidelines adopted by the EMA.
- *Advertising and promotion.* MAHs remain responsible for all advertising and promotion of its products, including promotional activities by other companies or individuals on their behalf and in some cases must conduct internal or regulatory pre-approval of promotional materials. Regulation in this area also covers interactions with healthcare practitioners and/or patient groups, and in some jurisdictions obligations to disclose such interactions exist.
- *Medical affairs/scientific service.* MAHs are required to disseminate scientific and medical information on its medicinal products to healthcare professionals, regulators and patients.
- *Legal representation and distributor issues.* MAHs are responsible for regulatory actions or inactions of their distributors and agents.
- *Preparation, filing and maintenance of the application and subsequent marketing authorization.* MAHs must maintain appropriate records, comply with the marketing authorization's terms and conditions, fulfill reporting obligations to regulators, submit renewal applications and pay all appropriate fees to the authorities.

We may hold any future marketing authorizations granted for our product candidates in our own name, or appoint an affiliate or a collaboration partner to hold marketing authorizations on our behalf. Any failure by an MAH to comply with these obligations may result in regulatory action against an MAH and ultimately threaten our ability to commercialize our products.

Reimbursement

In the European Union, the pricing and reimbursement mechanisms by private and public health insurers vary largely by country and even within countries. The public systems reimbursement for standard drugs is determined by guidelines established by the legislator or responsible national authority. The approach taken varies by Member State. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. Other Member States allow

companies to fix their own prices for medicines, but monitor and control company profits and may limit or restrict reimbursement. The downward pressure on healthcare costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products and some of EU countries require the completion of studies that compare the cost-effectiveness of a particular product candidate to currently available therapies in order to obtain reimbursement or pricing approval. Special pricing and reimbursement rules may apply to orphan drugs. Inclusion of orphan drugs in reimbursement systems tend to focus on the medical usefulness, need, quality and economic benefits to patients and the healthcare system as for any drug. Acceptance of any medicinal product for reimbursement may come with cost, use and often volume restrictions, which again can vary by country. In addition, results based rules of reimbursement may apply.

C. Organizational structure

Legal demerger of our Company was effectuated as per June 30, 2015. At December 31, 2015, ProQR Therapeutics N.V. is the ultimate parent company of the following entities:

- ProQR Therapeutics Holding B.V. (the Netherlands, 100%);
- ProQR Therapeutics I B.V. (the Netherlands, 100%);
- ProQR Therapeutics II B.V. (the Netherlands, 100%);
- ProQR Therapeutics III B.V. (the Netherlands, 100%);
- ProQR Therapeutics IV B.V. (the Netherlands, 100%);
- ProQR Therapeutics I Inc. (United States, 100%).

D. Property, plants and equipment

We lease facilities of approximately 753 square meters in total, located at Darwinweg in Leiden, the Netherlands, which forms our headquarters. This location comprises two lease agreements. Both will terminate in July 2016. In addition to the already leased facility of approximately 632 square meters from TNO, located at Zernikedreef in Leiden, the Netherlands, which houses our laboratories, we lease an extra 2,584 square meters, which brings our total office and laboratory facility to 3,216 square meters. These facilities will be reconstructed to fulfill our needs before we reallocate our headquarters to this location in the second quarter of 2016. The lease for this facility terminates on December 31, 2020, and subject to the provisions of the lease, may be subsequently renewed for subsequent 5 year terms. On October 1, 2015, we entered into an agreement to lease additional space of approximately 780 square meters in the U.S., located at Bryant Street, Palo Alto, CA. This lease will expire on September 30, 2020. We believe that our existing facilities are adequate to meet current needs and that suitable alternative spaces will be available in the future on commercially reasonable terms

Item 4A: Unresolved staff comments

Not applicable.

Item 5: Operating and Financial Review and Prospects

You should read the following discussion and analysis of our financial condition and results of operations together with the information under Item 3.A: "Selected financial data" and our audited financial statements, including the notes thereto, included elsewhere in this annual report. The following discussion is based on our financial statements prepared in accordance with International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standards Board, or IASB, which might differ in material respects from generally accepted accounting principles in the United States. The following discussion includes forward-looking statements that involve risks, uncertainties and assumptions. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of many factors, including but not limited to those described under Item 3.D: "Risk factors".

A. Operating results

Overview

We are an innovative biopharmaceutical company engaged in the discovery and development of RNA-based therapeutics for the treatment of severe genetic orphan disorders. Utilizing our unique proprietary RNA repair technologies we are building a pipeline of products that treat severe genetic disorders. We believe we can target rare genetic disorders in which a single protein is defective due

to certain types of genetic mutations. We design our therapeutic candidates to specifically target and repair the defective messenger RNA, or mRNA, that is transcribed from a mutated gene in order to restore functional or normal (wild-type) protein and therefore has the potential to modify the disease. This unique approach offers several advantages compared with small molecule, gene therapy and other therapeutic approaches in the treatment of certain genetic diseases. Our current clinical stage molecule is QR-010, a single stranded RNA-based oligonucleotide that is designed to repair the genetic defect in the most prevalent mutation in cystic fibrosis, or CF. We are currently studying this program in two global clinical trials in 80 CF patients. Our second molecule is QR-110, a single stranded RNA-based oligonucleotide that targets the most prevalent mutation in the CEP290 gene for LCA patients and is currently in pre-clinical development. Beyond that, our in-house discovery engine that we call the innovation unit has been very active in building a pipeline beyond CF and LCA based upon our toolbox of RNA technologies that we have in-licensed or developed in-house. We have launched a number of discovery programs including programs in dystrophic epidermolysis bullosa, Usher syndrome, Fuchs endothelial corneal dystrophy (FECD), Huntington's disease, Alzheimer's disease and Friedreich's ataxia.

To date, we have financed our operations primarily through our initial public offering, or IPO, and private placements of equity securities, and to a lesser extent from funding from governmental bodies and patient organizations, including Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation. From our inception on February 21, 2012 through December 31, 2015, we raised gross proceeds of approximately €45.6 million from private placements of equity securities, including €2,500,000 from the conversion of a convertible loan, €4,228,000 in loans from a governmental body and approximately €3,640,000 in grants from patient organizations and the European Commission. In September 2014, we raised gross proceeds of € 87,202,000 (net proceeds of €80,376,000) from our initial public offering of 8,625,000 ordinary shares. At December 31, 2015, we had cash and cash equivalents of €94,865,000. To date, we have not generated any revenues from royalties or product sales. Based on our current plans, we do not expect to generate royalty or product revenues for the foreseeable future.

We have generated losses since our inception in February 2012. For the years ended December 31, 2013, 2014 and 2015, we incurred net losses of approximately €3,253,000, €12,127,000 and €20,832,000, respectively. At December 31, 2015, we had an accumulated deficit of €36,630,000. We expect to continue incurring losses for the foreseeable future as we continue our pre-clinical studies of our product candidates, continue clinical development of our product candidate QR-010, advance QR-110 into clinical development, increase investments in our other research programs, apply for marketing approval of our product candidates and, if approved, build a sales and marketing infrastructure for the commercialization of our product candidates.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which we have prepared in accordance with IFRS as issued by the IASB. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenues and expenses during the reporting periods. Actual results may differ from these estimates under different assumptions or conditions. There have been no material adjustments to prior period estimates for any of the periods included in this annual report.

Our significant accounting policies are fully described in the notes to our financial statements appearing elsewhere in this annual report.

Recent Accounting Pronouncements

There are no IFRS standards as issued by the IASB or interpretations issued by the IFRS interpretations committee that are effective for the first time for the financial year beginning on or after January 1, 2015 that had a material impact on our financial position.

We have not applied a number of new and revised IFRSs as set forth in the financial statements included elsewhere in this annual report, that have been issued but are not yet effective. The adoption of these Standards and Interpretations are not expected to have a material effect on the financial statements.

JOBS Act and Foreign Private Issuer Exemptions

The JOBS Act contains provisions that, among other things, reduce certain reporting requirements for an "emerging growth company." As an emerging growth company, we are electing to take advantage of the following exemptions:

- not providing an auditor attestation report on our system of internal controls over financial reporting;

- not providing all of the compensation disclosure that may be required of non-emerging growth public companies under the U.S. Dodd-Frank Wall Street Reform and Consumer Protection Act;
- not disclosing certain executive compensation-related items such as the correlation between executive compensation and performance and comparisons of the chief executive officer's compensation to median employee compensation; and
- not complying with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements (auditor discussion and analysis).

The JOBS Act permits an "emerging growth company" such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies. We are choosing to "opt out" of this provision and, as a result, we will comply with new or revised accounting standards as required when they are adopted. This decision to opt out of the extended transition period under the JOBS Act is irrevocable.

These exemptions will apply for a period of five years following the completion of our initial public offering or until we no longer meet the requirements of being an "emerging growth company," whichever is earlier. We would cease to be an emerging growth company if we have more than $ 1.0 billion in annual revenue, have more than $ 700 million in market value of our ordinary shares held by non-affiliates or issue more than $ 1.0 billion of non-convertible debt over a three-year period.

Further, as a foreign private issuer, we are not subject to the same requirements that are imposed upon U.S. domestic issuers by the Securities and Exchange Commission, or SEC. Under the Exchange Act, we will be subject to reporting obligations that, in certain respects, are less detailed and less frequent than those of U.S. domestic reporting companies. For example, although we intend to report our financial results on a quarterly basis, we will not be required to issue quarterly reports, proxy statements that comply with the requirements applicable to U.S. domestic reporting companies, or individual executive compensation information that is as detailed as that required of U.S. domestic reporting companies. We will also have four months after the end of each fiscal year to file our annual reports with the SEC and will not be required to file current reports as frequently or promptly as U.S. domestic reporting companies. We may also present financial statements pursuant to IFRS instead of pursuant to U.S. GAAP. Furthermore, although the members of our management and supervisory boards will be required to notify the Dutch Authority for the Financial Markets of certain transactions they may undertake, including with respect to our ordinary shares, our officers, directors and principal shareholders will be exempt from the requirements to report transactions in our equity securities and from the short-swing profit liability provisions contained in Section 16 of the Exchange Act. These exemptions and leniencies will reduce the frequency and scope of information and protections available to you in comparison to those applicable to a U.S. domestic reporting companies.

Financial Operations Overview

Other Income

Other income is incidental by nature. In August 2014, we entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide us with up to $ 3 million to support the clinical development of QR-010.

In 2015, the European Commission (EC) through its Horizon 2020 program awarded us and our academic partners a grant of € 6 million to support the clinical development of QR-010 (ProQR: € 4.4 million). Horizon 2020 is one of the largest research and innovation programs in the European Union with nearly € 80 billion in available funding for qualified projects from 2014 to 2020.

Both grants are recognized in other income in the same period in which the related R&D costs are recognized. We expect to continue generating other income from CFFT and Horizon 2020 in 2016.

Research and Development Costs

Research and development expense consists principally of:

- salaries for research and development staff and related expenses, including social security costs and share-based compensation expenses;

- costs related to our pre-clinical and clinical activities and trials;
- costs for production of clinical and pre-clinical compounds and drug substances by contract manufacturers, including supporting studies such as stability studies and other analysis of the compounds;
- fees and other costs paid to contract research organizations, or CROs, in connection with additional pre-clinical testing;
- costs of related facilities, materials and equipment;
- costs associated with obtaining and maintaining patents and other intellectual property; and
- depreciation of tangible fixed assets used to develop our product candidates.

Our research and development expenses primarily relate to the following key programs:

- *QR-010 for the treatment of CF*

  The research and development costs relating to our lead product candidate, QR-010, primarily consist of salaries, costs for production of the compound for pre-clinical and toxicology studies, costs for production of the compound for clinical testing, and costs paid to CROs for our pre-clinical and clinical studies. Other significant costs are our internal laboratory costs, including the materials used in the labs and rent allocated to the lab space, as well as consultancy costs in the support of our research and development activities.

- *QR-110 for the treatment of LCA*

  The research and development costs relating to our product candidate, QR-110, primarily consist of salaries, costs for production of the compound for pre-clinical and toxicology studies and costs paid to CROs for our pre-clinical studies. Other significant costs are our internal laboratory costs, including the materials used in the labs and rent allocated to the lab space, as well as consultancy costs in the support of our research and development activities.

- *Other development programs*

  Other research and development expenses mainly relate to our innovation unit, which is our internal discovery engine, which has been very active in building a pipeline beyond CF and LCA based upon our toolbox of RNA technologies that we have in-licensed or developed in-house. These expenses primarily consist of salaries, costs for production of the pre-clinical compounds and costs paid to CROs for our pre-clinical studies.

For the years ended December 31, 2013, 2014 and 2015, we spent € 2,569,000, € 10,267,000 and € 23,401,000, respectively, on research and development.

Our research and development expense may vary substantially from period to period based on the timing of our research and development activities. Research and development expense is expected to increase as we continue clinical trials for QR-010, initiate and continue clinical trials for QR-110 and advance any other product candidates in pre-clinical studies. The successful development of our product candidates is highly uncertain. At this time we cannot reasonably estimate the nature, timing and estimated costs of the efforts that will be necessary to complete the development of, or the period, if any, in which material net cash inflows may commence from, any of our product candidates. This is due to numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- the scope, rate of progress and expense of our research and development activities;
- clinical trials and early-stage results;
- the terms and timing of regulatory approvals;
- the expense of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights; and

- the ability to market, commercialize and achieve market acceptance for QR-010, QR-110 or any other product candidate that we may develop in the future.

Any of these variables with respect to the development of QR-010, QR-110 or any other product candidate that we may develop could result in a significant change in the costs and timing associated with the development of such product candidate. For example, if the FDA, EMA or other regulatory authority were to require us to conduct pre-clinical and clinical studies beyond those which we currently anticipate will be required for the completion of clinical development or if we experience significant delays in enrollment in any clinical trials, we could be required to expend significant additional financial resources and time on the completion of our clinical development programs.

General and Administrative Costs

Our general and administrative expense consists principally of:

- salaries for employees other than research and development staff and related expenses, including social security costs and share-based compensation expenses;
- professional fees for auditors and other consulting expenses not related to research and development activities;
- professional fees for lawyers not related to the protection and maintenance of our intellectual property;
- cost of facilities, communication and office expenses;
- IT expenses; and
- amortization and depreciation of tangible and intangible fixed assets not related to research and development activities.

Since our IPO in September 2014 we have incurred additional costs associated with operating as a public company. These public company-related expenses include costs of additional personnel, additional legal fees, accounting and audit fees, managing directors' and supervisory directors' liability insurance premiums and costs related to investor relations. We expect that our general and administrative expense will increase further as our business expands.

Share-Based Compensation

Share-based compensation reflects the costs of our equity-settled, share option plan, which are measured at the fair value of the options at the grant date, and which are spread in line with each of the separate vesting tranches of the applicable vesting period of the options involved. The share-based compensation is recognized in the income statement, with a corresponding entry to the equity-settled employee benefits reserve, which is part of equity. We expect that our share-based compensation costs will increase in the future as the number of outstanding options increases. See notes 2(e) and 12(e) to the financial statements included elsewhere in this annual report for additional information on share-based compensation.

Finance Income

To date, our cash and cash equivalents have been deposited primarily in savings and short-term deposit accounts. Savings and deposit accounts generate a small amount of interest income. In 2015, as we held deposits in Euro and US dollars, the strong appreciation of the U.S. dollar against our functional currency (Euro) had a positive impact on our result.

Income tax

Due to the operating losses incurred since inception the Company has no tax provisions as of December 31, 2015. Realization of deferred tax assets is dependent on future earnings, if any, the timing and amount of which are uncertain. Accordingly, we have not yet recognized any deferred tax asset related to operating losses.

Results of Operations

Comparison of the periods ended December 31, 2015, 2014 and 2013

The following table sets forth our results of operations for the periods indicated.

	Year ended December 31,		
	2015	2014	2013
	(€ in thousands)		
Other income	3,235	313	116
Research and development costs	(23,401)	(10,267)	(2,569)
General and administrative costs	(6,837)	(6,507)	(786)
Operating result	**(27,003)**	**(16,461)**	**(3,239)**
Finance income and expense	6,171	4,334	(14)
Net loss (attributable to equity holders of the Company)	**(20,832)**	**(12,127)**	**(3,253)**
Other comprehensive income	1	—	—
Total comprehensive loss (attributable to equity holders of the Company)	**(20,831)**	**(12,127)**	**(3,253)**

Other income

For the periods ended December 31, 2015, 2014 and 2013, we had other income of € 3,235,000, € 313,000 and € 116,000, respectively. These amounts reflect the 2012 grant we received from the Cystic Fibrosis Foundation, for which we received the last payment during the first half of 2014, the grant received in August 2014 from CFFT and the Horizon 2020 grant received from the European Commission in May 2015.

Research and development costs

Research and development costs increased to € 23,401,000 for the year ended December 31, 2015 from € 10,267,000 for the year ended December 31, 2014 and € 2,569,000 for the year ended December 31, 2013. These costs were primarily related to our product candidates, QR-010 and QR-110, and our innovation unit. Our research and development expense is highly dependent on the development phases of our product candidates and is expected to continue to increase, although it fluctuates significantly from period to period.

The variances in research and development costs between the years ended December 31, 2015, 2014 and 2013 are mainly due to:

- costs we incurred on clinical trials for QR-010, particularly in 2015;
- increased staff costs as a result of increased staff working on (pre-)clinical development of our product candidates and the growth of our innovation unit. The number of full-time equivalent employees working on research and development increased from 12 at December 31, 2013 to 40 at December 31, 2014 and 72 at December 31, 2015;
- increased costs for externally conducted studies, including various *in vivo* studies, proof of concept studies and dose ranging and toxicity studies conducted in connection with the development of our product candidates;
- costs for the production of QR-010 and QR-110 compounds, including the costs of a GMP batch of QR-010 in preparation of our Phase 1b clinical study;
- increased laboratory costs including purchases of compounds and laboratory materials used by the research and development staff in proportion to the increase in the number of employees, and increased costs for the use of laboratories;
- increased project-related consultancy costs, including regulatory and intellectual property support; and

- increased share-based compensation, reflecting grants of share options to research and development staff made after we adopted our Option Plan in September 2013.

General and administrative costs

General and administrative costs increased to € 6,837,000 for the year ended December 31, 2015 from € 6,507,000 for the year ended December 31, 2014 and € 786,000 for the year ended December 31, 2013. The increase was primarily related to:

- increased staff costs associated with the increase of our general and administrative staff from 5 full-time equivalent employees at December 31, 2013 to 19 full-time equivalent employees at December 31, 2014 and 27 full-time equivalent employees at December 31, 2015;
- increased office and general costs, including office rent, information technology and communication costs, travel costs and office consumables, as well as costs to improve our internal control environment in 2015;
- increased costs for legal support, accounting and other consultancy costs, including costs incurred in preparation of our IPO amounting to € 1,763,000 in 2014, resulting in a modest increase of total G&A costs in 2015; and
- increased share-based compensation, reflecting grants of share options to non-research and development staff made after we adopted our Option Plan in September 2013.

We expect that general and administrative costs will increase in the future as our business expands.

Finance income and expense

We had net finance income of € 6,171,000 for the year ended December 31, 2015, as compared to a net income of € 4,334,000 for the year ended December 31, 2014 and a net expense of € 14,000 for the year ended December 31, 2013. The financial income in 2014 and 2015 mainly reflects foreign exchange benefits on cash and cash equivalents denominated in U.S. dollars.

B. Liquidity and capital resources

To date, we have financed our operations through our IPO, private placements of equity securities, a convertible loan and funding from governmental bodies and patient organizations.

Cash Flows

The table below summarizes our statement of cash flows for the years ended December 31, 2013, 2014 and 2015.

	Year ended December 31,		
	2015	2014	2013
	(€ in thousands)		
Net cash used in operating activities	(24,232)	(14,457)	(2,332)
Net cash used in investing activities	(1,324)	(1,233)	(137)
Net cash generated by financing activities	1,620	119,883	6,349
Net increase/(decrease) in cash and cash equivalents	**(23,936)**	**104,191**	**3,880**
Currency effect cash and cash equivalents	6,065	4,414	—
Cash and cash equivalents at the beginning of the period	112,736	4,129	249
Cash and cash equivalents at the end of the period	**94,865**	**112,736**	**4,129**

Net cash used in operating activities increased from € 2,332,000 in the year ended December 31, 2013 to € 14,457,000 in the year ended December 31, 2014 and € 24,232,000 in the year ended December 31, 2015. These increases were primarily due to the increased net loss from operating activities, adjusted for (non-cash) finance income and share-based payment expenses, partially offset by changes in working capital.

Net cash used in investing activities increased from € 137,000 in the year ended December 31, 2013 to € 1,233,000 in the year ended December 31, 2014 and € 1,324,000 in the year ended December 31, 2015. This increase was primarily due to our investments in laboratory equipment, office equipment and leasehold improvements in support of our growing operations.

Net cash generated by financing activities increased from € 6,349,000 in year ended December 31, 2013 to € 119,883,000 in the year ended December 31, 2014, and decreased to € 1,620,000 in the year ended December 31, 2015. In 2014, we completed a private placement of preferred shares to investors for total net proceeds of approximately € 40,366,000, after deducting expenses incurred in connection with the private placement, which includes the conversion of a convertible loan amounting to € 2,560,000 (non-cash item), as well as loans totaling € 1,667,000 from a governmental body. In September 2014, we raised gross proceeds of € 87,202,000 (net proceeds of € 80,376,000) from our initial public offering of 8,625,000 ordinary shares. In 2015, cash generated by financing activities primarily included loans totaling € 1,640,000 from a governmental body.

Cash and Funding Sources

The table below summarizes our main sources of financing for the years ended December 31, 2013, 2014 and 2015.

	Equity Capital	Convertible Loan	Government Borrowing	Total
		(€ in thousands)		
Year ended December 31, 2013	3,023	2,500	826	6,349
Year ended December 31, 2014	120,810	(2,500)	1,667	119,977
Year ended December 31, 2015	—	—	1,640	1,640
Total	123,833	—	4,133	127,966

Our source of financing in 2015 was funding from a governmental body amounting to € 1,640,000. We also established an ATM facility that may serve as a source of funding in upcoming years. Our sources of financing in 2014 were our IPO providing net proceeds of € 80,376,000, a private placement of equity securities and exercises of options providing total net proceeds of € 40,434,000, including conversion of a convertible loan of € 2,560,000, including interest, provided in 2013 by existing shareholders, and funding from a governmental body amounting to € 1,667,000. Our sources of financing in 2013 were private placements of equity securities providing total net proceeds of € 3,023,000, a convertible loan from existing shareholders of € 2,500,000 and funding from a governmental body amounting to € 826,000.

At December 31, 2015, we had non-current liabilities of € 4,824,000, which fully consisted of borrowings from a government body. Cash is denominated in both U.S. dollars and euros.

For a description of our financial commitments, see below.

Funding Requirements

We expect that our cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements for at least through mid-2017. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our present and future funding requirements will depend on many factors, including, among other things:

- the progress, timing and completion of pre-clinical testing and clinical trials for our current or any future product candidates;
- the number of potential new product candidates we identify and decide to develop;
- the costs involved in growing our organization to the size needed to allow for the research, development and potential commercialization of our current or any future product candidates;

- the costs involved in filing patent applications and maintaining and enforcing patents or defending against claims or infringements raised by third parties;
- the time and costs involved in obtaining regulatory approval for our product candidates and any delays we may encounter as a result of evolving regulatory requirements or adverse results with respect to any of these product candidates;
- any licensing or milestone fees we might have to pay during future development of our current or any future product candidates;
- selling and marketing activities undertaken in connection with the anticipated commercialization of our current or any future product candidates and costs involved in the creation of an effective sales and marketing organization; and
- the amount of revenues, if any, we may derive either directly or in the form of royalty payments from future sales of our product candidates, if approved.

For more information as to the risks associated with our future funding needs, see Item 3.D: "Risk Factors".

Capital Expenditures

The following table sets forth our capital expenditures for the years ended December 31, 2013, 2014 and 2015:

	Year ended December 31,		
	2015	2014	2013
	(€ in thousands)		
Investments in tangible fixed assets	1,441	1,109	137
Investments in intangible assets	28	124	—
Total	**1,469**	**1,233**	**137**

During 2014, we moved our laboratory facilities to increase and enhance our research and development capacity, which resulted in additional investments in laboratory and office equipment. To facilitate the growing needs of our company and accommodate the increased staff levels, we also moved our offices in March 2015. In addition, we opened our U.S. office in Palo Alto (CA) and invested in our IT infrastructure. These changes led to increasing investments in tangible fixed assets in 2015, funded from existing cash balances.

Contractual Obligations and Commitments

The table below analyzes ProQR's undiscounted liabilities into relevant maturity groupings based on the remaining period at December 31, 2015 until the contractual maturity date:

	Less than 1 year	Between 1 and 2 years	Between 2 and 5 years	Over 5 years
	(€ in thousands)			
At December 31, 2015				
Borrowings	—	1,691	3,133	—
Finance lease liabilities	15	—	—	—
Trade payables and other payables	5,471	—	—	—
Total	**5,486**	**1,691**	**3,133**	**—**

Commitments

Rent

Since 2012, the Company is domiciled in Leiden. We are currently a party to lease agreements for laboratory space and offices at two locations in the Netherlands and one office in the U.S.

The lease expenditure charged to the income statement for operating leases in 2015 amounts to € 703,000 (2014: € 258,000, 2013: € 113,000). The total commitment as at December 31, 2015 amount to € 9,049,000 (2014: € 786,000, 2013: € 194,000).

Patent license agreement

The Company and the General Hospital Corporation (MGH) have entered into a Patent License Agreement pursuant to which we may have certain royalty obligations based on the development or commercialization of QR-010, as well as the obligation to pay MGH up to $ 700,000 in milestone payments upon the achievement of certain development and regulatory milestones.

The Company and the Radboud University Medical Center have entered into a Patent License Agreement under which we were granted a world-wide exclusive license pursuant to which we may have certain royalty obligations in relation to our product candidate QR-110 for Leber's congenital amaurosis.

The Company and the Radboud University Medical Center have entered into a Patent License Agreement under which we were granted a world-wide exclusive license pursuant to which we may have certain royalty obligations in relation to Type II Usher Syndrome.

The Company and the Leiden University Medical Centre have entered into a Patent License Agreement under we were granted a world-wide exclusive license pursuant to which we may have certain royalty obligations in relation to several CNS diseases.

The Company and PARI Pharma GmbH entered into an agreement, pursuant to which the Company is granted an exclusive license to the use of PARI's eflow technology for the administration of oligonucleotide-based drugs in the ΔF508 mutation in cystic fibrosis, with the option to expand this exclusivity to the use in other CF mutations. Pursuant to the terms of the agreement, we have made an upfront payment, fees for development work and are obligated to make sales-based royalty payments after-market authorization.

Clinical support agreement

In August 2014, we entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide the Company with up to $ 3 million to support the clinical development of QR-010.

Pursuant to the terms of the agreement, we are obligated to make a one-time milestone payment to CFFT of up to approximately $ 80 million, payable in three equal annual installments following the first commercial sale of QR-010, the first of which is due within 90 days following the first commercial sale. We are also obligated to make a one-time milestone payment to CFFT of up to $ 3 million if net sales of QR-010 exceed $ 500 million in a calendar year. Lastly, we are obligated to make a payment to CFFT of up to approximately $ 6 million if it transfers, sells or licenses QR-010 other than for certain clinical or development purposes, or if we enter into a change of control transaction. Either CFFT or us may terminate the agreement for cause, which includes our material failure to achieve certain commercialization and development milestones. Our payment obligations survive the termination of the agreement.

Research and development commitments

The Company has committed itself to a number of obligations amounting to € 9,449,000 at December 31, 2015 (2014: € 1,758,000). Of these obligations an amount of € 9,053,000 is due in 2016, the remainder is due in 1 to 5 years.

Our commitments are set out in more detail in note 21 and 22 to the financial statements as included elsewhere in this annual report.

C. Research and development, patents and licenses, etc.

See Item 4.B: "Business Overview" and Item 5: "Operating and Financial Review and Prospects".

D. Trend information

See Item 5: "Operating and Financial Review and Prospects".

E. Off-balance sheet arrangements

During the periods presented in this annual report, we did not have any off-balance sheet arrangements.

F. Tabular disclosure of contractual obligations

See Item 5.B: "Liquidity and capital resources".

G. Safe harbor

Refer to "Forward-looking statements".

Item 6: Directors, Senior Management and Employees

A. Directors and senior management

We have a two-tier board structure consisting of our management board (raad van bestuur) and a separate supervisory board (raad van commissarissen). Below is a summary of relevant information concerning our supervisory board, management board and senior management.

Supervisory Board

The following table sets forth information with respect to each of our supervisory board members and their respective ages as of the date of this annual report. The terms of office of all our supervisory board members expire according to a rotation schedule drawn up by our supervisory board. The business address of our supervisory board members is our registered office address at Darwinweg 24, 2333 CR Leiden, the Netherlands.

Our supervisory board is currently composed of the following members, all of whom are independent under applicable NASDAQ standards and the DCGC:

Name	Date of Birth	Position	Member Since	Term expires
Dinko Valerio	August 3, 1956	Member of the Supervisory Board (Chairman)	January 1, 2014	2016
Alison Lawton	September 26, 1961	Member of the Supervisory Board	September 17, 2014	2018
Antoine Papiernik	July 21, 1966	Member of the Supervisory Board	January 1, 2014	2018
Henri Termeer	February 28, 1946	Member of the Supervisory Board	January 1, 2014	2016
Paul Baart	November 9, 1950	Member of the Supervisory Board	June 10, 2015	2019

The following sets forth biographical information regarding our Supervisory Board members. There are no family relationships among the members of our Supervisory Board, Management Board or Executive Officers.

Dinko Valerio is one of our founders and currently serves as the chairman of our supervisory board. Mr. Valerio has served on our supervisory board since January 2014. Mr. Valerio is a scientist and an experienced biotech entrepreneur with experience in both public and private companies as CEO and board member. Mr. Valerio is founder and former CEO of Crucell N.V., a Dutch biotech company, and founder and general partner of Aescap Venture, a life sciences venture capital firm. In 1999, Mr. Valerio was one of the founders of Galapagos Genomics N.V., a spinout from Crucell N.V. which develops novel mode of action medicines. Adding to his corporate experience, Mr. Valerio is a professor in the field of gene therapy of the hematopoietic system at the University of Leiden. He received his Master of Science degree in Biology from the University of Amsterdam in 1982 and completed his Ph.D. in Molecular Genetics with Honors at the University of Leiden in 1986. Mr. Valerio also was a visiting scientific specialist at Genentech Inc., San

Francisco in 1985 and a postdoctoral fellow at the Salk Institute, San Diego from 1986 to 1987. He is an author on more than 100 articles in peer-reviewed journals and an inventor on 11 patent-families. We believe that Mr. Valerio's experience in the venture capital industry, particularly with biopharmaceutical companies, and his experience serving on the boards of directors of a number of biopharmaceutical companies provide him with the qualifications and skills to serve as chairman of our supervisory board.

Alison Lawton has served on our supervisory board since September 2014. Ms Lawton is currently the Chief Operating Officer of Aura Biosciences Inc. From January 2013 to January 2014, Ms. Lawton served as Chief Operating Officer of OvaScience, Inc., a public life sciences company. From 1991 to 2013, Ms. Lawton worked at various positions of increasing responsibility at Genzyme Corporation, or Genzyme, and subsequently at Sanofi-Aventis, following its 2011 acquisition of Genzyme, each a global biopharmaceutical company. Ms. Lawton served as head of Genzyme Biosurgery, where she was responsible for Genzyme's global orthopedics, surgical and cell therapy and regenerative medicine businesses. Prior to that, Ms. Lawton oversaw Global Market Access at Genzyme, which included Regulatory Affairs, Global Health Outcomes and Strategic Pricing, Global Public Policy, and Global Product Safety & Risk Management. Before joining Genzyme, Ms. Lawton worked for seven years in the United Kingdom at Parke-Davis, a pharmaceutical company. Ms. Lawton serves on the board of directors of Verastem, Inc., a public biopharmaceutical company. She also served on the board of directors of Cubist Pharmaceuticals for three years until its acquisition by Merck & Co., Inc. in 2015. She currently consults for X4 Pharmaceuticals. She is past President and Chair of the Board of Regulatory Affairs Professional Society and past FDA Advisory Committee member for Cell and Gene Therapy Committee. In 2016 she is joining the board of directors of CoLucid Pharmaceuticals. She earned her BSc in Pharmacology, with honors, from King's College London. We believe that Ms. Lawton's significant operational, international, regulatory and senior management experience within the pharmaceutical and biotechnology industries, as well as experience serving on a board of directors within the industry, provide her with the qualifications and skills to serve as a member of our supervisory board.

Antoine Papiernik has served on our supervisory board since January 2014. Mr. Papiernik is managing partner at Sofinnova Partners, which he joined in 1997. Mr. Papiernik has been an initial investor and active board member in public companies like Actelion, Addex, Auris Medical, Orexo, NovusPharma (then sold to CTI), Movetis (then sold to Shire), Mainstay, Pixium and Stentys, which went public respectively on the Zurich Stock Exchange, the NASDAQ Global Market, the Stockholm Stock Exchange, the Milan Nuovo Mercato, the Belgium Stock Exchange, the Dublin Stock Exchange and EuroNext Paris, in Cotherix (initially NASDAQ listed, then sold to Actelion), Core Valve (sold to Medtronic), Fovea (sold to Sanofi Aventis) and Ethical Oncology Science (EOS, sold to ClovisOncology). Mr. Papiernik has also invested in and is a board member of private companies MD Start, ReCor, Shockwave Medical and Reflexion Medical. Mr. Papiernik has an MBA degree from the Wharton School of Business, University of Pennsylvania. We believe that Mr. Papiernik's experience in the venture capital industry, particularly with biopharmaceutical companies, and his experience serving on the boards of directors of a number of biopharmaceutical companies provide him with the qualifications and skills to serve as member of our supervisory board.

Henri Termeer is vice chairman and has served on our supervisory board since January 2014. From October 1983 to June 2011, Mr. Termeer served as chairman, president and chief executive officer of Genzyme Corporation. For ten years prior to joining Genzyme, Mr. Termeer worked for Baxter International Laboratories, Inc., a manufacturer of human health care products. Mr. Termeer resigned from Genzyme in June 2011 following the acquisition of Genzyme by Sanofi. Widely acknowledged for his contributions to the biotechnology industry and health care field, Mr. Termeer is active in the areas of humanitarian assistance, policy issues, and innovation in providing access to health care. He is a member of the board of each of Massachusetts General Hospital and Partners HealthCare and a member of the board of fellows of Harvard Medical School. Mr. Termeer is also a member of the board of the Massachusetts Institute of Technology and serves on its Executive Committee and a board member of the Biotechnology Industry Organization (BIO). He is a board member of the New England Healthcare Institute, a nonprofit, applied research health policy organization he was instrumental in founding and on the boards of Life Sciences Foundation, Boston Ballet, Museum of Science, WGBH and Project Hope. Mr. Termeer is also currently a board member of Abiomed Inc., Aveo Pharmaceuticals, Verastem, Inc., Moderna Therapeutics and was a board member of Allergan, Inc. from 2014 through its acquisition by Actavis in March 2015. Mr. Termeer was chairman of the Federal Reserve Bank of Boston's board of directors from 2010-2011. Mr. Termeer studied economics at the Economische Hogeschool (Erasmus University, the Netherlands) and earned an MBA from the Darden School at the University of Virginia. We believe that Mr. Termeer's experience in the pharmaceutical and biotechnology industries and his experience serving on the boards of directors of a number of biopharmaceutical companies provide him with the qualifications and skills to serve as member of our supervisory board.

Paul Baart has served on our supervisory board since June 2015. Mr Baart made his career in public accounting in both the Netherlands and the USA. At PwC the Netherlands he served on the management board and the supervisory board. He was also a member of the global board of PwC International. He has served many large (listed) and international clients in various industries. He held professional qualifications both in the Netherlands and in the USA. He was chairman of Royal NIVRA, the Dutch Institute of Registered Accountants (now NBA), member of the Dutch Council on Annual Reporting (RJ) and supervisory board member of Nyenrode Business University. Present roles include outside member Enterprise Chamber Amsterdam Court of Appeal (Ondernemingskamer) and chairman Supervisory Board Grant Thornton the Netherlands. He studied business economics at the Vrije

Universiteit in Amsterdam, where he also passed the Registeraccountantsexam. We believe that Mr. Baart's significant international experience in public accounting, as well as his broad experience in management, oversight and boardroom consulting provide him with the qualifications and skills to serve as member of our supervisory board and chairman of our audit committee.

Management Board

The following table sets out information with respect to each of our management board members, their respective ages and their positions at the company as of the date of this annual report. The business address of our management board members is our registered office address at Darwinweg 24, 2333 CR Leiden, the Netherlands.

Name	Date of Birth	Position	Date of Appointment	Term Expires
Daniel de Boer	April 12, 1983	Chief Executive Officer	February 21, 2012	2018
René Beukema	March 26, 1964	Chief Corporate Development Officer and General Counsel	April 17, 2014	2017

The following sets forth biographical information regarding our management board members.

Daniel de Boer is our founding Chief Executive Officer and has served as such since our incorporation in February 2012. Mr. de Boer is a passionate and driven entrepreneur and advocate for CF patients, and has assembled an experienced team of successful biotech executives as co-founders and early investors. As a serial entrepreneur in IT, he founded and led a number of tech companies through phases of growth, initiating development and launch of several IT related products in several European countries. Prior to founding ProQR, Mr. de Boer served as a founder and Chief Executive Officer of RNA Systems, founder and Chief Executive Officer of PC Basic, and founder and Chief Executive Officer of Running IT. Mr. de Boer is responsible for the overall strategy and general business in the company.

René Beukema has served as our Chief Corporate Development Officer and General Counsel since April 2014. Mr. Beukema joined us in September 2013 and is a seasoned in-house corporate lawyer in the Dutch biotechnology arena. Prior to joining us, Mr. Beukema served as general counsel and corporate secretary of Crucell N.V. for twelve years, following his experience as a senior legal counsel at GE Capital / TIP Europe and legal counsel at TNT Express Worldwide. Mr. Beukema was also a venture partner of Aescap Venture, a life sciences venture capital firm. Mr. Beukema is the co-founder and advisor of Mytomorrows N.V., a Dutch life sciences company, and a member of the VU Medical Cancer Center children in Amsterdam. He holds a post-doctoral degree in corporate law from the University of Nijmegen in co-operation with the Dutch Association of In-house Counsel (*Nederlands Genootschap van Bedrijfsjuristen*) and a Master's degree in Dutch law from the University of Amsterdam.

Officers

Our management board is supported by our officers. The following table sets forth information with respect to each of the officers, their respective ages and their positions as of the date of this annual report. The business address of our officers is our registered office address at Darwinweg 24, 2333 CR Leiden, the Netherlands.

Name	Date of Birth	Position
Noreen Henig	April 13, 1965	Chief Development Officer
Gerard Platenburg	February 24, 1964	Chief Innovation Officer
Smital Shah	April 25, 1976	Chief Financial Officer

Noreen Henig, M.D. has served as our Chief Development Officer since March 2014. Prior to joining us, Dr. Henig was Senior Director, Global Respiratory, from 2011 to 2014 and Director, Respiratory Therapeutics, from 2008 to 2011, at Gilead Sciences, Inc. Dr. Henig is a board certified physician in Pulmonary, Critical Care and board eligible in Allergy and Immunology and has over 15 years of experience in the cystic fibrosis field and as a director of Adult Cystic Fibrosis Care Centers from 1999 to 2008. Dr. Henig has basic, translational and clinical trial expertise and clinical experience in advanced lung disease including cystic fibrosis, pulmonary arterial hypertension, idiopathic pulmonary fibrosis and lung transplantation. Dr. Henig's experience at Gilead Sciences, Inc. in drug development includes building and leading a global medical affairs organization, strategic development of clinical trials Phase II-IV, regulatory strategy, corporate development, leadership of key alliances and commercial strategy. Dr. Henig received her medical degree from Albert Einstein College of Medicine of Yeshiva University in 1991 with a distinction in immunology. She also has a bachelor's degree from Yale University.

Gerard Platenburg has served as our Chief Innovation Officer since February 2014. Mr. Platenburg is a co-founder of our company and also served as the sole member of our supervisory board between August 2012 and December 2013. Mr. Platenburg has an extensive background in RNA modulation and orphan drug discovery and development and is in charge of our innovation unit. Mr. Platenburg has more than twenty years of senior managerial experience, which he gained during his different operational and leadership roles in growing biotech companies. Prior to joining our company, Mr. Platenburg worked at Isa Pharmaceuticals B.V. from June 2009 to January 2014. Mr. Platenburg co-founded Prosensa Holding N.V., growing it to become a well-known RNA modulation clinical stage company, and held various positions between April 2002 and May 2009, including Chief Executive Officer and Chief Development Officer. Mr. Platenburg also worked at Pharming B.V. from April 1990 to March 2002. He is a passionate and driven pioneer of early stage technologies. Mr. Platenburg has a master's degree in chemistry and molecular biology from Leiden University in 1987 and pursued PhD work at Leiden University.

Smital Shah has served as our Chief Financial Officer since October 2014. Ms. Shah has twelve years of experience in management and leadership positions in biopharmaceutical companies and investment banking, with particular experience in financial strategy and capital markets. Prior to joining us, Ms. Shah was at Gilead Sciences, where she managed their multi-billion dollar debt, cash and investment portfolios, from 2012 to 2014. Prior to Gilead, from 2007 to 2012, Ms. Shah spent several years in investment banking at Leerink Partners and JP Morgan focused on capital raising and strategic transactions in the biotechnology space. Previously, Ms. Shah held various research and development focused roles at Johnson & Johnson. Ms. Shah has bachelor's and master's degrees in Chemical Engineering and an MBA degree from the University of California at Berkeley.

B. Compensation

Under Dutch law and our articles of association, the general meeting of shareholders must upon the proposal of our supervisory board adopt the compensation policy for the management board, which includes the outlines of the compensation of any members who serve on our management board. On September 15, 2014, the general meeting of shareholders adopted the current compensation policy of our company. The supervisory board determines the compensation of the management board members in accordance with the compensation policy. A proposal by the supervisory board with respect to compensation schemes in the form of shares or rights to shares is submitted for approval by the supervisory board to the general meeting of shareholders. Such proposal must set out at least the maximum number of shares or rights to shares to be granted to the management board and supervisory board, including the criteria for granting such shares or changes to such grants. The general meeting of shareholders may determine the compensation of supervisory board. The supervisory board will be reimbursed for their expenses.

Compensation of the Supervisory Board

The remuneration of the supervisory board members in 2015 is set out in the table below:

	2015			
	Short term employee benefits	Post-employment benefits	Share-based payment[1]	Total
Mr. Dinko Valerio	36	—	12	48
Mr. Henri Termeer	34	—	11	45
Mr. Antoine Papiernik	73	—	—	73
Ms. Alison Lawton	31	—	48	79
Mr. Paul Baart[2]	73	—	—	73
	247	—	71	318

1 Share-based payment reflects the fair value of share options granted under our Option Plan during the year, as required by and determined in accordance with IFRS 2 - Share based payment (refer to Note 12(e) to the financial statements included elsewhere in this annual report).

2 Mr. Baart was appointed on June 10, 2015.

Members of our supervisory board receive a board fee of € 25,000 per year and the chairperson receives a board fee of € 30,000 per year. In addition, each board committee chairperson will receive € 5,000 per year for service on such committee, and each other member of a board committee will receive € 3,000 per year for service on such committee. The chairperson of the nominating and corporate governance committee will receive € 3,000 per year for service on that committee. On June 10, 2015, our shareholders approved an amendment of the compensation policy whereby members of the supervisory board may be granted an additional compensation in cash of € 40,000 per year or a grant of options with an underlying value of € 80,000 per year.

Compensation of the Management Board

The table below sets out a breakdown of the compensation in 2015 of each current member of the management board:

	2015			
	Short term employee benefits	Post-employment benefits	Share-based payment[1]	Total
	(€ in thousands)			
Mr. D.A. de Boer	397	7	164	568
Mr. R.K. Beukema	313	13	88	414
	710	**20**	**252**	**982**

1 Share-based payment reflects the fair value of share options granted under our Option Plan during the year, as required by and determined in accordance with IFRS 2 - Share based payment (refer to Note 12(e) to the financial statements included elsewhere in this annual report).

For further detail on compensation of members of our supervision board, management board and senior management, see Note 23 to the financial statements included elsewhere in this annual report.

C. Board practices

Supervisory Board

Our supervisory board is responsible for the supervision of the activities of our management board and our company's general affairs and business. Our supervisory board may, also on its own initiative, provide the management board with advice and may request any information from the management board that it deems appropriate. In performing its duties, the supervisory board is required to act in the interests of our company (including its stakeholders) and its associated business as a whole. The members of the supervisory board are not authorized to represent us in dealings with third parties.

Pursuant to Dutch law, members of the supervisory board must be natural persons. Under our articles of association, the number of supervisory board members is determined by our supervisory board itself, provided there will be at least three supervisory board members. Our articles of association provide that members of the supervisory board are appointed by the general meeting of shareholders upon a binding nomination by the supervisory board. Our general meeting of shareholders may at all times deprive such a nomination of its binding character by a resolution passed by at least two-thirds of the votes cast representing more than 50% of our issued share capital, following which our supervisory board shall draw up a new binding nomination.

Our supervisory board rules provide that members of our supervisory board will serve for a maximum duration of three four-year terms. Our articles of association provide that the supervisory board members must retire periodically in accordance with a rotation schedule adopted by the supervisory board. A supervisory board member who retires in accordance with the rotation schedule can be reappointed immediately. The rotation schedule provides that the terms of office of the members of our supervisory board are staggered, such that approximately one-fourth of our supervisory board members will be subject to election in any one year and which has the effect of creating a staggered board (which may in turn deter a takeover attempt). The supervisory board appoints a chairman from among its members.

Under our articles of association, the general meeting of shareholders may suspend or remove supervisory board members at any time. A resolution of our general meeting of shareholders to suspend or remove a supervisory board member may be passed by a simple majority of the votes cast, provided that the resolution is based on a proposal by our supervisory board. In the absence of a proposal by our supervisory board, a resolution of our general meeting of shareholders to suspend or remove a supervisory board member shall require a majority of at least two-thirds of the votes cast representing more than 50% of our issued share capital.

In a meeting of the supervisory board, each supervisory board member is entitled to cast one vote. A supervisory board member may grant a written proxy to another supervisory board member to represent him at a meeting of the supervisory board. All resolutions by our supervisory board are adopted by a simple majority of the votes cast unless our supervisory board rules provide otherwise. In case of a tie in any vote of the supervisory board, the chairman of the supervisory board shall have the casting vote. Our supervisory board may also adopt resolutions outside a meeting, provided that such resolutions are adopted in writing, all supervisory board members are familiar with the resolution to be passed and provided that no supervisory board member objects to such decision-making process.

Management Board

Our management board is responsible for the day-to-day management of our operations under the supervision of the supervisory board. The management board is required to:

- keep the supervisory board informed in a timely manner in order to allow the supervisory board to carry out its responsibilities;
- consult with the supervisory board on important matters; and
- submit certain important decisions to the supervisory board for its approval.

Our management board may perform all acts necessary or useful for achieving our corporate purposes, other than those acts that are prohibited by law or by our articles of association. The management board as a whole and any management board member individually, are authorized to represent us in dealings with third parties.

Under our articles of association, the number of management board members is determined by the supervisory board, and the management board must consist of at least one member. The supervisory board elects a CEO from among the members of the management board.

Members of the management board are appointed by the general meeting of shareholders upon a binding nomination of the supervisory board. Our general meeting of shareholders may at all times deprive such a nomination of its binding character by a resolution passed by at least two-thirds of the votes cast representing more than 50% of our issued share capital, following which our supervisory board shall draw up a new binding nomination.

Our management board rules provide that, unless the resolution appointing a management board member provides otherwise, members of our management board will serve for a maximum term of four years. Our articles of association provide that the management board members must retire periodically in accordance with a rotation schedule adopted by the management board. A management board member who retires in accordance with the rotation schedule may be reappointed immediately for a term of not more than four years at a time.

Service Agreements

We have entered into service agreements with both of our management board members. The service agreements contain a termination notice period of two months. Both service agreements may be terminated in the event of an urgent reason (*dringende reden*) at any time, without advance notice. The service agreements with Daniel de Boer and René Beukema provide for a lump-sum payment following a change in control subject to certain conditions. Such payment is equal to 24 months of the individual's monthly gross fixed salary in effect at the time of the change in control. The service agreements also contain certain restrictive covenants, including post termination non-competition and non-solicitation covenants, which survive for a period of 12 months post-termination.

Committees of the Supervisory Board

We have an audit committee, a compensation committee and a nominating and corporate governance committee. We have adopted a charter for each of these committees.

Audit Committee

Our audit committee consists of Paul Baart (chairman), Antoine Papiernik and Alison Lawton. Each member satisfies the independence requirements of the NASDAQ listing standards and Rule 10A-3(b)(1) under the Exchange Act. Both Paul Baart and Alison Lawton satisfy the criteria for independence set forth in best practice III.2.2 of the DCGC, and Paul Baart and Antoine Papiernik each qualifies as an "audit committee financial expert," as defined by the SEC in Item 16A: "Audit Committee Financial Expert" and as determined by our supervisory board. The audit committee oversees our accounting and financial reporting processes and the audits of our financial statements. The audit committee is responsible for, among other things:

- making recommendations to our supervisory board regarding the appointment by the general meeting of shareholders of our independent auditor(s);
- overseeing the work of our independent auditor(s), including resolving disagreements between the management board, the officers and the independent auditors relating to financial reporting;
- pre-approving all audit and non-audit services permitted to be performed by the independent auditor(s);
- reviewing the independence and quality control procedures of the independent auditor(s);
- discussing material off-balance sheet transactions, arrangements and obligations with the management board and the independent auditor(s);
- reviewing and approving all proposed related-party transactions;
- discussing the annual audited statutory financial statements with the management board;
- annually reviewing and reassessing the adequacy of our audit committee charter;
- meeting separately with the independent auditors to discuss critical accounting policies, recommendations on internal controls, the auditor's engagement letter and independence letter and other material written communications between the independent auditors and the management board and the officers; and
- attending to such other matters as are specifically delegated to our audit committee by our supervisory board from time to time.

Compensation Committee

Our compensation committee consists of Antoine Papiernik (chairman), Dinko Valerio, Henri Termeer and Alison Lawton. Each member satisfies the independence requirements of the NASDAQ listing standards as well as the criteria for independence set forth in best practice III.2.2 of the DCGC. The compensation committee assists our supervisory board in reviewing and approving or recommending our compensation structure, including all forms of compensation relating to our supervisory board members, our management board members and our officers. Members of our management board may not be present at any compensation committee meeting while their compensation is deliberated. Subject to and in accordance with the terms of the compensation policy approved by our general meeting of shareholders from time to time, as required by Dutch law, the compensation committee is responsible for, among other things:

- reviewing and making recommendations to the supervisory board with respect to compensation of our management board and supervisory board members;
- reviewing and approving the compensation, including equity compensation, change-of-control benefits and severance arrangements, of our officers (not part of our management board or supervisory board) as it deems appropriate;
- overseeing the evaluation of our management board members and our officers;
- reviewing periodically and making recommendations to our supervisory board with respect to any incentive compensation and equity plans, programs or similar arrangements;
- exercising the rights of our supervisory board under any equity plans, except for the right to amend any such plans unless otherwise expressly authorized to do so;
- attending to such other matters as are specifically delegated to our compensation committee by our supervisory board from time to time;
- approving the compensation package for the officers; and
- periodically reviewing, in consultation with our CEO, our management board and our officers succession planning.

Our supervisory board may also delegate certain tasks and powers under our Option Plan to the compensation committee.

Nominating and Corporate Governance Committee

Our nominating and corporate governance committee consists of Dinko Valerio (chairman), Paul Baart and Henri Termeer. Each member satisfies the independence requirements of the NASDAQ listing standards as well as the criteria for independence set forth in best practice III.2.2 of the DCGC. The nominating and corporate governance committee assists our supervisory board in selecting individuals qualified to become our supervisory board members and management board members and in determining the composition of the management board, supervisory board and its committees and our officers. The nominating and corporate governance committee is responsible for, among other things:

- recommending to the supervisory board persons to be nominated for election or re-election to the supervisory board and the management board at any meeting of the shareholders;
- overseeing the supervisory board's annual review of its own performance and the performance of its committees; and
- considering, preparing and recommending to the supervisory board a set of corporate governance guidelines.

Insurance and Indemnification of Management Board and Supervisory Board Members

Under Dutch law, management board members, supervisory board members and certain other representatives may be held liable for damages in the event of improper or negligent performance of their duties. They may be held jointly and severally liable for damages to the company for infringement of the articles of association or of certain provisions of the Dutch Civil Code. They may also be liable towards third parties for infringement of certain provisions of the Dutch Civil Code. In certain circumstances they may also incur additional specific civil and criminal liabilities.

Our articles of association provide that we will indemnify our management board members, supervisory board members, former management board members and former supervisory board members (each an "Indemnified Person") against (i) any financial losses or damages incurred by such Indemnified Person and (ii) any expense reasonably paid or incurred by such Indemnified Person in connection with any threatened, pending or completed suit, claim, action or legal proceedings, whether civil, criminal, administrative or investigative and whether formal or informal, in which he becomes involved, to the extent this relates to his position with the company, in each case to the fullest extent permitted by applicable law. No indemnification shall be given to an Indemnified Person (a) if a Dutch court has established, without possibility for appeal, that the acts or omissions of such Indemnified Person that led to the financial losses, damages, suit, claim, action or legal proceedings result from either an improper performance of his duties as an officer of the company or an unlawful or illegal act and (b) to the extent that his financial losses, damages and expenses are covered by an insurance and the insurer has settled these financial losses, damages and expenses (or has indicated that it would do so). Our supervisory board may stipulate additional terms, conditions and restrictions in relation to such indemnification.

D. Employees

As at December 31, 2015, we had a total of 99.5 employees (converted to FTE). Of these employees, 72.4 were engaged in research and development and 27.1 in general and administrative. For additional details we refer to note 17 to the financial statements. We do not currently have in place a works council as we consider our relations with employees to be good.

E. Share ownership

Refer to Item 7.A: "Major shareholders" in this annual report.

Item 7: Major Shareholders and Related Party Transactions

A. Major shareholders

The following table sets forth information with respect to the beneficial ownership of our ordinary shares as at December 31, 2015 by:

- each of the members of our supervisory board and management board; and

- each person, or group of affiliated persons, known by us to beneficially own more than 5% of our ordinary shares.

The percentage of shares beneficially owned is based on a total of 23,345,965 ordinary shares outstanding as at December 31, 2015. The numbers and percentages of ordinary shares beneficially owned are reported on the basis of regulations of the SEC governing the determination of beneficial ownership of securities. Under the applicable SEC rules, a person is deemed to be a "beneficial owner" of a security if that person has or shares voting power, which includes the power to vote or direct the voting of such security, or investment power, which includes the power to dispose of or to direct the disposition of such security, or to receive the economic benefit of ownership of the securities. A person is also deemed to be a beneficial owner of any securities of which that person has a right to acquire beneficial ownership within 60 days of December 31, 2015, and such securities are considered outstanding for the purpose of calculating the percentage ownership of that person but not for the purpose of calculating the percentage ownership of any other person. Under these rules, more than one person may be deemed beneficial owner of the same securities and a person may be deemed to be a beneficial owner of securities as to which such person has no economic interest. Except as otherwise indicated, each of the beneficial owners has, to our knowledge, sole voting and investment power with respect to the indicated ordinary shares, subject to community property laws, where applicable. Except as otherwise set forth below, the address of the beneficial owner is c/o ProQR Therapeutics N.V., Darwinweg 24, 2333 CR, Leiden, the Netherlands.

	Shares Beneficially Owned	
Name and Address of Beneficial Owner	**Number**	**Percentage**
5% or Greater Shareholders:		
Sofinnova Capital VII FCPR[1]	2,769,125	11.9%
Entities affiliated with Orbimed Advisors, LLC. [2]	2,271,500	9.7%
FMR LLC.[3]	2,259,801	9.7%
Henri Termeer[4]	1,745,069	7.5%
Appel B.V. [5]	1,213,201	5.2%
Supervisory Board Members and Management Board Members		
Henri Termeer[4]	1,745,069	7.5%
Dinko Valerio[6]	959,556	4.1%
Antoine Papiernik[7]	2,769,125	11.9%
Alison Lawton[8]	3,205	0.0%
Daniel de Boer[9]	1,233,175	5.3%
René Beukema[10]	348,439	1.5%
Paul Baart	0	0.0%
All supervisory board members and management board members as a group (7 persons) [11]	**7,058,569**	**30.3%**

1 Sofinnova Partners SAS, a French corporation and the management company of Sofinnova Capital VII FCPR, may be deemed to have sole voting and investment power, and the managing partners of Sofinnova Partners SAS, Dennis Lucquin, Antoine Papiernik, Dr. Tordjman and Monique Saulnier, may be deemed to have shared voting and investment power with respect to such shares. The address of Sofinnova Capital VII FCPR is 16-18 rue du Quatre-Septembre, Paris 75002, France.

2 Consists of 833,600 ordinary shares held by OrbiMed Advisors, LLC and 995,800 ordinary shares held by OrbiMed Capital LLC. OrbiMed Advisors LLC and OrbiMed Capital LLC are investment advisors in accordance with ss.240.13d-1(b)(1)(ii)(E). Samuel D. Isaly is a control person in accordance with ss.240.13d-1(b)(1)(ii)(G). The address of OrbiMed Advisors, LLC and OrbiMed Capital LLC is 601 Lexington Avenue, 54th Floor, New York, NY 10022.

3 Fidelity Management & Research Company, or Fidelity, 82 Devonshire Street, Boston, Massachusetts 02109, a wholly-owned subsidiary of FMR LLC and an investment adviser registered under Section 203 of the Investment Advisers Act of 1940, is the beneficial owner of ordinary shares as a result of acting as investment adviser to various investment companies registered under Section 8 of the Investment Company Act of 1940. Edward C. Johnson 3d and FMR LLC, through its control of Fidelity, and the funds, or Funds, each has sole power to dispose of the shares owned by the Funds. Members of the family of Edward C. Johnson 3d, Chairman of FMR LLC, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC. Neither FMR LLC nor Edward C. Johnson 3d, Chairman of FMR LLC, has the sole power to vote or direct the voting of the shares owned directly by the Fidelity Funds, which power resides with the Funds' Boards of Trustees. Fidelity carries out the voting of the shares under written guidelines established by the Funds' Boards of Trustees. The address of Fidelity is 245 Summer Street, Boston, Massachusetts 02210.

4 Consists of 1,730,714 ordinary shares and options to acquire 14,355 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2015.
5 Appel B.V. is owned and controlled by Daniel de Boer, our chief executive officer, and Mr. de Boer exercises sole voting and dispositive power over the shares owned by Appel B.V. The address for Appel B.V. is Postbus 11059, 2301 EB, Leiden, the Netherlands.
6 Consists of 488,457 ordinary shares and options to acquire 16,136 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2015. Also includes 454,963 shares held by the Valerio family foundation, Stichting Administratiekantoor Endavit, for which Mr. Valerio is the managing director. The address of Stichting Administratiekantoor Endavit is Vlielandstraat 5, 1181 HZ, Amstelveen, the Netherlands.
7 Consists of 2,769,125 ordinary shares held by Sofinnova Capital VII FCPR. Antoine Papiernik may be deemed to have shared voting and investment power with respect to such shares as a managing partner of Sofinnova Partners SAS, the management company of Sofinnova Capital VII FCPR.
8 Consists of options to acquire 3,205 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2015.
9 Consists of options to acquire 19,974 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2015, and 1,213,201 ordinary shares held by Appel, B.V., which is owned and controlled by Daniel de Boer, our chief executive officer, as sole director.
10 Consists of 284,720 ordinary shares and options to acquire 63,719 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2015.
11 Consists of 6,941,180 ordinary shares and options to acquire 117,389 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2015.

Holdings by U.S. Shareholders

As at December 31, 2015, approximately 47.3% of our outstanding shares were held by 33 record holders in the United States.

B. Related party transactions

Since January 1, 2015, there have been no material transactions that are unusual in their nature or conditions with any of our related parties, except for remuneration as set out in note 23 to the financial statements as included elsewhere in this report.

Registration Rights Agreement

We have entered into a registration rights agreement with certain of our existing shareholders pursuant to which we will grant them customary registration rights for the resale of their ordinary shares, as summarized below.

Demand registration rights. Certain of our shareholders that are party to the Registration Rights Agreement, dated as of September 17, 2014, among us and the other parties thereto (the "RRA Shareholders") are entitled to request that we effect up to an aggregate of two demand registrations under the Registration Rights Agreement, and no more than two demand registrations within any twelve-month period, covering the RRA Shareholders' ordinary shares ("registrable securities") that total at least one-third of the outstanding registrable securities and which have an anticipated aggregate net offering price of at least $10 million. In addition, when we are eligible to use Form F-3, RRA Shareholders holding an aggregate of at least 30% of the registrable securities and which have an anticipated aggregate net offering price of at least $ 5 million have the right to request that we file a registration statement on Form F-3. These demand registration rights are subject to certain customary conditions and limitations, including customary underwriter cutback rights and deferral rights.

Piggyback registration rights. If we propose to register any ordinary shares (other than in registration statements covering share options under our equity incentive plans, a Rule 145 transaction or a dividend reinvestment plan), the RRA Shareholders are entitled to notice of such registration and to include their registrable securities in that registration. The managing underwriter has the right to limit the number of registrable securities included in a piggyback registration if the managing underwriter believes it would interfere with the successful marketing of the ordinary shares.

Subject to limited exceptions, the Registration Rights Agreement provides that we must pay all registration expenses in connection with a demand, piggyback or shelf registration. The Registration Rights Agreement contains customary indemnification and contribution provisions. The registration rights summarized above terminate upon the earliest of the occurrence of a sale event of our company, such time as Rule 144 or another similar exemption under the Securities Act is available for the sale of all of each RRA Shareholder's shares without limitation during a three-month period without registration, or the fifth anniversary of our initial public offering.

C. Interests of experts and counsel

Not applicable.

Item 8: Financial Information

A. Consolidated Statements and Other Financial Information

Consolidated financial statements

Consolidated financial statements are filed as part of this annual report, starting page F-1.

Legal proceedings

From time to time we could be involved in legal proceedings that arise in the ordinary course of business. As at December 31, 2015, we believe no proceedings exists of which the outcome, if determined adversely, will have a material adverse effect on our financial position. During the period covered by the audited and approved financial statements contained herein, we have not been a party to or paid any damages in connection with litigation that has had a material adverse effect on our financial position. Any future litigation may result in substantial costs and be a distraction to management and employees. No assurance can be given that future litigation will not have a material adverse effect on our financial position. Refer to Item 3.D: "Risk factors."

Dividends and other Distributions

We may only make distributions to our shareholders and other persons entitled to distributable profits, to the extent that our shareholders' equity exceeds the sum of the paid-up and called-up share capital plus the reserves as required to be maintained by Dutch law or by our articles of association.

Under our articles of association, a (cumulative) dividend is first paid out of the profit, if available for distribution, on any preferred shares. Any amount remaining out of the profit is carried to reserve as the management board determines. After reservation by the management board of any profit, the remaining profit will be at the disposal of the general meeting of shareholders. The management board is permitted, subject to certain requirements and subject to approval of the supervisory board, to declare interim dividends without the approval of the general meeting of shareholders.

Distributions shall be payable in such currency as determined by our management board. We intend that distributions, if any, shall be payable on such date as determined by our management board. Our management board will set the date that will be applied in order to establish which shareholders (or usufructuaries or pledgees, as the case may be) are entitled to the distribution, such date not being earlier than the date on which the distribution was announced. Claims for payment of dividends and other distributions not made within five years from the date that such dividends or distributions became payable, will lapse and any such amounts will be considered to have been forfeited to us (*"verjaring"*).

We have never declared or paid any dividends on our ordinary shares, and we currently do not plan to declare dividends on our ordinary shares in the foreseeable future.

B. Significant Changes

There have been no significant changes since the date of the annual financial statements.

Item 9: The Offer and Listing

A. Offering and listing details

See "Item 9.C The Offer and Listing—Markets."

B. Plan of distribution

Not applicable.

C. Markets

The following table sets forth the high and low sales prices as reported by NASDAQ for each quarter, the most recent six months and the first trading day:

	High	Low
	(in $)	
Annual highs and lows		
Year ended December 31, 2014 (from September 18, 2014)	23.02	11.00
Year ended December 31, 2015	27.60	6.95
Quarterly highs and lows		
Third quarter 2014 (from September 18, 2014)	21.87	14.12
Fourth quarter 2014	23.02	11.00
First quarter 2015	27.60	15.80
Second quarter 2015	22.97	15.74
Third quarter 2015	20.05	12.99
Fourth quarter 2015	16.23	6.95
Monthly highs and lows		
September 2015	20.05	13.54
October 2015	16.23	11.78
November 2015	15.51	8.47
December 2015	10.54	6.95
January 2016	8.96	4.94
February 2016	5.61	3.48

Since September 18, 2014, our ordinary shares have been listed on the NASDAQ Global Market under ticker symbol PRQR. On March 30, 2016, the closing price per share reported on the NASDAQ Global Market was $3.64.

D. Selling shareholders

Not applicable.

E. Dilution

Not applicable.

F. Expenses of the issue

Not applicable.

Item 10: Additional Information

A. Share capital

Not applicable.

B. Memorandum and articles of association

Our shareholders adopted the Amended Articles of Association filed as Exhibit 3.3 to our registration statement on Form F-1 (file no. 333-198151) with the SEC on August 14, 2014.

We incorporate by reference into this Annual Report the description of our amended articles of association contained in our F-1 registration statement (File No. 333-198151) originally filed with the SEC on August 14, 2014, as amended. Our articles of association were amended and we converted our company into a public company with limited liability (naamloze venootschap) effective September 23, 2014.

C. Material contracts

Except as otherwise disclosed in this annual report (including the Exhibits), we are currently not, and have not been in the two years preceding publication of this annual report, party to any material contract, other than contracts entered into in the ordinary course of business.

D. Exchange controls

Cash dividends payable on our ordinary shares may be officially transferred from the Netherlands to non-residents and converted into any other currency without legal restrictions imposed by Dutch law, except that for statistical purposes such payments and transactions must be reported to the Dutch Central Bank, and furthermore, no payments, including dividend payments, may be made to jurisdictions subject to sanctions adopted by the government of the Netherlands and implementing resolutions of the Security Council of the United Nations.

E. Taxation

Taxation in the Netherlands

General

The following is a general summary of certain material Dutch tax consequences of the holding and disposal of the ordinary shares. This summary does not purport to describe all possible tax considerations or consequences that may be relevant to all categories of investors, some of which may be subject to special treatment under applicable law (such as trusts or other similar arrangements), and in view of its general nature, it should be treated with corresponding caution. Holders should consult with their tax advisors with regard to the tax consequences of investing in the ordinary shares in their particular circumstances. The discussion below is included for general information purposes only.

Please note that this summary does not describe the tax considerations for:

(i) holders of ordinary shares if such holders, and in the case of individuals, his/her partner or certain of their relatives by blood or marriage in the direct line (including foster children), have a substantial interest or deemed substantial interest in us under the Dutch Income Tax Act 2001 (in Dutch: "*Wet inkomstenbelasting 2001*"). Generally speaking, a holder of securities in a company is considered to hold a substantial interest in such company, if such holder alone or, in the case of individuals, together with his/her partner (statutorily defined term), directly or indirectly, holds (i) an interest of 5% or more of the total issued and outstanding capital of that company or of 5% or more of the issued and outstanding capital of a certain class of shares of that company; or (ii) rights to acquire, directly or indirectly, such interest; or (iii) certain profit sharing rights in that company that relate to 5% or more of the company's annual profits and/or to 5% or more of the company's liquidation proceeds. A deemed substantial interest may arise if a substantial interest (or part thereof) in a company has been disposed of, or is deemed to have been disposed of, on a non-recognition basis;

(ii) holders of ordinary shares in us that qualify or qualified as a participation for purposes of the Dutch Corporate Income Tax Act 1969 (in Dutch: "*Wet op de vennootschapsbelasting 1969*"). Generally, a taxpayer's shareholding of 5% or more in a company's nominal paid-up share capital qualifies as a participation. A holder may also have a participation if such holder does not have a 5% shareholding but a related entity (statutorily defined term) has a participation or if the company in which the shares are held is a related entity (statutorily defined term);

(iii) holders of ordinary shares who are individuals for whom the ordinary shares or any benefit derived from the ordinary shares are compensation or deemed to be compensation for employment activities, including deemed employment activities performed by such holders or certain individuals related to such holders (as defined in the Dutch Income Tax Act 2001); and

(iv) pension funds, investment institutions (in Dutch: "*fiscale beleggingsinstellingen*"), exempt investment institutions (in Dutch: "*vrijgestelde beleggingsinstellingen*") and other entities that are, in whole or in part, not subject to or exempt from corporate income tax in the Netherlands, as well as entities that are exempt from corporate income tax in their country of residence, such country of residence being another state of the European Union, Norway, Liechtenstein, Iceland or any other state with which the Netherlands have agreed to exchange information in line with international standards.

Except as otherwise indicated, this summary only addresses national tax legislation and published regulations in the Netherlands, whereby the Netherlands means the part of the Kingdom of the Netherlands located in Europe, as in effect on the date hereof and as interpreted in published case law until this date, without prejudice to any amendment introduced at a later date and implemented with or without retroactive effect.

Withholding Tax

Dividends distributed by us generally are subject to Dutch dividend withholding tax at a rate of 15%. The expression "dividends distributed" includes, among other things:

- distributions in cash or in kind, deemed and constructive distributions and repayments of paid-in capital not recognized for Dutch dividend withholding tax purposes;
- liquidation proceeds, proceeds of redemption of ordinary shares, or proceeds of the repurchase of ordinary shares by us or one of our subsidiaries or other affiliated entities to the extent such proceeds exceed the average paid-in capital of those shares as recognized for purposes of Dutch dividend withholding tax;
- an amount equal to the par value of ordinary shares issued or an increase of the par value of ordinary shares, to the extent that it does not appear that a contribution, recognized for purposes of Dutch dividend withholding tax, has been made or will be made; and
- partial repayment of the paid-in capital, recognized for purposes of Dutch dividend withholding tax, if and to the extent that we have net profits (in Dutch: "zuivere winst"), unless the holders of ordinary shares have resolved in advance at a general meeting to make such repayment and the par value of the ordinary shares concerned has been reduced by an equal amount by way of an amendment of our articles of association.

If a holder of ordinary shares is resident in a country other than the Netherlands and if a double taxation convention is in effect between the Netherlands and such other country, such holder of ordinary shares may, depending on the terms of that double taxation convention, be eligible for a full or partial exemption from, or refund of, Dutch dividend withholding tax.

Individuals and corporate legal entities who are resident or deemed to be resident in the Netherlands for Dutch tax purposes ("Dutch Resident Individuals" and "Dutch Resident Entities" as the case may be), can generally credit the Dutch dividend withholding tax against their income tax or corporate income tax liability. The same generally applies to holders of ordinary shares that are neither resident nor deemed to be resident of the Netherlands if the ordinary shares are attributable to a Dutch permanent establishment of such non-resident holder.

In general, we will be required to remit all amounts withheld as Dutch dividend withholding tax to the Dutch tax authorities. However, under certain circumstances, we are allowed to reduce the amount to be remitted to the Dutch tax authorities by the lesser of:

- 3% of the portion of the distribution paid by us that is subject to Dutch dividend withholding tax; and
- 3% of the dividends and profit distributions, before deduction of foreign withholding taxes, received by us from qualifying foreign subsidiaries in the current calendar year (up to the date of the distribution by us) and the two preceding calendar years, as far as such dividends and profit distributions have not yet been taken into account for purposes of establishing the above mentioned reduction.

Although this reduction reduces the amount of Dutch dividend withholding tax that we are required to remit to the Dutch tax authorities, it does not reduce the amount of tax that we are required to withhold on dividends distributed.

Pursuant to legislation to counteract "dividend stripping", a reduction, exemption, credit or refund of Dutch dividend withholding tax is denied if the recipient of the dividend is not the beneficial owner as described in the Dutch Dividend Withholding Tax Act 1965 (in Dutch: "*Wet op de dividendbelasting 1965*"). This legislation generally targets situations in which a shareholder retains its economic interest in shares but reduces the withholding tax costs on dividends by a transaction with another party. It is not required for these rules to apply that the recipient of the dividends is aware that a dividend stripping transaction took place. The Dutch State Secretary of Finance takes the position that the definition of beneficial ownership introduced by this legislation will also be applied in the context of a double taxation convention.

Taxes on Income and Capital Gains

Dutch Resident Individuals

If a holder of ordinary shares is a Dutch Resident Individual, any benefit derived or deemed to be derived from the ordinary shares is taxable at the progressive income tax rates (with a maximum of 52%), if:

(a) the ordinary shares are attributable to an enterprise from which the Dutch Resident Individual derives a share of the profit, whether as an entrepreneur or as a person who has a co-entitlement to the net worth (in Dutch: *"medegerechtigd tot het vermogen"*) of such enterprise, without being an entrepreneur or a shareholder, as defined in the Dutch Income Tax Act 2001; or

(b) the holder of the ordinary shares is considered to perform activities with respect to the ordinary shares that go beyond ordinary asset management (in Dutch: "*normaal, actief vermogensbeheer*") or derives benefits from the ordinary shares that are taxable as benefits from other activities (in Dutch "*resultaat uit overige werkzaamheden*").

If the above-mentioned conditions (a) and (b) do not apply to the individual holder of ordinary shares, the ordinary shares are recognized as investment assets and included as such in such holder's net investment asset base *(*in Dutch: "*rendementsgrondslag*"). Such holder will be taxed annually on a deemed income of 4% of his or her net investment assets for the year at an income tax rate of 30%. The net investment assets for the year are the fair market value of the investment assets less the allowable liabilities on January 1 of the relevant calendar year. A tax free allowance may be available. Actual benefits derived from the ordinary shares are as such not subject to Dutch income tax.

Dutch Resident Entities

Any benefit derived or deemed to be derived from the ordinary shares held by Dutch Resident Entities, including any capital gains realized on the disposal thereof, will generally be subject to Dutch corporate income tax at a rate of 25% (a corporate income tax rate of 20% applies with respect to taxable profits up to € 200,000).

Non-Residents of the Netherlands

A holder of ordinary shares will not be subject to Netherlands taxes on income or on capital gains in respect of any payment under the ordinary shares or any gain realized on the disposal or deemed disposal of the ordinary shares, provided that:

(i) such holder is neither a resident nor deemed to be resident in the Netherlands for Dutch tax purposes and, if such holder is an individual, such holder has not made an election for the application of the rules of the Dutch Income Tax Act 2001 as they apply to residents of the Netherlands;

(ii) such holder does not have an interest in an enterprise or a deemed enterprise (statutorily defined term) which, in whole or in part, is either effectively managed in the Netherlands or is carried out through a permanent establishment, a deemed permanent establishment or a permanent representative in the Netherlands and to which enterprise or part of an enterprise the ordinary shares are attributable or deemed attributable; and

(iii) in the event such holder is an individual, such holder does not carry out any activities in the Netherlands with respect to the ordinary shares that go beyond ordinary asset management and does not derive benefits from the ordinary shares that are taxable as benefits from other activities in the Netherlands.

Gift and Inheritance Taxes

Residents of the Netherlands

Gift and inheritance taxes will arise in the Netherlands with respect to a transfer of the ordinary shares by way of a gift by, or on the death of, a holder of ordinary shares who is resident or deemed to be resident in the Netherlands at the time of the gift or his/her death.

Non-residents of the Netherlands

No Dutch gift or inheritance taxes will arise on the transfer of the ordinary shares by way of gift by, or on the death of, a holder of ordinary shares who is neither resident nor deemed to be resident in the Netherlands, unless:

(i) in the case of a gift of ordinary shares by an individual who at the date of the gift was neither resident nor deemed to be resident in the Netherlands, such individual dies within 180 days after the date of the gift, while being resident or deemed to be resident in the Netherlands; or

(ii) the transfer is otherwise construed as a gift or inheritance made by, or on behalf of, a person who, at the time of the gift or death, is or is deemed to be resident in the Netherlands.

For purposes of Dutch gift and inheritance taxes, amongst others, a person that holds the Dutch nationality will be deemed to be resident in the Netherlands if such person has been resident in the Netherlands at any time during the ten years preceding the date of the gift or his/her death. Additionally, for purposes of Dutch gift tax, amongst others, a person not holding the Dutch nationality will be deemed to be resident in the Netherlands if such person has been resident in the Netherlands at any time during the twelve months preceding the date of the gift. Applicable tax treaties may override deemed residency.

Other Taxes and Duties

No Dutch VAT and no Dutch registration tax, stamp duty or any other similar documentary tax or duty will be payable by a holder of ordinary shares on any payment in consideration for the holding or disposal of the ordinary shares.

Certain Material U.S. Federal Income Tax Considerations

The following is a summary of certain material U.S. federal income tax considerations relating to the ownership and disposition of our ordinary shares by a U.S. holder (as defined below). This summary addresses only the U.S. federal income tax considerations for U.S. holders that will hold our ordinary shares as capital assets. This summary does not address all U.S. federal income tax matters that may be relevant to a particular U.S. holder. This summary does not address tax considerations applicable to a holder of ordinary shares that may be subject to special tax rules including, without limitation, the following:

- banks, financial institutions or insurance companies;
- brokers, dealers or traders in securities, currencies, commodities, or notional principal contracts;
- tax-exempt entities or organizations, including an “individual retirement account” or “Roth IRA” as defined in Section 408 or 408A of the Code (as defined below), respectively;
- real estate investment trusts, regulated investment companies or grantor trusts;
- persons that hold the ordinary shares as part of a “hedging,” “integrated” or “conversion” transaction or as a position in a “straddle” for U.S. federal income tax purposes;
- partnerships (including entities classified as partnerships for U.S. federal income tax purposes) or other pass-through entities, or persons that will hold our shares through such an entity;
- S corporations;
- certain former citizens or long term residents of the United States;

- persons that received our shares as compensation for the performance of services;
- persons that acquire ordinary shares as a result of holding or owning our preferred shares;
- holders that own directly, indirectly, or through attribution 10% or more of the voting power or value our shares; and
- holders that have a "functional currency" other than the U.S. dollar.

Further, this summary does not address the U.S. federal estate, gift, or alternative minimum tax considerations, or any U.S. state, local, or non-U.S. tax considerations of the ownership and disposition of our ordinary shares.

This description is based on the U.S. Internal Revenue Code of 1986, as amended, or the Code, existing, proposed and temporary U.S. Treasury Regulations promulgated thereunder and administrative and judicial interpretations thereof, in each case as in effect and available on the date hereof. All the foregoing is subject to change, which change could apply retroactively, and to differing interpretations, all of which could affect the tax considerations described below. There can be no assurances that the U.S. Internal Revenue Service, or the IRS, will not take a position concerning the tax consequences of the ownership and disposition of our ordinary shares or that such a position would not be sustained. Holders should consult their own tax advisers concerning the U.S. federal, state, local and non-U.S. tax consequences of owning and disposing of our ordinary shares in their particular circumstances.

For the purposes of this summary, a "U.S. holder" is a beneficial owner of ordinary shares that is (or is treated as), for U.S. federal income tax purposes:

- a citizen or resident of the United States;
- a corporation, or other entity that is treated as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust, if a court within the United States is able to exercise primary supervision over its administration and one or more U.S. persons have the authority to control all of the substantial decisions of such trust or has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a United States person.

If a partnership (or any other entity treated as a partnership for U.S. federal income tax purposes) holds ordinary shares, the U.S. federal income tax consequences relating to an investment in our ordinary shares will depend in part upon the status of the partner and the activities of the partnership. Such a partner or partnership should consult its tax advisor regarding the U.S. federal income tax considerations of owning and disposing of our ordinary shares in its particular circumstances.

As indicated below, this discussion is subject to U.S. federal income tax rules applicable to a "passive foreign investment company," or a PFIC.

Persons considering an investment in our ordinary shares should consult their own tax advisors as to the particular tax consequences applicable to them relating to the ownership and disposition of our ordinary shares, including the applicability of U.S. federal, state and local tax laws and non-U.S. tax laws.

Distributions

Subject to the discussion under "Passive Foreign Investment Company Considerations," below, the gross amount of any distribution (including any amounts withheld in respect of Dutch withholding tax) actually or constructively received by a U.S. holder with respect to ordinary shares will be taxable to the U.S. holder as a dividend to the extent of our current and accumulated earnings and profits as determined under U.S. federal income tax principles. Distributions in excess of earnings and profits will be non-taxable to the U.S. holder to the extent of, and will be applied against and reduce, the U.S. holder's adjusted tax basis in the ordinary shares. Distributions in excess of earnings and profits and such adjusted tax basis will generally be taxable to the U.S. holder as either long-term or short-term capital gain depending upon whether the U.S. holder has held our ordinary shares for more than one year as of the time such distribution is received. However, since we do not calculate our earnings and profits under U.S. federal income tax principles, it is expected that any distribution will be reported 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. Non-corporate U.S. holders may qualify for the preferential rates of taxation with respect to dividends on ordinary shares applicable to long-term capital gains (i.e., gains from the sale of capital assets

held for more than one year) applicable to qualified dividend income (as discussed below). The Company, which is incorporated under the laws of the Kingdom of the Netherlands, believes that it qualifies as a resident of the Netherlands for purposes of, and is eligible for the benefits of, the Convention between the United States of America and the Kingdom of the Netherlands for the Avoidance of Double Taxation and the Prevention of Fiscal Evasion with respect to Taxes on Income, signed on December 18, 1992, as amended and currently in force, or the U.S.-Netherlands Tax Treaty, although there can be no assurance in this regard. Further, the IRS has determined that the U.S.-Netherlands Tax Treaty is satisfactory for purposes of the qualified dividend rules and that it includes an exchange-of-information program. Therefore, subject to the discussion under "Passive Foreign Investment Company Considerations," below, if the U.S.-Netherlands Tax Treaty is applicable, such dividends will generally be "qualified dividend income" in the hands of individual U.S. holders, provided that certain conditions are met, including holding period and the absence of certain risk reduction transaction requirements are met. The dividends will not be eligible for the dividends-received deduction generally allowed to corporate U.S. holders.

A U.S. holder generally may claim the amount of Dutch income withholding tax withheld as either a deduction from gross income or a credit against U.S. federal income tax liability. However, the foreign tax credit is subject to numerous complex limitations that must be determined and applied on an individual basis. Generally, the credit cannot exceed the proportionate share of a U.S. holder's U.S. federal income tax liability that such U.S. holder's taxable income bears to such U.S. holder's worldwide taxable income. In applying this limitation, a U.S. holder's various items of income and deduction must be classified, under complex rules, as either "foreign source" or "U.S. source." In addition, this limitation is calculated separately with respect to specific categories of income. The amount of a distribution with respect to the ordinary shares that is treated as a "dividend" may be lower for U.S. federal income tax purposes than it is for Dutch income tax purposes, potentially resulting in a reduced foreign tax credit for the U.S. holder. Each U.S. holder should consult its own tax advisors regarding the foreign tax credit rules.

In general, the amount of a distribution paid to a U.S. holder in a foreign currency will be the dollar value of the foreign currency calculated by reference to the spot exchange rate on the day the U.S. holder receives the distribution, regardless of whether the foreign currency is converted into U.S. dollars at that time. Any foreign currency gain or loss a U.S. holder realizes on a subsequent conversion of foreign currency into U.S. dollars will be U.S. source ordinary income or loss. If dividends received in a foreign currency are converted into U.S. dollars on the day they are received, a U.S. holder should not be required to recognize foreign currency gain or loss in respect of the dividend.

Sale, exchange or other taxable disposition of our ordinary shares

A U.S. holder will generally recognize gain or loss for U.S. federal income tax purposes upon the sale, exchange or other taxable disposition of ordinary shares in an amount equal to the difference between the U.S. dollar value of the amount realized from such sale or exchange and the U.S. holder's tax basis for those ordinary shares. Subject to the discussion under "*Passive Foreign Investment Company Considerations*" below, this gain or loss will generally be a capital gain or loss and will generally be treated as from sources within the United States. The adjusted tax basis in an ordinary share generally will be equal to the cost of such ordinary share. Capital gain from the sale, exchange or other taxable disposition of ordinary shares of a non-corporate U.S. holder is generally eligible for a preferential rate of taxation applicable to capital gains, if the non-corporate U.S. holder's holding period determined at the time of such sale, exchange or other taxable disposition for such ordinary shares exceeds one year (i.e., such gain is long-term taxable gain). The deductibility of capital losses for U.S. federal income tax purposes is subject to limitations under the Code. Any such gain or loss that a U.S. holder recognizes generally will be treated as U.S. source income or loss for foreign tax credit limitation purposes.

For a cash basis taxpayer, units of foreign currency paid or received are translated into U.S. dollars at the spot rate on the settlement date of the purchase or sale. In that case, no foreign currency exchange gain or loss will result from currency fluctuations between the trade date and the settlement date of such a purchase or sale. An accrual basis taxpayer, however, may elect the same treatment required of cash basis taxpayers with respect to purchases and sales of our ordinary shares that are traded on an established securities market, provided the election is applied consistently from year to year. Such election may not be changed without the consent of the IRS. For an accrual basis taxpayer who does not make such election, units of foreign currency paid or received are translated into U.S. dollars at the spot rate on the trade date of the purchase or sale. Such an accrual basis taxpayer may recognize exchange gain or loss based on currency fluctuations between the trade date and the settlement date. Any foreign currency gain or loss a U.S. Holder realizes will be U.S. source ordinary income or loss.

Medicare Tax

Certain U.S. holders that are individuals, estates or trusts are subject to a 3.8% tax on all or a portion of their "net investment income," which may include all or a portion of their dividend income and net gains from the disposition of ordinary shares. Each U.S. holder that is an individual, estate or trust is urged to consult its tax advisors regarding the applicability of the Medicare tax to its income and gains in respect of its investment in our ordinary shares.

Passive foreign investment company considerations

If we are classified as a passive foreign investment company, or PFIC, in any taxable year, a U.S. holder would be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A corporation organized outside the United States generally will be classified as a PFIC for U.S. federal income tax purposes in any taxable year in which, after applying certain look-through rules with respect to the income and assets of its subsidiaries, either: (i) at least 75% of its gross income is "passive income" or (ii) at least 50% of the average quarterly value of its total gross assets (which, assuming we are not a CFC for the year being test, would be measured by fair market value of the assets, and for which purpose the total value of our assets may be determined in part by the market value of our ordinary shares, which is subject to change) is attributable to assets that produce "passive income" or are held for the production of "passive income."

Passive income for this purpose generally includes dividends, interest, royalties, rents, gains from commodities and securities transactions, the excess of gains over losses from the disposition of assets which produce passive income, and includes amounts derived by reason of the temporary investment of funds raised in offerings of our ordinary shares. If a non-U.S. corporation owns directly or indirectly at least 25% by value of the stock of another corporation, the non-U.S. corporation is treated for purposes of the PFIC tests as owning its proportionate share of the assets of the other corporation and as receiving directly its proportionate share of the other corporation's income. If we are classified as a PFIC in any year with respect to which a U.S. holder owns our ordinary shares, we will continue to be treated as a PFIC with respect to such U.S. holder in all succeeding years during which the U.S. holder owns our ordinary shares, regardless of whether we continue to meet the tests described above.

Although the matter is not free from doubt, we believe that we were not a PFIC during our 2015 taxable year. Our status for any taxable year will depend on our assets and activities in each year, and because this is a factual determination made annually after the end of each taxable year, there can be no assurance that we will not be considered a PFIC for the current taxable year or any future taxable year. The market value of our assets may be determined in large part by reference to the market price of our ordinary shares, which is likely to fluctuate.

If we are a PFIC, and you are a U.S. holder, then unless you make one of the elections described below, a special tax regime will apply to both (a) any "excess distribution" by us to you (generally, your ratable portion of distributions in any year which are greater than 125% of the average annual distribution received by you in the shorter of the three preceding years or your holding period for our ordinary shares) and (b) any gain realized on the sale or other disposition of the ordinary shares. Under this regime, any excess distribution and realized gain will be treated as ordinary income and will be subject to tax as if (a) the excess distribution or gain had been realized ratably over your holding period, (b) the amount deemed realized in each year had been subject to tax in each year of that holding period at the highest marginal rate for such year (other than income allocated to the current period or any taxable period before we became a PFIC, which would be subject to tax at the U.S. holder's regular ordinary income rate for the current year and would not be subject to the interest charge discussed below), and (c) the interest charge generally applicable to underpayments of tax had been imposed on the taxes deemed to have been payable in those years. In addition, dividend distributions made to you will not qualify for the lower rates of taxation applicable to long-term capital gains discussed above under "Distributions."

Certain elections exist that may alleviate some of the adverse consequences of PFIC status and would result in an alternative treatment (such as mark-to-market treatment) of our ordinary shares. If a U.S. holder makes the mark-to-market election, the U.S. holder generally will recognize as ordinary income any excess of the fair market value of the ordinary shares at the end of each taxable year over their adjusted tax basis, and will recognize an ordinary loss in respect of any excess of the adjusted tax basis of the ordinary shares over their fair market value at the end of the taxable year (but only to the extent of the net amount of income previously included as a result of the mark-to-market election). If a U.S. holder makes the election, the U.S. holder's tax basis in the ordinary shares will be adjusted to reflect these income or loss amounts. Any gain recognized on the sale or other disposition of ordinary shares in a year when we are a PFIC will be treated as ordinary income and any loss will be treated as an ordinary loss (but only to the extent of the net amount of income previously included as a result of the mark-to-market election). The mark-to-market election is available only if we are a PFIC and our ordinary shares are "regularly traded" on a "qualified exchange." Our ordinary shares will be treated as "regularly traded" in any calendar year in which more than a de minimis quantity of the ordinary shares are traded on a qualified exchange on at least 15 days during each calendar quarter (subject to the rule that trades that have as one of their principle purposes the meeting of the trading requirement as disregarded). The NASDAQ Global Market is a qualified exchange for this purpose and, consequently, if the ordinary shares are regularly traded, the mark-to-market election will be available to a U.S. holder.

We do not currently intend to provide the information necessary for U.S. holders to make qualified electing fund elections if we were treated as a PFIC for any taxable year. U.S. Holders should consult their tax advisors to determine whether any of these elections would be available and if so, what the consequences of the alternative treatments would be in their particular circumstances.

If we are determined to be a PFIC, the general tax treatment for U.S. Holders described in this section would apply to indirect distributions and gains deemed to be realized by U.S. Holders in respect of any of our subsidiaries that also may be determined to be PFICs.

If a U.S. holder owns ordinary shares during any taxable year in which we are a PFIC and the U.S. holder recognizes gain on a disposition of our ordinary shares or receives distributions with respect to our ordinary shares, the U.S. holder generally will be required to file an IRS Form 8621 (Information Return by a Shareholder of a Passive Foreign Investment Company or Qualified Electing Fund) with respect to the company, generally with the U.S. holder's federal income tax return for that year. If our company were a PFIC for a given taxable year, then you should consult your tax advisor concerning your annual filing requirements.

The U.S. federal income tax rules relating to PFICs are complex. U.S. investors are urged to consult their own tax advisers with respect to the ownership and disposition of our ordinary shares, the consequences to them of an investment in a PFIC, any elections available with respect to our ordinary shares and the IRS information reporting obligations with respect to the ownership and disposition of our ordinary share.

Backup Withholding and Information Reporting

U.S. holders generally will be subject to information reporting requirements with respect to dividends on ordinary shares and on the proceeds from the sale, exchange or disposition of ordinary shares that are paid within the United States or through U.S.-related financial intermediaries, unless the U.S. holder is an "exempt recipient." In addition, U.S. holders may be subject to backup withholding on such payments, unless the U.S. holder provides a taxpayer identification number and a duly executed IRS Form W-9 or otherwise establishes an exemption. Backup withholding is not an additional tax, and the amount of any backup withholding will be allowed as a credit against a U.S. holder's U.S. federal income tax liability and may entitle such holder to a refund, provided that the required information is timely furnished to the IRS.

Foreign Asset Reporting

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 shares held in accounts maintained by U.S. financial institutions) by filing IRS Form 8938 (Statement of Specified Foreign Financial Assets) with their federal income tax return. U.S. holders are urged to consult their tax advisors regarding their information reporting obligations, if any, with respect to their ownership and disposition of our ordinary shares.

THE DISCUSSION SET OUT ABOVE IS INCLUDED FOR GENERAL INFORMATION ONLY AND MAY NOT BE APPLICABLE DEPENDING UPON A HOLDER'S PARTICULAR SITUATION. IT DOES NOT COVER ALL TAX MATTERS THAT MAY BE OF IMPORTANCE TO A HOLDER. EACH HOLDER IS URGED TO CONSULT THEIR TAX ADVISOR WITH RESPECT TO THE TAX CONSEQUENCES TO THEM OF THE OWNERSHIP AND DISPOSITION OF THE SHARES INCLUDING TAX CONSEQUENCES UNDER STATE, LOCAL AND OTHER TAX LAWS AND THE POSSIBLE TAX EFFECTS OF CHANGES IN THE UNITED STATES FEDERAL AND OTHER TAX LAWS.

F. Dividends and paying agents

Not applicable.

G. Statement by experts

Not applicable.

H. Documents on display

We are subject to certain reporting requirements of the Exchange Act. As a foreign private issuer, we are exempt from the rules under the Exchange Act prescribing certain disclosure and procedural requirements for proxy solicitations, and our officers, directors and principal shareholders are exempt from the reporting and "short swing" profit recovery provisions contained in Section 16 of the Exchange Act, with respect to their purchases and sales of shares. In addition, we are not required to file reports and Financial Statements with the Commission as frequently or as promptly as companies that are not foreign private issuers whose securities are registered under the Exchange Act. However, we are required to file with the Commission, within four months after the end of each fiscal year, an Annual Report on Form 20-F containing Financial Statements audited by an independent accounting firm. We publish unaudited interim financial information after the end of each quarter. We furnish this quarterly financial information to the Commission under cover of a Form 6-K.

It is possible to read and copy documents referred to in the 2015 Form 20-F that have been filed with the SEC at the SEC's public reference room located at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the public reference rooms and their copy charges. ProQR SEC filings are also publicly available through the SEC's website at www.sec.gov.

I. Subsidiary information

Not applicable.

Item 11: Quantitative and Qualitative Disclosures about Market Risk

We are exposed to a variety of financial risks: market risk (including foreign exchange risk and interest rate risk), credit risk and liquidity risk. Our overall risk management program focuses on the unpredictability of financial markets.

Our cash management policy is focused on optimizing the net interest result of funds invested in deposits while accepting limited risk (minimum ratings of P2 or A3 for short-term and long-term, respectively by Moody's and A2 or A- for short-term and long-term, respectively, by Standard and Poor's). Individual commitments exceeding a defined threshold in foreign currencies may be hedged against our functional currency, the euro, to avoid foreign currency exposure affecting the income statement in comparison to budget.

Market Risk

Foreign exchange risk arises from future commercial transactions and recognized assets and liabilities in foreign currencies, primarily with respect to the U.S. Dollar. We have exposure associated with the time delay between entering into a contract, budget or forecast and the realization thereof. To minimize economic exposure related to currency fluctuations, currencies on the balance sheet will be matched to the cash flows on an annual basis to ensure the availability of at least 12 months of liquidity per currency per the approved budget. The impact of fair value measurements on the financial statements is limited.

At December 31, 2015 there was a net liability in U.S. Dollars of € 1.1 million (2014: € 0.7 million). Foreign currency denominated receivables and trade payables are short term in nature (generally 30 to 45 days). As a result foreign exchange rate movements on receivables and trade payables, during the years presented had an immaterial effect on the financial statements.

Our interest rate risk exposure is limited due to the use of loans with fixed rates. At December 31, 2015, we had one loan and a financial lease with fixed interest, totaling € 4,839,000 (2014: € 2,863,000).

Credit Risk

Credit risk represents the risk of financial loss caused by default of the counterparty. We have no large receivables balances with external parties. Our principal financial assets are cash and cash equivalents which are, in line with our cash policy, placed at ABN Amro and Rabobank which meet our defined minimum credit ratings.

Liquidity Risk

We believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements for at least through mid-2017. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Item 12: Description of Securities other that Equity Securities

A. Debt securities

Not applicable.

B. Warrants and rights

Not applicable.

C. Other securities

Not applicable.

D. American depositary shares

Not applicable.

Part II

Item 13: Defaults, Dividend Arrearages and Delinquencies

No matters to report.

Item 14: Material Modifications to the Rights of Security Holders and Use of Proceeds

The following use of proceeds information relates to our initial public offering, at $ 13.00 per ordinary share, of 8,625,000 ordinary shares, which included the exercise in full of the underwriters' option to purchase additional 1,125,000 ordinary shares. The aggregate offering price and the amount that we registered in connection with our initial public offering was $ 112,125,000, before underwriting discounts and commissions and offering expenses payable by us. The registration statement on Form F-1 (file no. 333-198151) for our initial public offering was filed on August 14, 2014 and subsequently amended, and declared effective by the SEC on September 17, 2014, and Form F-1MEF (File No. 333-198806), which was filed on September 17, 2014 and declared effective on September 17, 2014. Following the sale of the shares in connection with the closing of our initial public offering, the offering terminated. The offering did not terminate before all the securities registered in the registration statements were sold. Leerink Partners LLC and Deutsche Bank Securities Inc. acted as joint book-running managers for the offering. JMP Securities LLC acted as lead manager, and H.C. Wainwright & Co., LLC acted as co-manager for the offering.

We received proceeds of € 80.4 million from our initial public offering, net of € 8.6 million of underwriting discounts and offering expenses payable by us. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning ten percent or more of any class of our equity securities or to any other affiliates. To date, we have used € 31.2 million of the net proceeds of the offering, primarily to fund our research and development activities, but also to fund investments in our new location and laboratory equipment as well as general and administrative costs. We intend to use the net proceeds we received from our initial public offering as disclosed in our Registration Statement on Form F-1.

We intend to invest the net proceeds of this offering in a variety of capital preservation investments, which may include term deposits, other short-term, investment-grade, interest-bearing instruments and government securities, all in accordance with our investment policy.

Item 15: Controls and Procedures

A. Disclosure controls and procedures

Under the supervision and with the participation of our Chief Executive Officer (CEO) and Chief Financial Officer (CFO), the effectiveness of the design and operation of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934) has been evaluated as of the end of the period covered by the Annual Report (December 31, 2015). The term "disclosure controls and procedures" means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms and that such information required to be disclosed by us in the reports that we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosures.

Based on that evaluation, the Chief Executive Officer and Chief Financial Officer have concluded that these disclosure controls and procedures are effective as at December 31, 2015.

B. Management's annual report on internal control over financial reporting

Our management is responsible for establishing and maintaining adequate "internal control over financial reporting," as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. This rule defines internal control over financial reporting as a process designed by, or under the supervision of, a company's chief executive officer and chief financial officer and effected by our board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and

expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

The Company's internal control over financial reporting is a process designed to provide reasonable, but not absolute, assurance regarding the reliability of financial reporting and the preparation of the consolidated financial statements in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting is not intended to provide absolute assurance that a misstatement of our financial statements would be prevented or detected.

In connection with the preparation of the Company's annual consolidated financial statements, management has undertaken an assessment of the effectiveness of the Company's internal control over financial reporting as of December 31, 2015. Based on this assessment, management concluded that the Company's internal control over financial reporting was effective as at December 31, 2015.

C. Attestation report of the registered public accounting firm

This Annual Report does not include an attestation report of the company's registered public accounting firm because "emerging growth companies" are not subject to the attestation requirements pursuant to the JOBS Act.

D. Changes in internal control over financial reporting

During the year ended December 31, 2015, there have been no changes in our internal control over financial reporting that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 16A: Audit Committee Financial Expert

Currently, Paul Baart and Antoine Papiernik each qualify as an "audit committee financial expert," as defined by the SEC and as determined by our supervisory board. Both members satisfy the independence requirements of the NASDAQ listing standards and Rule 10A-3(b)(1) under the Exchange Act. Paul Baart satisfies the criteria for independence set forth in best practice III.2.2 of the DCGC.

Item 16B: Code of Ethics

We have adopted a Code of Business Conduct and Ethics applicable to all of our management board and supervisory board members and our employees, including our CEO, CFO, controller or principal accounting officers, or other persons performing similar functions, which is a "code of ethics" as defined by the SEC. The full text of the Code of Business Conduct and Ethics is posted on our company website at www.ProQR.com.

If we make any amendment to the Code of Business Conduct and Ethics or grant any waivers, including any implicit waiver, from a provision of the Code of Business Conduct and Ethics, we will disclose the nature of such amendment or waiver on our website within five working days to the extent required by the rules and regulations of the SEC.

The Code of Business Conduct and Ethics includes the whistleblower policy as contemplated in the DCGC.

Item 16C: Principal Accountant Fees and Services

The information required is included in note 24 to the financial statements.

Item 16D: Exemptions from the Listing Standards for Audit Committees

Not applicable.

Item 16E: Purchases of Equity Securities by the Issuer and Affiliated Purchasers

Historically, we hold treasury shares which relate to ordinary shares that have legally been issued, but that are within our control. In 2015, no purchases of our registered equity securities were made by or on our behalf or on the behalf of any affiliated purchaser.

Item 16F: Change in Registrant's Certifying Accountant

None.

Item 16G: Corporate Governance

The Sarbanes-Oxley Act of 2002, as well as related rules subsequently implemented by the SEC, requires foreign private issuers, including our company, to comply with various corporate governance practices. As a foreign private issuer, subject to certain exceptions, the NASDAQ listing standards permit a foreign private issuer to follow its home country practice in lieu of the NASDAQ listing standards. In addition, a foreign private issuer must disclose in its annual reports filed with the SEC each such requirement that it does not follow and describe the home country practice followed instead of any such requirement.

The home country practices followed by our company in lieu of NASDAQ rules are described below:

- We do not intend to follow NASDAQ's quorum requirements applicable to meetings of shareholders. In accordance with Dutch law and generally accepted business practice, our articles of association do not provide quorum requirements generally applicable to general meetings of shareholders.
- We do not intend to follow NASDAQ's requirements regarding the provision of proxy statements for general meetings of shareholders. Dutch law does not have a regulatory regime for the solicitation of proxies and the solicitation of proxies is not a generally accepted business practice in the Netherlands. We do intend to provide shareholders with an agenda and other relevant documents for the general meeting of shareholders and shareholders will be entitled to give proxies and voting instructions to us and/or third parties.

We intend to take all actions necessary for us to maintain compliance as a foreign private issuer under the applicable corporate governance requirements of the Sarbanes-Oxley Act of 2002, the rules adopted by the SEC and NASDAQ's listing standards.

Certain NASDAQ corporate governance requirements are not reflected in the Dutch Corporate Governance Code ("DCGC") or Dutch law. Accordingly, our shareholders may not be afforded the same protection as provided under NASDAQ corporate governance rules to the extent the DCGC or Dutch law does not provide similar protections. Furthermore, as a foreign private issuer, we will be exempt from the rules and regulations under the Exchange Act related to the furnishing and content of proxy statements, and our officers, directors and principal shareholders will be exempt from the reporting and short swing profit recovery provisions contained in Section 16 of the Exchange Act. In addition, we will not be required under the Exchange Act to file annual, quarterly and current reports and financial statements with the SEC as frequently or as promptly as domestic companies whose securities are registered under the Exchange Act.

Item 16H: Mine Safety Disclosure

Not applicable.

Part III

Item 17: Financial Statements

Financial Statements are filed as part of this annual report, starting on page F-1.

Item 18: Financial Statements

Financial Statements are filed as part of this annual report, starting on page F-1.

Item 19: Exhibits

Index of Exhibits

Exhibit No.	Description
1.1	Amended Articles of Association of the Registrant (incorporated by reference to Exhibit 3.3 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
2.1	Form of Registration Rights Agreement by and between the Registrant and the shareholders party thereto (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.1#	ProQR Therapeutics B.V. Stock Option Plan and forms of notice of grant thereunder (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)
4.2#	ProQR Therapeutics N.V. Stock Option Plan and forms of notice of grant thereunder (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.3#	Form of Management Services Agreement by and between the Registrant and Daniel Anton de Boer (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.4#	Form of Management Services Agreement by and between the Registrant and René Beukema (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.5	Form of Call Option Agreement by and between the Registrant and Stichting Continuity ProQR Therapeutics (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 16, 2014)
4.6	Sublease of Office Accommodation dated as of September 5, 2013 by and between the Registrant and Pharming Technologies B.V. (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)
4.7	Sublease Agreement dated as of April 1, 2013 by and between the Registrant and MicroSafe Laboratories (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)
4.8†	Exclusive Patent License Agreement dated as of May 29, 2012 by and between the Registrant and The General Hospital Corporation d/b/a Massachusetts General Hospital (incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 16, 2014)
4.9†	Agreement dated as of August 1, 2014 by and between the Registrant and Cystic Fibrosis Foundation Therapeutics, Inc. (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)

Exhibit No.	Description
4.10#	Form of Indemnification Agreement for the Managing Directors, Supervisory Directors and officers of the Registrant (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.11†	License and Clinical Supply Agreement, dated as of October 8, 2014, between the Registrant and PARI Pharma GmbH (incorporated by reference to Exhibit 10.1 to the Registrant's Report of Foreign Private Issuer (File No. 001-36622) filed on October 9, 2014)
8.1*	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)
12.1*	Certification by Principal Executive Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
12.2*	Certification by Principal Financial Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
13.1**	Certification by Principal Executive Officer and Principal Financial Officer Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
15.1*	Consent of Deloitte Accountants B.V., Independent Registered Public Accounting Firm

* Filed herewith

** The certifications furnished in Exhibit 13.1 hereto are deemed to accompany this Annual Report on Form 20-F and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended. Such certifications will not be deemed to be incorporated by reference into any filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

† Confidential treatment has been granted as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission

Management contract or compensatory plan or arrangement

Signatures

The registrant hereby certifies that it meets all of the requirements for filing on Form 20-F and that it has duly caused and authorized the undersigned to sign this annual report on its behalf.

Leiden, March 31, 2016

PROQR THERAPEUTICS N.V.

By: /s/ Daniel de Boer
Name: Daniel de Boer
Title: Chief Executive Officer

By: /s/ Smital Shah
Name: Smital Shah
Title: Chief Financial Officer

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Report of the Independent Registered Public Accounting Firm

To: the Shareholders and Supervisory Board of ProQR Therapeutics N.V.

We have audited the accompanying consolidated statements of financial position of ProQR Therapeutics N.V. ("the Company") as of December 31, 2015 and 2014, and the related consolidated statements of comprehensive loss, changes in equity, and cash flows for each of the three years in the period ended December 31, 2015 (further the "financial statements"). These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements present fairly, in all material respects, the financial position of ProQR Therapeutics N.V. as at December 31, 2015 and 2014, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2015, in conformity with International Financial Reporting Standards as issued by the International Accounting Standards Board.

/s/ Deloitte Accountants B.V.

Amsterdam, the Netherlands

March 31, 2016

PROQR THERAPEUTICS N.V.

Consolidated Statement of Financial Position

		December 31, 2015	December 31, 2014
		(€ in thousands)	
Assets			
Intangible assets	*7*	141	163
Property, plant and equipment	*8*	2,199	1,187
Non-current assets		**2,340**	**1,350**
Social security and other taxes	*9*	956	426
Prepayments and other receivables	*10*	1,948	735
Cash and cash equivalents	*11*	94,865	112,736
Current assets		**97,769**	**113,897**
Total assets		**100,109**	**115,247**
Shareholders' equity			
Share capital		934	934
Share premium reserve		123,595	123,581
Equity settled employee benefits reserve		1,899	687
Translation reserve		1	—
Accumulated deficit		(36,630)	(15,798)
Total equity	*12*	**89,799**	**109,404**
Liabilities			
Borrowings		4,824	2,814
Finance lease liabilities		—	15
Non-current liabilities	*13*	**4,824**	**2,829**
Finance lease liabilities		15	34
Trade payables		885	1,247
Social security and other taxes		235	341
Pension premiums		16	127
Deferred income		144	—
Other current liabilities		4,191	1,265
Current liabilities	*14*	**5,486**	**3,014**
Total liabilities		**10,310**	**5,843**
Total equity and liabilities		**100,109**	**115,247**

The accompanying notes are an integral part of these financial statements.

PROQR THERAPEUTICS N.V.

Consolidated Statement of Profit or Loss and Comprehensive Income

		Year Ended December 31,		
		2015	2014	2013
		(€ in thousands)		
Other income	*15*	3,235	313	116
Research and development costs	*16*	(23,401)	(10,267)	(2,569)
General and administrative costs		(6,837)	(6,507)	(786)
Total operating costs		(30,238)	(16,774)	(3,355)
Operating result		**(27,003)**	**(16,461)**	**(3,239)**
Financial income and expense	*18*	6,171	4,334	(14)
Result before corporate income taxes		**(20,832)**	**(12,127)**	**(3,253)**
Income taxes	*19*	—	—	—
Net loss (attributable to equity holders of the Company)		**(20,832)**	**(12,127)**	**(3,253)**
Other comprehensive income				
Items that will never be reclassified to profit or loss		—	—	—
Items that are or may be reclassified to profit or loss				
Foreign operations – foreign currency translation differences		1	—	—
Total comprehensive loss (attributable to equity holders of the Company)		**(20,831)**	**(12,127)**	**(3,253)**
Share information	*20*			
Weighted average number of shares outstanding		23,343,262	11,082,801	5,517,688
Earnings per share for result attributable to the equity holders of the Company (expressed in Euro per share)				
Basic and diluted loss per share		€ (0.89)	€ (1.09)	€ (0.59)

The accompanying notes are an integral part of these financial statements.

PROQR THERAPEUTICS N.V.

Consolidated Statement of Changes in Equity

	Attributable to Equity Holders of the Company					
	Share Capital (€ in thousands)	Share Premium Reserve (€ in thousands)	Equity Settled Employee Benefit Reserve (€ in thousands)	Translation Reserve (€ in thousands)	Accumulated Deficit (€ in thousands)	Total Equity (€ in thousands)
Balance at January 1, 2013	**33**	**484**	**—**	**—**	**(418)**	**99**
Net loss	—	—	—	—	(3,253)	(3,253)
Recognition of share-based payments	—	—	41	—	—	41
Shares issued in the period	35	2,998	—	—	—	3,033
Treasury shares issued	(9)	—	—	—	—	(9)
Balance at December 31, 2013	**59**	**3,482**	**41**	**—**	**(3,671)**	**(89)**
Net loss	—	—	—	—	(12,127)	(12,127)
Recognition of share-based payments	—	—	646	—	—	646
Shares issued in the period	880	122,291	—	—	—	123,171
Conversion of preferred shares	—	—	—	—	—	—
Treasury shares issued	(5)	(2,192)	—	—	—	(2,197)
Balance at December 31, 2014	**934**	**123,581**	**687**	**—**	**(15,798)**	**109,404**
Net loss	—	—	—	—	(20,832)	(20,832)
Other comprehensive income	—	—	—	1	—	1
Recognition of share-based payments	—	—	1,212	—	—	1,212
Shares options exercised	0	14	—	—	—	14
Balance at December 31, 2015	**934**	**123,595**	**1,899**	**1**	**(36,630)**	**89,799**

The accompanying notes are an integral part of these financial statements.

PROQR THERAPEUTICS N.V.

Consolidated Statement of Cash Flows

	Year Ended December 31,		
	2015	2014	2013
	(€ in thousands)		
Cash flow from operating activities			
Net loss	(20,831)	(12,127)	(3,253)
Adjustments for:			
Depreciation	480	126	24
Share-based payment expenses	1,212	646	41
Financial income and expense	(6,171)	(4,334)	14
Changes in working capital	637	1,090	829
Corporate income tax paid	—	—	—
Interest received	441	142	13
Net cash used in operating activities	**(24,232)**	**(14,457)**	**(2,332)**
Cash flow from investing activities			
Purchases of intangible assets	(28)	(124)	—
Purchases of property, plant and equipment	(1,296)	(1,109)	(137)
Net cash used in investing activities	**(1,324)**	**(1,233)**	**(137)**
Cash flow from financing activities			
Net proceeds from issuance of shares	—	118,250	3,023
Proceeds from exercise of share options	14	—	—
Proceeds from borrowings	1,640	1,667	3,326
Redemption of financial lease	(34)	(34)	—
Net cash generated by financing activities	**1,620**	**119,883**	**6,349**
Net increase/(decrease) in cash and cash equivalents	**(23,936)**	**104,193**	**3,880**
Currency effect cash and cash equivalents	6,065	4,414	—
Cash and cash equivalents at the beginning of the year	112,736	4,129	249
Cash and cash equivalents at the end of the year	**94,865**	**112,736**	**4,129**

The accompanying notes form an integral part of these financial statements.

PROQR THERAPEUTICS N.V.

Notes to the Consolidated Financial Statements

1. General Information

ProQR Therapeutics N.V., or "ProQR" or the "Company", is a development stage company domiciled in the Netherlands that primarily focuses on the development and commercialization of novel therapeutic medicines.

Since September 18, 2014, the Company's ordinary shares are listed on the NASDAQ Global Market under ticker symbol PRQR.

The Company was incorporated in the Netherlands, on February 21, 2012 and was reorganized from a private company with limited liability to a public company with limited liability on September 23, 2014. The Company has its statutory seat in Leiden, the Netherlands. The address of its headquarters and registered office is Darwinweg 24, 2333 CR Leiden, the Netherlands.

Legal demerger of our Company was effectuated as per June 30, 2015. At December 31, 2015, ProQR Therapeutics N.V. is the ultimate parent company of the following entities:

- ProQR Therapeutics Holding B.V. (the Netherlands, 100%);
- ProQR Therapeutics I B.V. (the Netherlands, 100%);
- ProQR Therapeutics II B.V. (the Netherlands, 100%);
- ProQR Therapeutics III B.V. (the Netherlands, 100%);
- ProQR Therapeutics IV B.V. (the Netherlands, 100%);
- ProQR Therapeutics I Inc. (United States, 100%).

As used in these consolidated financial statements, unless the context indicates otherwise, all references to "ProQR", the "Company" or the "Group" refer to ProQR Therapeutics N.V. including its subsidiaries.

2. Basis of preparation

(a) Statement of compliance

These consolidated financial statements have been prepared in accordance with International Financial Reporting Standards, or IFRS, as issued by the IASB.

(b) Basis of measurement

The financial statements have been prepared on the historical cost basis except for financial instruments and share-based payment obligations which have been based on fair value. Historical cost is generally based on the fair value of the consideration given in exchange for assets.

(c) Functional and presentation currency

These consolidated financial statements are presented in euro, which is the Company's functional currency. All amounts have been rounded to the nearest thousand, unless otherwise indicated.

(d) Going Concern

The management board of ProQR has, upon preparing and finalizing the 2015 financial statements, assessed the Company's ability to fund its operations for a period of at least one year after the date of signing these financial statements.

The management board of the Company is confident about the continuity of the Company based on its existing funding, taking into account the Company's current cash position and the projected cash flows based on the activities under execution on the basis of ProQR's business plan and budget, which includes, amongst other activities, clinical studies using QR-010 in patients suffering from cystic fibrosis.

(e) Use of estimates and judgements

In preparing these consolidated financial statements, management has made judgements, estimates and assumptions that affect the application of accounting policies and the reported amounts of assets, liabilities, income and expenses. Actual results may differ from these estimates.

Estimates and underlying assumptions are reviewed on an ongoing basis. Revisions to accounting estimates are recognized in the period in which the estimate is revised if the revision affects only that period or in the period of the revision and future periods if the revision affects both current and future periods.

Information about assumptions and estimation uncertainties that may have a significant risk of resulting in a material adjustment is included below.

(i) Share-based payments

Share options granted to employees and consultants are measured at the fair value of the equity instruments granted. Fair value is determined through the use of an option-pricing model considering, among others, the following variables:

a) The exercise price of the option;

b) The expected life of the option;

c) The current value of the underlying shares;

d) The expected volatility of the share price;

e) The dividends expected on the shares; and

f) The risk-free interest rate for the life of the option.

For the Company's share option plans, management's judgment is that the Black-Scholes valuation method is the most appropriate for determining the fair value of the Company's share options.

Initially, the Company's ordinary shares were not publicly traded and consequently the Company needed to estimate the fair value of its share and the expected volatility of that value. The expected volatility of all options granted was therefore based on the average historical volatility of the Company's peers over a period that agrees with the expected option life. All assumptions and estimates are further discussed in Note 12(e) to the financial statements. The value of the underlying shares was determined on the basis of the prior sale of company stock method. As such, the Company has benchmarked the value per share to external transactions of Company shares and external financing rounds.

For options granted from the moment of listing, the Company uses the closing price of the ordinary shares on the previous business day as exercise price of the options granted.

The result of the share option valuations and the related compensation expense is dependent on the model and input parameters used. Even though Management considers the fair values reasonable and defensible based on the methodologies applied and the information available, others might derive a different fair value for the Company's share options.

(ii) Corporate income taxes

The Company recognizes deferred tax assets arising from unused tax losses or tax credits only to the extent that the Company has sufficient taxable temporary differences or there is convincing evidence that sufficient taxable profit will be available against which the unused tax losses or unused tax credits can be utilized. Management's judgment is that such convincing evidence is currently not sufficiently available and a deferred tax asset is therefore only recognized to the extent that the Company has sufficient taxable temporary differences.

(iii) Grant income

Grants (to be) received are reflected in the balance sheet as other receivables or deferred income. At each balance sheet date, for grants approved, the Company estimates the associated costs incurred, the level of service performed and the progress of the associated projects. Based on this analysis grant income is recognized.

(iv) Research and development expenditures

Research expenditures are currently not capitalized but are reflected in the income statement because the criteria for capitalization are not met. At each balance sheet date, the Company estimates the level of service performed by the vendors and the associated costs incurred for the services performed.

Although we do not expect the estimates to be materially different from amounts actually incurred, the understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in reporting amounts that are too high or too low in any particular period.

(f) Changes in accounting policies

The financial statements have been prepared on the basis of International Financial Reporting Standards ("IFRS"), as issued by the International Accounting Standards Board ("IASB"). New Standards and Interpretations, which became effective as of January 1, 2015, did not have a material impact on our financial statements.

3. Significant Accounting Policies

The Company has consistently applied the following accounting policies to all periods presented in these consolidated financial statements.

(a) Basis of consolidation

(i) Subsidiaries

Subsidiaries are entities controlled by the Group. The Group controls an entity when it is exposed to, or has rights to, variable returns from its involvement with the entity and has the ability to affect those returns through its power over the entity. The financial statements of subsidiaries are included in the consolidated financial statements from the date on which control commences until the date on which control ceases.

(ii) Loss of control

When the Group loses control over a subsidiary, it derecognises the assets and liabilities of the subsidiary, and any non-controlling interests and other components of equity. Any resulting gain or loss is recognised in profit or loss. Any interest retained in the former subsidiary is measured at fair value when control is lost.

(iii) Transactions eliminated on consolidation

Intra-group balances and transactions, and any unrealised income and expenses arising from intra-group transactions, are eliminated. Unrealised gains arising from transactions with equity-accounted investees are eliminated against the investment to the extent of the Group's interest in the investee. Unrealised losses are eliminated in the same way as unrealised gains, but only to the extent that there is no evidence of impairment.

(b) Classes of financial instruments

Financial instruments are both primary financial instruments, such as receivables and payables, and financial derivatives. For primary financial instruments, reference is made to the treatment per the corresponding balance sheet item.

Financial derivatives are valued at fair value. Upon first recognition, financial derivatives are recognized at fair value and then revalued as at balance sheet date.

(c) Foreign currencies

(i) Foreign currency transactions

Foreign currency transactions are translated into the functional currency using the exchange rates prevailing at the dates of the transactions.

Monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rate at the reporting date. Non-monetary assets and liabilities denominated in foreign currencies that are measured at fair value are translated into the functional currency at the exchange rate when the fair value was determined. Foreign currency differences are generally recognized in profit or loss. Non-monetary items that are measured based on historical cost in a foreign currency are not translated.

(ii) Foreign operations

The assets and liabilities of foreign operations are translated into euro at exchange rates at the reporting date. The income and expenses of foreign operations are translated into euros at the exchange rates at the dates of the transactions. Foreign currency differences are recognized in OCI and accumulated in the translation reserve, except to the extent that the translation difference is allocated to NCI.

(d) Recognition of other income

Other income includes amounts earned from third parties and are recognized when earned in accordance with the substance and under the terms of the related agreements and when it is probable that the economic benefits associated with the transaction will flow to the entity and the amount of the income can be measured reliably. The grants are recognized in other income in the same period in which the related R&D costs are recognized.

(e) Government grants—WBSO

The WBSO (“afdrachtvermindering speur- en ontwikkelingswerk”) is a Dutch fiscal facility that provides subsidies to companies, knowledge centers and self-employed people who perform research and development activities (as defined in the WBSO Act). Under this Act, a contribution is paid towards the labor costs of employees directly involved in research and development. The contribution is in the form of a reduction of payroll taxes and social security contributions. Subsidies relating to labor costs are deferred and recognized in the income statement as negative labor costs over the period necessary to match them with the labor costs that they are intended to compensate.

(f) Employee benefits

(i) Short-term employee benefits

Short-term employee benefits are expensed as the related service is provided. A liability is recognized for the amount expected to be paid if the Group has a present legal or constructive obligation to pay this amount as a result of past service provided by the employee and the obligation can be estimated reliably.

(ii) Share-based payment transactions

The grant-date fair value of equity-settled share-based payment awards granted to employees is generally recognized as an expense, with a corresponding increase in equity, over the vesting period of the awards. The amount recognized as an expense is adjusted to reflect the number of awards for which the related service and non-market performance conditions are expected to be met, such that the amount ultimately recognized is based on the number of awards that meet the related service and non-market performance conditions at the vesting date. For share-based payment awards with non-vesting conditions, the grant-date fair value of the share-based payment is measured to reflect such conditions and there is no true-up for differences between expected and actual outcomes.

(iii) Pension obligations

The Company operates defined contribution pension plans for all employees funded through payments to insurance companies. The Company has no legal or constructive obligation to pay further contributions once the contributions have been paid. The contributions are recognized as employee benefit expense when they are due. Prepaid contributions are recognized as an asset to the extent that a cash refund or a reduction in the future payments is available.

(g) Taxation

Income tax expense represents the sum of the tax currently payable and deferred tax. It is recognized in profit or loss except to the extent that it relates to a business combination, or items recognized directly in equity or in OCI.

(i) Current tax

The tax currently payable is based on taxable profit for the year. Taxable profit differs from profit as reported in the income statement because of items of income or expense that are taxable or deductible in other years and items that are never taxable or deductible. The Company's liability for current tax is calculated using tax rates that have been enacted or substantively enacted by the end of the reporting period.

(ii) Deferred tax

Deferred tax is recognized on differences between the carrying amounts of assets and liabilities in the financial statements and the corresponding tax bases used in the computation of taxable profit.

The carrying amount of deferred tax assets is reviewed at the end of each reporting period and reduced to the extent that it is no longer probable that sufficient taxable profits will be available to allow all or part of the asset to be recovered. Since the Company does not expect to be profitable in the foreseeable future, its deferred tax assets are valued at nil.

Deferred tax assets and liabilities are measured at the tax rates that are expected to apply in the period in which the liability is settled or the asset realized, based on tax rates (and tax laws) that have been enacted or substantively enacted by the end of the reporting period. The measurement of deferred tax liabilities and assets reflects the tax consequences that would follow from the manner in which the Company expects, at the end of the reporting period, to recover or settle the carrying amount of its assets and liabilities.

(h) Intangible assets

(i) Licenses

Acquired patents have a finite useful life and are carried at cost less accumulated amortization and impairment losses. Amortization is calculated using the straight-line method to allocate the cost of patents over their estimated useful lives (generally 10 years unless a patent expires prior to that date). Amortization begins when an asset is available for its intended use.

(ii) Research and development

Research expenditures are recognized as expenses as incurred. Costs incurred on development projects are recognized as intangible assets of the date that it can be established that it is probable that future economic benefits that are attributable to the asset will flow to the Company considering its commercial and technological feasibility, generally when filed for regulatory approval for commercial production, and when costs can be measured reliably. Given the current stage of the development of the Company's products no development expenditures have yet been capitalized.

Registration costs for patents are part of the expenditures for the research and development project. Therefore, registration costs for patents are expensed as incurred as long as the research and development project concerned does not yet meet the criteria for capitalization.

(iii) Other intangible assets

Other intangible assets, including software, that are acquired by the Company and have finite useful lives are measured at cost less accumulated amortization and accumulated impairment losses.

(iv) Amortization

Amortization is calculated to write off the cost of intangible assets less their estimated residual values using the straight-line method over their estimated useful lives, and is recognized in profit or loss.

The estimated useful lives for current and comparative periods are as follows:

- Software : 3 years.

Amortization methods, useful lives and residual values are reviewed at each reporting date and adjusted if appropriate.

(i) Property, plant and equipment

(i) Recognition and measurement

Items of property, plant and equipment are measured at cost less accumulated depreciation and any accumulated impairment losses. If significant parts of an item of property, plant and equipment have different useful lives, then they are accounted for as separate items (major components) of property, plant and equipment. Any gain or loss on disposal of an item of property, plant and equipment is recognized in profit or loss.

(ii) Depreciation

Depreciation is calculated to write off the cost of items of property, plant and equipment less their estimated residual values using the straight-line method over their estimated useful lives, and is recognized in profit or loss. Leased assets are depreciated over the shorter of the lease term and their useful lives unless it is reasonably certain that the Company will obtain ownership by the end of the lease term.

The estimated useful lives of property, plant and equipment for current and comparative periods are as follows:

- Leasehold improvements : 5 - 10 years.
- Laboratory equipment : 5 years.
- Other : 3 - 5 years.

Depreciation methods, useful lives and residual values are reviewed at each reporting date and adjusted if appropriate.

(j) Impairment of tangible and intangible assets

At the end of each reporting period, the Company reviews the carrying amounts of its tangible and intangible assets to determine whether there is any indication that those assets have suffered an impairment loss. If any such indication exists, the recoverable amount of the asset is estimated in order to determine the extent of the impairment loss (if any). Where it is not possible to estimate the recoverable amount of an individual asset, the Company estimates the recoverable amount of the cash-generating unit to which the asset belongs. Where a reasonable and consistent basis of allocation can be identified, corporate assets are also allocated to individual cash-generating units, or otherwise they are allocated to the smallest group of cash-generating units for which a reasonable and consistent allocation basis can be identified.

Intangible assets with indefinite useful lives and intangible assets not yet available for use are tested for impairment at least annually, and whenever there is an indication that the asset may be impaired.

The recoverable amount is the higher of fair value less costs to sell and value in use. In assessing value in use, the estimated future cash flows are discounted to their present value using a pre-tax discount rate that reflects current market assessments of the time value of money and the risks specific to the asset for which the estimates of future cash flows have not been adjusted.

If the recoverable amount of an asset (or cash-generating unit) is estimated to be less than its carrying amount, the carrying amount of the asset (or cash-generating unit) is reduced to its recoverable amount. An impairment loss is recognized immediately in profit or loss, unless the relevant asset is carried at a revalued amount, in which case the impairment loss is treated as a revaluation decrease.

Where an impairment loss subsequently reverses, the carrying amount of the asset (or cash-generating unit) is increased to the revised estimate of its recoverable amount, but so that the increased carrying amount does not exceed the carrying amount that would have been determined had no impairment loss been recognized for the asset (or cash-generating unit) in prior years. A reversal of an impairment loss is recognized immediately in profit or loss, unless the relevant asset is carried at a revalued amount, in which case the reversal of the impairment loss is treated as a revaluation increase.

(k) Financial assets

All financial assets are recognized and derecognized on the trade date where the purchase or sale of a financial asset is under a contract whose terms require delivery of the financial asset within the timeframe established by the market concerned, and are initially measured at fair value, plus transaction costs, except for those financial assets classified as at fair value through profit or loss, which are initially measured at fair value.

Loans and receivables

Trade receivables, loans and other receivables that have fixed or determinable payments that are not quoted in an active market are classified as “loans and receivables”. Loans and receivables are measured at amortized cost using the effective interest method, less any impairment.

An allowance for doubtful accounts is established when there is objective evidence that the Company will not be able to collect all amounts due according to the original terms of receivables. Significant financial difficulties of the debtor, probability that the debtor will enter into bankruptcy or financial reorganization, and default or delinquency in payments are considered indicators that the trade receivable is impaired. Loans and receivables are included in ‘current assets’, except for maturities greater than 12 months after the balance sheet date, which are classified as ‘non-current assets’.

For all financial assets, the fair value approximates its carrying value.

(l) Cash and cash equivalents

Cash and cash equivalents include cash on hand and all highly liquid investments with original maturities of three months or less that are convertible to a known amount of cash and bear an insignificant risk of change in value.

(m) Financial liabilities and equity instruments

Debt and equity instruments are classified as either financial liabilities or as equity in accordance with the substance of the contractual arrangement.

Equity instruments

An equity instrument is any contract that evidences a residual interest in the assets of an entity after deducting all of its liabilities. Equity instruments issued by the Company are recognized at the proceeds received, net of direct issue costs.

Other financial liabilities

Other financial liabilities, including borrowings, are initially measured at fair value, net of transaction costs incurred, and are subsequently measured at amortized cost using the effective interest method, with interest expense recognized on an effective yield basis.

The effective interest method is a method of calculating the amortized cost of a financial liability and of allocating interest expense over the relevant period. The effective interest rate is the rate that exactly discounts estimated future cash payments through the expected life of the financial liability, or, where appropriate, a shorter period.

Borrowings and other financial liabilities are classified as 'non-current liabilities,' other than liabilities with maturities up to one year, which are classified as "current liabilities".

The Company derecognizes financial liabilities when the liability is discharged, cancelled or expired. For all financial liabilities, the fair value approximates its carrying amount.

(n) Leases

(i) Determining whether an arrangement contains a lease

At inception of an arrangement, the Company determines whether such an arrangement is or contains a lease.

At inception or on reassessment of an arrangement that contains a lease, the Company separates payments and other consideration required by such an arrangement into those for the lease and those for other elements on the basis of their relative fair values. If the Company concludes for a finance lease that it is impracticable to separate the payments reliably, then an asset and a liability are recognized at an amount equal to the fair value of the underlying asset. Subsequently, the liability is reduced as payments are made and an imputed finance cost on the liability is recognized using the Company's incremental borrowing rate.

(ii) Leased assets

Assets held by the Company under leases that transfer to the Company substantially all of the risks and rewards of ownership are classified as finance leases. The leased assets are measured initially at an amount equal to the lower of their fair value and the present value of the minimum lease payments. Subsequent to initial recognition, the assets are accounted for in accordance with the accounting policy applicable to that asset.

Assets held under other leases are classified as operating leases and are not recognized in the Company's statement of financial position.

(iii) Lease payments

Payments made under operating leases are recognized in profit or loss on a straight-line basis over the term of the lease. Lease incentives received are recognized as an integral part of the total lease expense, over the term of the lease.

Minimum lease payments made under finance leases are apportioned between the finance expense and the reduction of the outstanding liability. The finance expense is allocated to each period during the lease term so as to produce a constant periodic rate of interest on the remaining balance of the liability.

4. New standards and interpretations not yet adopted

A number of new standards, amendments to standards and interpretations are effective for annual periods beginning after 1 January 2016, and have not been applied in preparing these consolidated financial statements. Those which may be relevant to the Group are set out below. The Group does not plan to adopt these standards early.

IFRS 9 Financial Instruments

IFRS 9, published in July 2014, replaces the existing guidance in IAS 39 Financial Instruments: Recognition and Measurement. IFRS 9 includes revised guidance on the classification and measurement of financial instruments, including a new expected credit loss model for calculating impairment on financial assets, and the new general hedge accounting requirements. It also carries forward the guidance on recognition and derecognition of financial instruments from IAS 39.

IFRS 9 is effective for annual reporting periods beginning on or after 1 January 2018, with early adoption permitted.

IFRS 15 Revenue from Contracts with Customers

IFRS 15 establishes a comprehensive framework for determining whether, how much and when revenue is recognised. It replaces existing revenue recognition guidance, including IAS 18 Revenue, IAS 11 Construction Contracts and IFRIC 13 Customer Loyalty Programmes.

IFRS 15 is effective for annual reporting periods beginning on or after 1 January 2017, with early adoption permitted.

IFRS 16 Leases

IFRS 16 specifies how a company will recognise, measure, present and disclose leases. The standard provides a single lessee accounting model, requiring lessees to recognise assets and liabilities for all leases unless the lease term is 12 months or less or the underlying asset has a low value. Lessors continue to classify leases as operating or finance, with IFRS 16's approach to lessor accounting substantially unchanged from its predecessor, IAS 17.

IFRS 16 is effective for annual reporting periods beginning on or after 1 January 2019, with early adoption permitted.

The adoption of these Standards and Interpretations are not expected to have a material effect on the financial statements.

5. Financial Risk Management

5.1 Financial risk factors

The Company's activities expose it to a variety of financial risks: market risk (including currency risk, interest rate risk and price risk), credit risk and liquidity risk. The Company's overall financial risk management seeks to minimize potential adverse effects resulting from unpredictability of financial markets on the Company's financial performance.

Risk management is carried out by the finance department. The finance department identifies and evaluates financial risks and proposes mitigating actions if deemed appropriate.

(a) Market risk

Market risk is the risk that changes in market prices – such as foreign exchange rates, interest rates and equity prices – will affect the Company's income or the value of its holdings of financial instruments. The objective of market risk management is to manage and control market risk exposures within acceptable parameters, while optimizing the return.

Foreign exchange risk

Foreign exchange risk arises from future commercial transactions and recognized assets and liabilities in foreign currencies, primarily with respect to the U.S. Dollar. The Company has an exposure associated with the time delay between entering into a contract, budget or forecast and the realization thereof. The Company operates a foreign exchange policy to manage the foreign exchange risk against the functional currency based on the Company's cash balances and the projected future spend per major currency.

At December 31, 2015 there was a net liability in U.S. Dollars of € 1.1 million (2014: € 0.7 million). Foreign currency denominated receivables and trade payables are short term in nature (generally 30 to 45 days). As a result foreign exchange rate movements on receivables and trade payables, during the years presented had an immaterial effect on the financial statements.

At year-end, a substantial amount of our cash balances are denominated in U.S. Dollars. This amount reflects our current expectation of future expenditure in U.S. dollars.

A reasonably possible strengthening (weakening) of the U.S. Dollar by 10% against all other currencies at December 31 would have affected the measurement of our cash balances denominated in a U.S. Dollar and affected equity and profit or loss by € 5.2 million (2014: € 4.3 million). The analysis assumes that all other variables, in particular interest rates, remain constant.

Price risk

The market prices for the production of preclinical and clinical materials and services as well as external contracted research may vary over time. Currently, the commercial prices of any of the Company's product candidates is uncertain. When the development products near the regulatory approval date or potential regulatory approval date, the uncertainty of the potential sales price decreases. The Company is not exposed to commodity price risk.

Furthermore the Company does not hold investments classified as available-for-sale or at fair value through profit or loss, therefore are not exposed to equity securities price risk.

Cash flow and fair value Interest rate risk

The Company's exposure to interest rate risks is limited due to the use of loans with fixed rates. The Company has one loan and a financial lease with a fixed interest, totaling € 4,839,000 at December 31, 2015 (2014: € 2,863,000). Details on the interest rates and maturities of these loans are provided in Note 13.

(b) Credit risk

Credit risk represents the risk of financial loss caused by default of the counterparty. The Company has no large receivables balances with external parties. The Company's principal financial assets are cash and cash equivalents which are placed at ABN Amro and Rabobank. Our cash management policy is focused on preserving capital, providing liquidity for operations and optimizing yield while accepting limited risk (Short-term credit ratings must be rated A-1/P-1/F1 at a minimum by at least one of the Nationally Recognized Statistical Rating Organizations (NRSROs) specifically Moody's, Standard & Poor's or Fitch. Long-term credit rating must be rated A- or A3 at a minimum by at least one NRSRO).

As of December 31, 2015 and December 31, 2014, substantially all of our cash and cash equivalents were placed at two large institutions, Rabobank and ABN Amro. Both institutions are highly rated (ratings of Aa2 and A2 respectively) with sufficient capital adequacy and liquidity metrics.

There are no financial assets past due date or impaired. No credit limits were exceeded during the reporting period.

(c) Liquidity risk

Liquidity risk represents the risk that an entity will encounter difficulty in meeting obligations associated with its financial liabilities. Prudent liquidity risk management implies ensuring sufficient availability of cash resources for funding of operations and planning to raise cash if and when needed, either through issue of shares or through credit facilities. Management monitors rolling forecasts of the Company's liquidity reserve on the basis of expected cash flow.

The table below analyzes ProQR's undiscounted liabilities into relevant maturity groupings based on the remaining period at year-end until the contractual maturity date:

	Less than 1 year	Between 1 and 2 years	Between 2 and 5 years	Over 5 years
		(€ in thousands)		
At December 31, 2015				
Borrowings	—	1,691	4,712	—
Finance lease liabilities	15	—	—	—
Trade payables and other payables	5,471	—	—	—
Total	**5,486**	**1,691**	**4,712**	**—**
At December 31, 2014				
Borrowings	—	—	3,884	—
Finance lease liabilities	34	15	—	—
Trade payables and other payables	2,980	—	—	—
Total	**3,014**	**15**	**3,884**	**—**

5.2 Capital risk management

The Company's objectives when managing capital are to safeguard the Company's ability to continue as a going concern in order to provide returns for shareholders, benefits for other stakeholders and to maintain an optimal capital structure to reduce the cost of capital.

In order to maintain or adjust the capital structure, the Company may adjust the amount of dividends paid to shareholders (although at this time the Company does not have retained earnings and is therefore currently unable to pay dividends), return capital to shareholders, issue new shares or sell assets to reduce debt.

The total amount of equity as recorded on the balance sheet is managed as capital by the Company.

5.3 Fair value measurement

For financial instruments that are measured on the balance sheet at fair value, IFRS 13 requires disclosure of fair value measurements by level of the following fair value measurement hierarchy:

- Quoted prices (unadjusted) in active markets for identical assets or liabilities (level 1);
- Inputs other than quoted prices included within level 1 that are observable for the asset or liability, either directly (that is, as prices) or indirectly (that is, derived from prices) (level 2); and
- Inputs for the asset or liability that are not based on observable market data (that is, unobservable inputs) (level 3).

The Company has no assets and liabilities that are measured at fair value at December 31, 2015 and 2014.

The carrying amount of all financial assets and financial liabilities is a reasonable approximation of the fair value and therefore information about the fair values of each class has not been disclosed.

6. Segment Information

The Company operates in one reportable segment, which comprise of the discovery and development of innovative, RNA based therapeutics. The management board is identified as the chief operating decision maker. The management board reviews the operating results regularly to make decisions about resources and to assess overall performance.

The Company has not generated any sales revenues since inception.

All non-current assets of the Company are located in the Netherlands. The amounts provided to the management board with respect to total assets and liabilities are measured in a manner consistent with that of the financial statements.

7. Intangible Assets

	Licenses (€ in thousands)	Software (€ in thousands)	Total (€ in thousands)
Balance at January 1, 2014			
Cost	39	—	39
Accumulated amortization	—	—	—
Carrying amount	39	—	39
Additions	—	124	124
Movement for the period	**—**	**124**	**124**
Balance at December 31, 2014			
Cost	39	124	163
Accumulated amortization	—	—	—
Carrying amount	**39**	**124**	**163**
Additions	—	28	28
Amortization	—	(50)	(50)
Movement for the period	**—**	**(22)**	**(22)**
Balance at December 31, 2015			
Cost	39	152	191
Accumulated amortization	—	(50)	(50)
Carrying amount	**39**	**102**	**141**

In 2012, the Company acquired an exclusive license from the Massachusetts General Hospital. The initial payment in respect of the license, in the amount of € 39,000, will be amortized over the commercial life of products based on the license during the patent-life.

The amortization charge is included in the research and development costs for € nil (2014: nil) and in the general and administrative costs for an amount of € 50,000 (2014: € nil).

8. Property, Plant and Equipment ('PP&E')

	Leasehold improvements (€ in thousands)	Laboratory equipment (€ in thousands)	Other (€ in thousands)	Total (€ in thousands)
Balance at January 1, 2014				
Cost	5	190	33	228
Accumulated depreciation	(1)	(19)	(4)	(24)
Carrying amount	**4**	171	**29**	**204**
Additions	321	579	209	1,109
Depreciation	(16)	(85)	(25)	(126)
Disposals	—	—	—	—
Movement for the period	**305**	**494**	**184**	**983**
Balance at December 31, 2014				
Cost	326	769	242	1,337
Accumulated depreciation	(17)	(104)	(29)	(150)
Carrying amount	**309**	**665**	**213**	**1,187**
Additions	659	367	415	1,441
Depreciation	(77)	(201)	(145)	(423)
Disposals	—	—	(6)	(6)
Movement for the period	**582**	**166**	**264**	**1,012**
Balance at December 31, 2015				
Cost	985	1,136	651	2,772
Accumulated depreciation	(94)	(305)	(174)	(573)
Carrying amount	**891**	**831**	**477**	**2,199**

The depreciation charge is included in the research and development costs for an amount of € 361,000 (2014: € 119,000) and in the general and administrative costs for an amount of € 62,000 (2014: € 7,000).

9. Social Security and Other Taxes

	December 31, 2015	December 31, 2014
	(€ in thousands)	
Value added tax	953	426
Wage tax	3	—
	956	426

All receivables are considered short-term and due within one year.

10. Prepayments and Other Receivables

	December 31, 2015	December 31, 2014
	(€ in thousands)	
Prepayments	1,401	408
Other receivables	547	327
	1,948	735

All receivables are considered short-term and due within one year.

11. Cash and Cash Equivalents

	December 31, 2015	December 31, 2014
	(€ in thousands)	
Cash at banks	94,865	83,084
Bank deposits	—	29,652
	94,865	112,736

The cash at banks is at full disposal of the Company. Bank deposits are convertible into cash upon request of the Company.

12. Shareholders' Equity

(a) Share capital

	Number of shares 2015		Number of shares 2014		Number of shares 2013	
	Ordinary	Preferred	Ordinary	Preferred	Ordinary	Preferred
In issue at January 1	23,338,154	—	6,108,152	—	3,413,292	—
Issued for cash	—	—	9,490,336	8,265,179	3,592,773	—
Conversion of preferred shares	—	—	8,265,179	(8,265,179)	—	—
Exercise of share options	7,811	—	—	—	—	—
Treasury shares issued	—	—	(525,513)	—	(897,913)	—
In issue at December 31 – fully paid	**23,345,965**	**—**	**23,338,154**	**—**	**6,108,152**	**—**

The authorized share capital of the Company amounting to € 934,000 consists of 23,345,965 ordinary shares with a par value of € 0.04 per share. All issued shares have been fully paid in cash.

On April 17, 2014, the Company authorized and issued a total of 8,265,179 preferred shares, of which 619,682 preferred shares were issued as a result of the conversion of the outstanding convertible loan. In addition, on the same date, 444,884 ordinary shares were issued to the Foundation "Stichting ProQR Therapeutics Participation". The gross proceeds from this share issuance (excluding the shares issued to the Foundation) amounted to € 41,998,000 while the transaction costs amounted to € 1,632,000, resulting in net proceeds of € 40,366,000. The net proceeds received in cash amounted to € 37,806,000, while non-cash proceeds as a result of the conversion of the convertible loan amounted to € 2,560,000.

On September 15, 2014, the general meeting of shareholders of the Company resolved to approve and effect a capital reorganization, including a share split and bonus share issuance. The combined effect of the share split and bonus share issuance was a 101.804232-for-1 share split of the outstanding ordinary and preferred shares held by the Company's shareholders. This share split became effective on September 15, 2014.

All share, per-share and related information presented in the comparative figures of these financial statements and accompanying footnotes have been retroactively adjusted, where applicable, to reflect the impact of the share split.

On September 18, 2014, the Company was listed at the NASDAQ Global Market under ticker symbol PRQR. In connection with this listing, the Company issued a total of 8,625,000 ordinary shares at the initial public offering price of $ 13.00, resulting in gross proceeds of $ 112,125,000 (€ 87,202,000). The number of shares issued includes the exercise of the overallotment option granted to the underwriters. The net proceeds raised in the offering amounted to € 80,376,000, net of € 8,589,000 of underwriting discounts and offering expenses, of which € 6,826,000 was processed through share premium and € 1,763,000 was included in the statement of comprehensive income as general and administrative costs.

All of the issued preferred shares were converted into the Company's ordinary shares. The conversion rate for the preferred shares was one-to-one, adjusted for the stock splits.

(b) Treasury shares

All treasury shares presented in the statement of changes in equity relate to ordinary shares that have legally been issued, but that are within control of the Company. At 31 December 2015, the Company held 1,174,849 of the Company's shares (2014: 1,182,660).

(c) Equity settled employee benefit reserve

The costs of share options for employees, members of the supervisory board and members of the management board are recognized in the income statement, together with a corresponding increase in equity during the vesting period, taking into account (deferral of) corporate income taxes. The accumulated expense of share options recognized in the income statement is shown separately in the equity category 'equity settled employee benefit reserve' in the 'statement of changes in equity'.

(d) Translation reserve

The translation reserve comprises all foreign currency differences arising from the translation of the financial statements of foreign operations.

(e) Share options

The Company operates an equity-settled share-based compensation plan which was introduced in 2013. Options may be granted to employees, members of the supervisory board, members of the management board and consultants. The compensation expenses included in operating costs for this plan were € 1,212,000 in 2015 (2014: € 646,000, 2013: € 41,000), of which € 801,000 (2014: € 404,000, 2013: € 19,000) was recorded in general and administrative costs and € 411,000 (2014: € 242,000, 2013: € 22,000) was recorded in research and development costs.

Options granted under this stock option plan are exercisable once vested. Any vesting schedule may be attached to the granted options, however the typical vesting period is four years (25% after every year). The options expire ten years after date of grant. Options granted under the stock option plan are granted at exercise prices which equal the fair value of the ordinary shares of the Company at the date of the grant.

The Company accounts for its employee stock options under the fair value method. The fair value of the options is estimated at the date of grant using the Black-Scholes option-pricing model, with on average the following assumptions:

	Options granted in 2015	Options granted in 2014	Options granted in 2013
Risk-free interest rate	1.497%	0.616%	0.942%
Expected dividend yield	0%	0%	0%
Expected volatility	86.8%	88.6%	93.8%
Expected life in years	5 years	5 years	5 years

The resulting weighted average grant date fair value of the options amounted to € 10.35 in 2015 (2014: € 2.58, 2013: € 0.79). The stock options granted have a 10 year life following the grant date and are assumed to be exercised five years from date of grant for all awards.

Movements in the number of options outstanding and their related weighted average exercise prices are as follows:

	2015		2014		2013	
	Number of options	Average exercise price	Number of options	Average exercise price	Number of options	Average exercise price
Balance at January 1	998,765	€ 2.78	379,323	€ 1.11	—	—
Granted	125,798	€ 15.27	691,722	€ 3.52	380,341	€ 1.11
Forfeited	(7,817)	€ 4.64	(11,095)	€ 1.20	(1,018)	€ 1.11
Exercised	(7,811)	€ 1.78	(61,185)	€ 1.11	—	—
Lapsed	—	—	—	—	—	—
Balance at December 31	**1,108,935**	**€ 4.19**	**998,765**	**€ 2.78**	**379,323**	**€ 1.11**
Exercisable at December 31	339,352		94,729		—	

The options outstanding at December 31, 2015 had an exercise price in the range of € 1.11 to € 20.34 (2014: € 1.11 to € 12.15, 2013: € 1.11) and a weighted-average contractual life of 8.3 years (2014: 9.2 years, 2013: 9.7 years).

The weighted-average share price at the date of exercise for share options exercised in 2015 was € 19.30 (2014: € 3.04, 2013: no options exercised).

Please refer to Note 23 for the options granted to key management personnel.

13. Non-current liabilities

(a) Borrowings

	December 31, 2015	December 31, 2014
	(€ in thousands)	
Innovation credit	4,228	2,588
Accrued interest on innovation credit	596	226
	4,824	2,814

Innovation credit ("Innovatiekrediet")

On June 1, 2012, ProQR was awarded an Innovation credit by the Dutch government, through its agency RVO (previously: "AgentschapNL") of the Ministry of Economic Affairs, for the Company's cystic fibrosis program. Amounts were drawn under this facility in the course of 2013, 2014 and 2015. The credit covers 35% of the costs incurred in respect of the program up to an initial maximum of € 5.0 million through December 31, 2016.

The credit is interest-bearing at a rate of 10% per annum. The credit, including accrued interest, is repayable in three instalments on August 31, 2017, August 31, 2018 and August 31, 2019, depending on the technical success of the program.

The assets which are co-financed with the granted innovation credit are subject to a right of pledge for the benefit of RVO.

(b) Finance lease liabilities

	2015	2014
	(€ in thousands)	
Balance at January 1	49	83
Initial recognition new finance leases	—	—
Interest expense accrued	—	—
Payment of finance lease liabilities	(34)	(34)
Balance at December 31	**15**	**49**
Current portion at December 31	(15)	(34)
	—	**15**

Certain of the Company's property, plant and equipment items are subject to finance leases. These leases relate to laboratory equipment. The net carrying amount of leased assets amounts to € 48,000 (2014: € 64,000).

Future minimum lease payments under finance leases as at December 31, 2015 are as follows:

	2015		2014	
	Minimum payments	Present value of payments	Minimum payments	Present value of payments
	(€ in thousands)			
Less than 1 year	15	15	34	34
Between 1 and 5 years	—	—	15	15
More than 5 years	—	—	—	—

The interest used for the present value of payments is 2%.

14. Current Liabilities

	December 31, 2015	December 31, 2014
	(€ in thousands)	
Current portion finance lease liabilities	15	34
Trade payables	885	1,247
Social securities and other taxes	235	341
Pension premiums	16	127
Deferred income	144	—
Accrued expenses and other liabilities	4,191	1,265
	5,486	**3,014**

At December 31, 2015, current liabilities includes deferred income resulting from receipt of the first installment of the € 6 million grant from the European Commission (EC) under the Horizon 2020 program to finance the clinical development of QR-010.

The majority of the Company's current liabilities are denominated in euros.

15. Other income

	2015	2014	2013
	(€ in thousands)		
Grant income	3,188	313	116
Rental income from property subleases	47	—	—
	3,235	**313**	**116**

In August 2014, the Company entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide the Company with up to $ 3 million to support the clinical development of QR-010. The grant is recognized in other income in the same period in which the related R&D costs are recognized.

In 2015, the European Commission (EC) through its Horizon 2020 program awarded ProQR and its academic partners a grant of € 6 million (ProQR: € 4.4 million) to support the clinical development of QR-010 in the period up till December 31, 2017. Horizon 2020 is one of the largest research and innovation programs in the European Union with nearly € 80 billion in available funding for qualified projects from 2014 to 2020.

Both grants are recognized in other income in the same period in which the related R&D costs are recognized.

16. Research and Development Costs

Research and development costs amounted to € 23,401,000 in 2015 (2014: € 10,267,000, 2013: € 2,569,000) and comprise allocated employee costs, the costs of materials and laboratory consumables, the costs of external studies including, amongst others, clinical studies and toxicology studies and external research, license- and IP-costs and allocated other costs.

17. Employee Benefits

	2015	2014	2013
	(€ in thousands)		
Wages and salaries	7,128	3,845	677
Social security costs	596	320	112
Pension costs — defined contribution plans	478	217	49
Equity-settled share based payments	1,212	646	41
	9,414	**5,028**	**879**
Average number of employees for the period	86.1	37.8	13.4

Employees per activity at December 31 (converted to FTE):

	December 31, 2015	December 31, 2014	December 31, 2013
Research and Development	72.4	40.1	12.0
General and Administrative	27.1	18.7	5.2
Total number of employees at December 31 (converted to FTE)	**99.5**	**58.8**	**17.2**

Of all employees 94.5 FTE are employed in the Netherlands (2014: 54.8 FTE).

Included in the wages and salaries for 2015 is a credit of € 372,000 (2014: € 301,000, 2013: € 150,000) with respect to WBSO subsidies.

18. Financial Income and Expense

	2015	2014	2013
	(€ in thousands)		
Interest income:			
Current accounts and deposits	501	183	24
Interest costs:			
Interest on loans and borrowings	(395)	(265)	(38)
Foreign exchange result:			
Net foreign exchange benefit/(loss)	6,065	4,416	—
	6,171	**4,334**	**(14)**

19. Income Taxes

The calculation of the tax charge is as follows:

	2015	2014	2013
	(€ in thousands)		
Income tax based on domestic rate (25%)	5,208	3,032	813
Tax effect of:			
Non-deductible expenses	(309)	(207)	(13)
Tax incentives	136	2,065	891
Current year losses for which no deferred tax asset was recognized	(5,035)	(4,890)	(1,691)
Income tax charge	—	—	—
Effective tax rate	0%	0%	0%

Due to the operating losses incurred since inception the Company has no tax provisions as of the balance sheet date. Furthermore, no significant temporary differences exist between accounting and tax results.

Realization of deferred tax assets is dependent on future earnings, if any, the timing and amount of which are uncertain. Accordingly, the Company has not yet recognized any deferred tax asset related to operating losses. As per December 31, 2015, the Company has a total amount of € 46.9 million (2014: € 26.8 million, 2013: € 7.2 million) tax loss carry-forwards available for offset against future taxable profits. According to current tax regulations the first amount of the tax loss carry-forwards will expire in 2021.

20. Earnings Per Share

(a) Basic and diluted earnings per share

Basic earnings per share are calculated by dividing the result attributable to equity holders of the Company by the weighted average number of shares outstanding during the year.

	2015	2014	2013
Result attributable to equity holders of the Company (€ in thousands)	(20,832)	(12,127)	(3,253)
Weighted average number of shares	23,343,262	11,082,801	5,517,688
Basic (and diluted) earnings per share (€ per share)	**€ (0.89)**	**€ (1.09)**	**€ (0.59)**

(b) Diluted earnings per share

For the periods included in these financial statements, the share options are not included in the diluted earnings per share calculation as the Company was loss-making in all periods. Due to the anti-dilutive nature of the outstanding options, basic and diluted earnings per share are equal.

(c) Dividends per share

The Company did not declare dividends for any of the years presented in these financial statements.

21. Operational Leases

Since 2012, the Company is domiciled in Leiden. It currently has concluded rental agreements for laboratory space and offices at two locations and one office in the US.

The lease expenditure charged to the income statement in 2015 amounts to € 703,000 (2014: € 258,000, 2013: € 113,000). The future aggregate minimum lease payments under non-cancellable operating leases are as follows:

	December 31, 2015	December 31, 2014	December 31, 2013
		(€ in thousands)	
Less than 1 year	1,938	509	194
Between 1 and 5 years	7,212	277	—
More than 5 years	—	—	—
Total	**9,150**	**786**	**194**

The Company leases out a part of its offices in the US. In 2015, total sublease income amounted to € 47,000 (2014: nil; 2013: nil). At 31 December, the future minimum lease payments under non-cancellable leases are receivable as follows:

	December 31, 2015	December 31, 2014	December 31, 2013
		(€ in thousands)	
Less than 1 year	185	—	—
Between 1 and 5 years	—	—	—
More than 5 years	—	—	—
Total	**185**	**—**	**—**

22. Commitments and Contingencies

(a) Claims

There are no claims known to management related to the activities of the Company.

(b) Patent license agreement

The Company and the General Hospital Corporation (MGH) have entered into a Patent License Agreement pursuant to which the Company may have certain royalty obligations. The Company is also obligated to pay MGH up to $ 700,000 in milestone payments upon the achievement of certain development and regulatory milestones and, beginning after its first commercial sale of a product covered by the licensed patent rights, a $ 10,000 annual license fee which is creditable against royalties due to MGH in the same calendar year. In addition, the Company is obligated to pay MGH 2% of any net sales by the Company, its affiliates or sublicensees on licensed products made or sold in the United States, as well as a low double-digit percentage of any payments the Company may receive from any sublicensee anywhere in the world.

The Company and the Radboud University Medical Center have entered into a Patent License Agreement under which the Company is granted a world-wide exclusive license pursuant to which the Company may have certain royalty obligations in relation to its product QR-110 for Leber's congenital amaurosis. Pursuant to the terms the Company has made an upfront payment and has to make sales-based royalty payments after market authorization. The Company has the option to make a one-time payment in case the company terminates the agreement before or after regulatory approval of the product. The Company may terminate the agreement for any reason.

The Company and the Radboud University Medical Center have entered into a Patent License Agreement under which the Company is granted a world-wide exclusive license under which the Company may have certain royalty obligations in relation to Type II Usher Syndrome. Pursuant to the terms the Company has made an upfront payment and has to make sales-based royalty payments after market authorization. The Company has the option to make a one-time payment in case the Company terminates the agreement before or after regulatory approval of the product. The Company may terminate the agreement for any reason.

The Company and the Leiden University Medical Centre have entered into a Patent License Agreement under we were granted a world-wide exclusive license pursuant to which we may have certain royalty obligations in relation to several CNS diseases. The Company is also obligated to pay LUMC up to € 910,000 in milestone payments upon the achievement of certain development and regulatory milestones and, beginning after its first commercial sale of a product covered by the licensed patent rights, a € 50,000 annual license fee which is creditable against royalties due to LUMC in the same calendar year. In addition, the Company is obligated to pay LUMC 3% of any net sales by the Company, its affiliates or sublicensees on licensed products. The Company has the right to buy off the royalty obligations by a one-time payment of € 50 million.

The Company and PARI Pharma GmbH entered into an agreement pursuant to which the Company is granted an exclusive license to the use of PARI's eflow technology for the administration of oligonucleotide-based drugs in the □ΔF508 mutation in cystic fibrosis, with the option to expand this exclusivity to the use in other CF mutations. Pursuant to the terms of the agreement, we have made an upfront payment, fees for development work and are obligated to make sales-based royalty payments after market authorization.

(c) Clinical support agreement

In August 2014, the Company entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide the Company with up to $ 3 million to support the clinical development of QR-010.

Pursuant to the terms of the agreement, the Company is obligated to make a one-time milestone payment to CFFT of up to approximately $ 80 million, payable in three equal annual installments following the first commercial sale of QR-010, the first of which is due within 90 days following the first commercial sale. The Company is also obligated to make a one-time milestone payment to CFFT of up to $ 3 million if net sales of QR-010 exceed $ 500 million in a calendar year. Lastly, the Company is obligated to make a payment to CFFT of up to approximately $ 6 million if it transfers, sells or licenses QR-010 other than for certain clinical or development purposes, or if the Company enters into a change of control transaction. Either CFFT or the Company may terminate the agreement for cause, which includes the Company's material failure to achieve certain commercialization and development milestones. The Company's payment obligations survive the termination of the agreement.

(d) Research and development commitments

The Company has research and development commitments, mainly with CRO's, amounting to € 9,481,000 at December 31, 2015 (2014: € 1,758,000). Of these obligations an amount of € 9,084,000 is due in 2016, the remainder is due in 1 to 5 years.

23. Related-Party Transactions

Details of transactions between the Company and related parties are disclosed below.

(a) Compensation of the Supervisory Board

On June 10, 2015, a new member, Mr. Paul Baart, was appointed to our supervisory board. The remuneration of the supervisory board members in 2015 is set out in the table below:

	2015			
	Short term employee benefits	Post employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. Dinko Valerio	36	—	12	48
Mr. Henri Termeer	34	—	11	45
Mr. Antoine Papiernik	73	—	—	73
Ms. Alison Lawton	31	—	48	79
Mr. Paul Baart	73	—	—	73
	247	**—**	**71**	**318**

The remuneration of the supervisory board members in 2014 is set out in the table below:

	2014			
	Short term employee benefits	Post employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. Dinko Valerio	33	—	65	98
Mr. Henri Termeer	33	—	57	90
Mr. Antoine Papiernik	—	—	—	—
Ms. Alison Lawton	10	—	8	18
	76	**—**	**130**	**206**

The 2013 remuneration is set out in the table below:

	2013		
	Advisory fees	Share-based payment	Total
	(€ in thousands)		
G.J. Platenburg	22	12	34
	22	**12**	**34**

As at December 31, 2015:

- Mr. Valerio holds 943,420 ordinary shares in the Company, as well as 32,272 options. In 2014, Mr. Valerio was granted 64,646 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an exercise price of € 1.11 per option. Under this option grant, 32,374 options were exercisable immediately, while the remaining 32,272 options vest in four annual equal tranches of 25% starting for the first time as of the first anniversary of the date of grant. Mr. Valerio exercised 32,374 options on June 30, 2014, for which he received 32,374 depositary receipts issued for ordinary shares after payment of the exercise price. These depositary receipts have been included in his total number of ordinary shares held.
- Mr. Termeer holds 1,730,714 ordinary shares in the Company as well as 28,709 options. In 2014, Mr. Termeer was granted 57,520 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an exercise price of € 1.11 per option. Under this option grant 28,811 options were exercisable immediately, while the remaining 28,709 options vest in four annual equal tranches of 25% starting for the first time as of the first anniversary of the date of grant. Mr. Termeer exercised 28,811 options on June 30, 2014, for which he received 28,811 depositary receipts issued for ordinary shares after payment of the total exercise price. These depositary receipts have been included in his total number of ordinary shares.

- Mr. Antoine Papiernik does not hold any shares or options in the Company. As a managing partner of Sofinnova Partners SAS, the management company of Sofinnova Capital VII FCPR, holder of 2,769,125 ordinary shares, Mr. Papiernik may be deemed to have share voting and investment power with respect to such shares.
- Ms. Lawton holds 12,820 options. In 2014, Ms. Lawton was granted 7,850 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an exercise price of € 10.03 per option. In 2015, she was granted 4,970 options with an exercise price of € 16.10 per option. Under these option grants options vest in four annual equal tranches of 25% starting for the first time as of the first anniversary of the date of grant.
- Mr. Paul Baart does not hold any shares or options in the Company.

(b) Compensation of key management personnel

Our management board is supported by our officers, or senior management. The total remuneration of the management board and senior management in 2015 amounted to € 2,420,000 with the details set out in the table below:

	2015			
	Short term employee benefits	Post employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. D.A. de Boer	397[1]	7	164	568
Mr. R.K. Beukema	313[2]	13	88	414
Management Board	710	20	252	982
Senior Management	943	27	468	1,438
	1,653	**47**	**720**	**2,420**

1 Short term employee benefits in 2015 includes a bonus for Mr. Daniel de Boer, of € 100,000.
2 Short term employee benefits in 2015 includes a bonus for Mr. René Beukema, of € 46,000.

The total remuneration of the management board and senior management in 2014 amounted to € 1,818,000 with the details set out in the table below:

	2014			
	Short term employee benefits	Post employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. D.A. de Boer	696[1]	10	195	901
Mr. R.K. Beukema	154[2]	17	55	226
Management Board	850	27	250	1,127
Senior Management	448	41	202	691
	1,298	**68**	**452**	**1,818**

1 Short-term employee benefits in 2014 includes a bonus for our chief executive officer, Mr. Daniel de Boer, of € 500,000. Share-based payments includes € 165,000 of employee benefits resulting from the repayment of the loan by Mr. De Boer.
2 Mr. René Beukema joined the Company on September 1, 2013 and was appointed to the management board on April 17, 2014. The table includes his remuneration received since January 1, 2014.

The total remuneration of the management board and senior management in 2013 amounted to € 355,000 with the details set out in the table below:

	2013			
	Short term employee benefits	Post employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. D.A. de Boer	180	8	7	195
Senior Management	134	11	15	160
	314	19	22	355

As at December 31, 2015:

- Mr. de Boer holds 1,213,201 ordinary shares in the Company as well as 79,894 options. In 2014, Mr. de Boer was awarded a total number of 55,992 options to acquire ordinary shares at € 3.04 per option. In 2015, he was awarded 23,902 options at an exercise price of € 16.10 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 8.7 years at December 31, 2015.
- Mr. Beukema holds 284,720 ordinary shares in the Company as well as 147,065 options. In 2014, Mr. Beukema was awarded 30,541 options to acquire ordinary shares at € 3.04 per option. In 2015, he was awarded 8,713 options at an exercise price of € 16.10 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 8.0 years at December 31, 2015.

ProQR does not grant any loans, advanced payments and guarantees to members of the Management and Supervisory Board.

24. Auditor fees

The fees for services provided by our external auditor, Deloitte Accountants B.V., are specified below for each of the financial years indicated:

	2015	2014	2013
	(€ in thousands)		
Audit fees	193	390	30
Audit-related fees	—	—	—
Tax fees	—	—	—
All other fees	—	—	—
	193	**390**	**30**

Audit fees

Consist of aggregate fees for professional services provided in connection with the annual audit of our financial statements, the review of our quarterly financial statements, consultations on accounting matters directly related to the audit, and comfort letters, consents and assistance with and review of documents filed with the SEC. Audit fees for 2014 also included fees associated with our initial public offering.

25. Subsequent events

Material subsequent events have not been identified.

Exhibit 8.1

SUBSIDIARIES OF PROQR THERAPEUTICS N.V.

The following is a list of subsidiaries of the Company as of December 31, 2015.

Legal Name	Jurisdiction of Formation
ProQR Therapeutics Holding B.V.	Netherlands
ProQR Therapeutics I B.V.	Netherlands
ProQR Therapeutics II B.V.	Netherlands
ProQR Therapeutics III B.V.	Netherlands
ProQR Therapeutics IV B.V.	Netherlands
ProQR Therapeutics I Inc.	Delaware

Exhibit 12.1

Certification by the Principal Executive Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Daniel de Boer, certify that:

1. I have reviewed this annual report on Form 20-F of ProQR Therapeutics N.V. (the "Company");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the Company as of, and for, the periods presented in this report;

4. The Company's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the Company and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the Company, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the Company's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the Company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the Company's internal control over financial reporting; and

5. The Company's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the Company's auditors and the audit committee of the Company's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the Company's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the Company's internal control over financial reporting.

Date: March 31, 2016

By: /S/ Daniel de Boer
Name: Daniel de Boer
Title: *Chief Executive Officer*
(Principal Executive Officer)

Exhibit 12.2

Certification by the Principal Financial Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Smital Shah, certify that:

1. I have reviewed this annual report on Form 20-F of ProQR Therapeutics N.V. (the "Company");

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the Company as of, and for, the periods presented in this report;

4. The Company's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the Company and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the Company, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the Company's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the Company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the Company's internal control over financial reporting; and

5. The Company's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the Company's auditors and the audit committee of the Company's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the Company's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the Company's internal control over financial reporting.

Date: March 31, 2016

By: /S/ Smital Shah
Name: Smital Shah
Title: *Chief Financial Officer*
(Principal Financial Officer)

Exhibit 13.1

Certification by the Chief Executive Officer and Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

In connection with the Annual Report on Form 20-F of ProQR Therapeutics N.V. (the "Company") for the year ended December 31, 2015, as filed with the U.S. Securities and Exchange Commission on the date hereof (the "Report"), the undersigned Daniel de Boer, as Chief Executive Officer of the Company, and Smital Shah, as Chief Financial Officer of the Company, each hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of his or her knowledge:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 31, 2016

By: /S/ Daniel de Boer
Name: Daniel de Boer
Title: *Chief Executive Officer*
(Principal Executive Officer)

By: /S/ Smital Shah
Name: Smital Shah
Title: *Chief Financial Officer*
(Principal Financial Officer)

Exhibit 15.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To: the Supervisory Board and Shareholders of ProQR Therapeutics N.V.

We hereby consent to the incorporation by reference in the Registration Statement on Form S-8 (No. 333-199451) and Form F-3 (No. 333-207245) of our report dated March 31, 2016 relating to the consolidated financial statements of ProQR Therapeutics N.V. appearing in the Annual Report on Form 20-F of ProQR Therapeutics N.V. for the year ended December 31, 2015.

/s/Deloitte Accountants B.V.

Amsterdam, the Netherlands
March 31, 2016